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FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

***Joint Peripheral and Central Nervous System Drugs Advisory
Committee and Drug Safety and Risk Management Advisory
Committee Meeting***

**Intravenous Phenytoin and Fosphenytoin Safety Concerns
Background Package**

November 3, 2010

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DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought this issue to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Suggested questions/discussion topics for the Phenytoin AC

(Combined OND/OSE v1: 9/24/2010)

1. Is phenytoin-associated Purple Glove Syndrome (PGS) a well-recognized and understood adverse drug event? Is it under-diagnosed or misdiagnosed?
2. Does the committee believe that the Division has adequate information to determine if there is an association between fosphenytoin and Purple Glove Syndrome?
 - a. If the answer for (2) is affirmative, does the Committee believe that there are differences in the risk of PGS between IV phenytoin and IV fosphenytoin?
3. Is there adequate information to determine how often severe PGS (with clinically significant outcomes such as surgical intervention) occurs as opposed to the milder and moderate forms?
 - a. For phenytoin?
 - b. For fosphenytoin?
4. Can the committee suggest additional regulatory actions to optimize use of IV phenytoin or fosphenytoin? Should there be changes in labeling for phenytoin and/or fosphenytoin (the addition of contraindications for some populations, addition of more detailed administration instructions [e.g., catheter size, rate of infusion], a Boxed warning, etc.).
5. Can fosphenytoin be used interchangeably with IV phenytoin for:
 - a. All indications and therapeutic uses (e.g., arrhythmias)?
 - b. In all settings of use (e.g., crash carts), considering the need for fosphenytoin refrigeration?
 - c. For all age groups (e.g., pediatrics)?
 - d. Are there settings where one agent is preferred over the other?
 - e. Are there settings where one of these agents should *not* be used?
6. Are there differences in risk for other clinically significant events with serious sequelae, (including cardiovascular events and/or hypotension, or medication errors) between IV phenytoin and fosphenytoin?
7. How does the frequency, the clinical phenotype (i.e., the characteristics of mild, moderate, and severe forms) and typical outcomes (i.e., spontaneous recovery, hospitalization, disability, amputation) of PGS compare to other safety concerns for IV phenytoin and/or fosphenytoin?
8. With the above in mind, which regulatory action would the committee recommend FDA take regarding phenytoin:
 - a. Allow continued marketing of phenytoin without changes to the labeling
 - b. Allow continued marketing of phenytoin with revisions to the current label (e.g., the addition of contraindications for some populations, addition of more detailed administration instructions [e.g. catheter size, rate of infusion], a Boxed warning)
 - c. Request marketing suspension of phenytoin

MEMORANDUM

DATE: October 4, 2010

FROM: Russell Katz, M.D.
Director
Division of Neurology Products/HFD-120

TO: Members of the Peripheral and Central Nervous Systems Drugs
Advisory Committee (PCNS AC) and Invited Guests

SUBJECT: Briefing Memo for the November 3, 2010 PCNS AC meeting to
discuss potential regulatory actions related to Intravenous (IV)
Phenytoin

As you know, we will be convening a meeting of the PCNS AC, supplemented with additional experts in relevant fields, on November 3, 2010, to discuss the comparative adverse event profiles of IV phenytoin and fosphenytoin, with the purpose of determining if any (and if so, what) regulatory actions would be appropriate for either product at this time.

The primary reason for convening the November 3 PCNS AC meeting is to consider the relative safety of IV phenytoin and fosphenytoin.

Specifically, questions have been raised about the propriety of permitting the continued marketing of IV phenytoin, given the well-known capacity of IV phenytoin to cause Purple Glove Syndrome (PGS), a potentially very serious local reaction of unclear etiology, and the belief that fosphenytoin, a product that could effectively substitute for IV phenytoin, is not associated with cases of PGS. Given this concern, the Agency has decided to bring this question to the AC.

Intravenous phenytoin has been marketed in this country since 1956 for the control of status epilepticus of the grand mal type and prevention and treatment of seizures occurring during neurosurgery. Fosphenytoin is a phosphate ester pro-drug of phenytoin that rapidly yields similar free phenytoin plasma levels as those produced by IV phenytoin, and was approved in 1996. It was ostensibly developed because it was assumed, based on differences between its formulation and that of IV phenytoin's (primarily related to pH and the lack of propylene glycol), that it would have fewer cardiac effects and be free of the risk of PGS. Fosphenytoin is indicated for short-term administration when "...other means of phenytoin administration are unavailable, inappropriate or deemed less advantageous...". Fosphenytoin sodium injection can be used for the control of generalized convulsive status epilepticus and prevention and treatment of seizures occurring during neurosurgery. It can also be substituted, short-term, for oral phenytoin." Fosphenytoin was approved on a showing of bioequivalence

to IV phenytoin; there were no controlled effectiveness trials performed with fosphenytoin.

At the time of approval of fosphenytoin, there was considerable concern that clinicians would have great difficulty calculating the correct dose of fosphenytoin to be given when converting from phenytoin to fosphenytoin (and even for those patients being treated with fosphenytoin de novo, the dosing for phenytoin was so well established and widely known that there were significant concerns about whether dosing with fosphenytoin could be done correctly and reliable). For this reason, dosing instructions for fosphenytoin were written to be given in mg Phenytoin Equivalents (mg PE; that is, one mg PE of fosphenytoin is equivalent to one mg of phenytoin), so that prescribers would not need to perform complicated molecular weight-based dose adjustments when converting between fosphenytoin and phenytoin doses.

Of course, if we are to consider the question of the continued marketing of IV phenytoin, it is important to compare, as completely as we can, the full panoply of important adverse reactions, as well as any potential advantages, associated with each drug, so that a fully informed decision can be made.

Toward this end, the Agency has performed several reviews of the relevant information available to us for both drugs, and these reviews are included in this package. Specifically, the following reviews have been included:

- 1) Purple Glove Syndrome: Drs. Andrew Fine and Jasmine Gatti, of the Division of Pharmacovigilance 1, Office of Surveillance and Epidemiology (OSE)
- 2) Adverse Effects and Current Clinical Considerations for Use of Phenytoin versus Fosphenytoin, Excluding Purple Glove Syndrome: Drs. Gatti and Fine
- 3) Purple Glove Syndrome: Dr. Kate Galleria, Division of Epidemiology, Office of Surveillance and Epidemiology
- 4) IV Phenytoin and Fosphenytoin Utilization Review: Dr. Grace Chai, Division of Epidemiology, Office of Surveillance and Epidemiology
- 5) Medication Error Review: Dr. Anne Crandall, Division of Medication Error Prevention and Analysis
- 6) Pediatric Dosing: Dr. Hristina Dimova, Office of Clinical Pharmacology
- 7) Supervisory OSE Review of PGS and other adverse events: Dr. Allen Brinker, Division of Pharmacovigilance, Office of Surveillance and Epidemiology

In addition, we have included a list of draft questions we would like the committee to discuss. At the time that we are sending you this package, the questions are not final, but do, in general, cover the issues we would like the committee to discuss. At the time of the meeting, the specific question list may differ somewhat from the list included with this package.

In this memo, I will very briefly summarize the more important data in these areas. The details of all of these issues are described in the various reviews included in this package.

Purple Glove Syndrome (PGS)

Definitions of PGS vary, but it has been reasonably defined as including edema, discoloration, and pain related to intravenous treatment with phenytoin. It may begin with discoloration at or near the injection site, beginning within hours, and may progress with increasing edema and further discoloration spreading distally, followed by (in most cases), resolution over days to weeks. Although most cases resolve, it can be associated with necrosis of the skin and ischemia, and, in some (as far as we know, rare) cases, skin grafting, fasciotomies, and even amputations have been necessary.

The Agency has examined our spontaneous adverse event reporting system (AERS), as well as the literature and Pfizer's (the manufacturer of IV Dilantin and Cerebyx) assessment of the available data on the association of IV phenytoin and fosphenytoin and PGS.

Although spontaneous reports frequently do not provide adequate information, since marketing, a total of 43 cases of PGS (defined for these purposes as having been reported as PGS or one in which a temporal relationship existed between treatment and discoloration and edema or pain, with no reasonable alternative explanation) have been reported for phenytoin, and 4 possible cases have been reported with fosphenytoin (for fosphenytoin, there were 4 additional cases that did not meet the case definition, but were considered serious, and included swelling and blisters [1 case], and 2 cases with "necrosis"). None of the fosphenytoin cases required any surgical procedure, but several were treated with Silvadene cream. The sponsor's assessment added one additional case that was classified as either possible or probable PGS and that was not also identified in AERS.

Although there are no literature reports of PGS associated with fosphenytoin (either case reports or from studies of any kind), there are numerous case reports and reports of observational studies examining this question with IV phenytoin. These studies, which include case-control, retrospective and prospective observational studies, and even prospective randomized trials, produce estimates of PGS with IV phenytoin that vary from 0-6%. For example, researchers in a 1998 study at the Mayo Clinic examined their records and found 152 patients who received IV phenytoin during one 3 month period. A total of 9 (5.9%) were diagnosed with PGS. A 2001 study at the Henry Ford Hospital in Detroit prospectively identified 179 administrations of IV phenytoin, with 2 (1.7%) episodes of PGS. A 2004 report of a small (N=14 to 16/group) randomized trial

in California compared patients who received either oral phenytoin, IV phenytoin (infused at 50 mg/min) or IV phenytoin (infused at 150 mg/min). No cases of PGS were seen, and in a randomized study of IV phenytoin (N=77) and fosphenytoin (N=202), no cases of PGS were seen.

Other Adverse Events

As noted earlier, it is important to examine the full panoply of important adverse events with both drugs in order to make a meaningful assessment of the relative merits of the products.

Again, in an effort to assess these non-PGS adverse events, the Agency has examined its spontaneous reporting system, the literature, and the sponsor's (Pfizer's) own evaluations. The Agency's examination focused primarily on cardiovascular risks, including hypotension, largely because of the well-known association of IV phenytoin with arrhythmias and hypotension. However, other serious adverse events were also examined.

Current labeling limits the infusion rate of IV phenytoin to a maximum of 50 mg/min (and to 150 mg PE/min for fosphenytoin) because of the risk of cardiac toxicity and hypotension at faster infusion rates.

Briefly, from the date of marketing of each product to July 31, 2010, there were 78 CV events reported to the Agency's spontaneous reporting system for fosphenytoin and 99 CV events for phenytoin. In addition, there were 53 and 44 cases of hypotension reported for fosphenytoin and IV phenytoin, respectively. The CV events included asystole, bradycardia, cardiac arrest, ventricular tachycardia, as well as others, and included deaths. A more complete listing of the more recent cases is given in Table 7 of the review by Drs. Gatti and Fine. It is worth noting that cases have been reported in which the infusion rate did not exceed the labeled upper limits.

In contrast to the lack of literature reports of PGS with fosphenytoin, there are numerous reports of arrhythmias and hypotension in association with fosphenytoin, as there are for IV phenytoin. The literature also contains reports of trials (randomized and non-randomized) that purport to demonstrate similar types and rates of arrhythmias and similar rates (and degrees) of hypotension with each product.

Regarding other adverse events, there is a general similarity in the incidence and type (based on the few comparative studies available), although one randomized study comparing fosphenytoin (N=90) to IV phenytoin (N=22) revealed a 49% incidence of pruritus with fosphenytoin compared to 4.5% with phenytoin. Although the literature does not report any cases of Stevens Johnson Syndrome

(SJS) with fosphenytoin, but does with IV phenytoin, there are spontaneous reports of SJS with both products.

Other Concerns-Medication Errors

Since the approval of fosphenytoin, errors in dosing, sometimes with serious outcomes, including death, have occurred. These errors have been primarily related to two aspects of the product labeling.

As noted earlier, dosing with fosphenytoin is to be given in mg PEs (phenytoin equivalents), specifically so that the practitioner could avoid having to make complicated molecular weight-based dosing adjustments. However, the concept of mg PE with fosphenytoin has produced, over the years, its own confusion, sometimes resulting in significant dosing errors.

In addition, significant overdoses of fosphenytoin have occurred because practitioners have mistakenly read the concentration listed on the container label as representing the total amount of drug in the vial (for example, the bottle label stated “50 mg PE/mL” for a bottle with 10 mL; this bottle contained 500 mg PE of fosphenytoin, and some practitioners administered 10 bottles to achieve a dose of 500 mg PE [actually administering 5000 mg PE], because they assumed there were 50 mg PE **total** in the bottle). These overdoses resulted in 10 deaths, mostly in pediatric patients.

Because of these errors, numerous changes to the carton and container labels, as well as to the package insert, have been made (for example, to address the latter concern, the total amount of drug has been more prominently displayed on the labels), and in recent years there have been very few errors of the first type, and none of the second type, reported, despite increasing use of fosphenytoin (see below).

Drug Usage

Contributing to the difficulty in making comparisons between rates of adverse events based on spontaneous reports is the issue of comparative use. The Agency has attempted to assess the comparative use of these two products.

Briefly, use of fosphenytoin has steadily increased, while the use of IV phenytoin has decreased. For example, in 2004, based on the number of discharges from the hospital with a billing code for IV phenytoin or fosphenytoin, there were about 283,000 discharges with a code for phenytoin (about 66% of the fosphenytoin-phenytoin market) compared to 148,000 for fosphenytoin (about 34% of the share). In 2009, however, the numbers were about 149,000 discharges (41% of the share) and about 210,000 (59% of the share), for phenytoin and

fosphenytoin, respectively. Interestingly, since 2004, fosphenytoin has represented the vast majority of use in the pediatric population (72-85% of the share).

At the same time, the price of fosphenytoin has dropped dramatically. In 2004, the average price per vial of IV phenytoin was \$1.92 compared to \$29.49 for fosphenytoin. In 2009, the prices were \$1.31 and \$2.61, for phenytoin and fosphenytoin, respectively.

It should also be pointed out that all IV phenytoin currently marketed in the US is generic; there are many generic manufacturers of fosphenytoin as well, though the innovator product, Cerebyx, is still marketed.

Summary Comments

As noted earlier, questions have been raised about the propriety of allowing IV phenytoin to remain on the market, given its capacity to cause PGS, and the availability of fosphenytoin, a drug that can, for all intents and purposes, substitute for IV phenytoin. Also as noted above, in order to adequately address this question, we have attempted to compare the risks (in toto) of both products.

IV phenytoin is widely regarded to cause PGS. The incidence of PGS caused by IV phenytoin is impossible to know with any accuracy, given the data sources available to us, and the varying definitions of PGS that have been proposed. As noted earlier, estimates of PGS vary from 0 to 6%. Post-marketing data cannot provide useful incidence estimates, given under-reporting and only estimates of usage. Further, establishing causality from post-marketing reports at all is ordinarily highly questionable, given the paucity of details in many of these reports, as well as the lack of reliable comparative or background rates. However, for events like PGS, which are acute and for which it is reasonable to assume that the background rate (in the absence of confounders) is essentially nil, causality can be reasonably assessed (given adequate details).

Given these uncertainties, it appears reasonable to conclude that IV phenytoin can cause PGS, however reasonably defined. Although the true incidence cannot be known from the data, the rate is presumably low, and, importantly, the rate of PGS with serious clinical consequences (those, for example, that necessitated fasciotomy, debridement, or amputation [or, very rarely, resulted in death], and presumably those that are the basis for contemplating IV phenytoin's removal from the market) must be quite substantially lower still.

It is more difficult to determine if the data support the conclusion that fosphenytoin causes PGS. There are no reports of fosphenytoin-induced PGS in the literature (either as case reports, or from studies). However, there are

several (a total of 9 non-duplicated reports obtained either from AERS or the sponsor's examination) post-marketing reports that could represent cases of PGS. These cases are relatively poorly described, and none can stand alone, given the details included (or more importantly, excluded), as an absolutely definitive case of PGS, but certainly they are suggestive, and permit a reasonable inference that fosphenytoin may cause PGS. Importantly, there are no reports of cases with significant clinical sequelae. Again, it is impossible to know the rate of PGS with fosphenytoin, if it exists at all.

There are many factors that have been raised as possibly contributing to the disparity in reporting rates for PGS for these two products (besides the possibility that they differ, in reality, in their capacity to cause PGS).

The package insert (PI) for IV phenytoin describes PGS as a potential adverse event; the label for fosphenytoin does not. What, if any, effect this might have on reporting practices is hard to know. One could imagine that this might suggest to practitioners that PGS cannot occur with fosphenytoin, so potential cases may be dismissed, and hence not reported. The knowledge that IV phenytoin causes PGS might result in marked under-reporting of those cases as well, or might stimulate reporting of these cases by practitioners who believe that fosphenytoin does not cause PGS, and wish to make these differences more apparent, for various reasons. It is difficult, if not impossible, to make a reliable assessment of the reasons for the apparent differences in the rate of reported cases of PGS for the two products. However, the lack of reported cases in the literature is of interest: Given that fosphenytoin is "reputed" to be free of the risk of PGS, one might think that if a fosphenytoin case occurred, there would be motivation to report it. Also of interest, as noted by Dr. Gelperin in her 11/26/08 review, there were no reports of possible PGS from outside the US, although, as she notes, there were sales in France, Canada, and Sweden, all of which, "...are countries with sophisticated pharmacovigilance systems."

However, as noted in several of the included reviews, questions have been raised about the adequacy of post-marketing reporting by Pfizer, the manufacturer of Cerebyx, and, therefore, questions about whether the Agency is aware of all possible cases that should have been reported. Specifically, most of the fosphenytoin post-marketing reports are "direct" reports; that is, they are reports to AERS directly from consumers, practitioners, pharmacists, etc., and not from the sponsor. Typically, the vast percentage of AERS reports for all drugs come from the manufacturers (about 94%), but between 1997 and 2008 about 56% of all reports for fosphenytoin were direct reports.

The division had asked Pfizer, in December 2008, to implement special reporting requirements for potential cases of PGS, but the Office of Compliance found that these requirements were not being met, and issued, for this and other reasons, an enforcement letter to Pfizer in May, 2010. Pfizer responded to this letter in June, 2010, and asserted that they had been completely compliant with the

special reporting requirements between February and May 2010 (and that there were no cases in that interval). These potential reporting problems at least raise the question about whether or not all possible cases of PGS that might have (or should have) come to Pfizer's attention, were, in fact, reported to the Agency.

Regarding a comparison of other adverse events, it appears that both products are capable of causing similar arrhythmias and hypotension. Again, it is impossible to provide an adequate assessment of the relative incidence of these events, but the data (such as it is) suggests that there are no major differences in either the kind or frequency of cardiac events, or the rate and degree of hypotension, that the two drugs can cause (again, causality itself is difficult to establish, but, to some extent, as with PGS, the acute nature of the events of interest makes it reasonable to assign causality, at least in some cases).

With regard to medication errors, the use of fosphenytoin has been associated with several errors that have been specifically related to its labeling. Specifically, practitioners have mistakenly interpreted the label on the vial with regard to the amount of drug in the vial, resulting in overdoses, and they have also been confused about the dose of fosphenytoin to be given, this latter related to the unusual nomenclature (i.e., mg PEs). However, reports of these two types of errors have markedly diminished, presumably in (large) part to aggressive education and labeling changes (of course, this diminution may just be in **reporting**, not in actual occurrence).

However, as noted by Dr. Crandall, there are also numerous medication errors related to the use of IV phenytoin, including related to its inability to be diluted with dextrose solutions, and incorrect rate of infusion, as well as other reasons.

There are, of course, other differences between the products.

As is well known, IV phenytoin is highly basic, with a pH of 12, whereas the pH of fosphenytoin is about 8.6-9. IV phenytoin contains propylene glycol to enhance solubility, whereas fosphenytoin does not. The very high pH and/or the propylene glycol have been considered to possibly contribute to the occurrence of PGS and perhaps cardiac toxicity of IV phenytoin, although this has not been established (and the occurrence of similar cardiac adverse events with fosphenytoin seems to argue against any significant contribution of propylene glycol to the genesis of these events). The role of either of these factors in the production of PGS is unknown at this time.

As noted above, IV phenytoin cannot be mixed with commonly used dextrose solutions, whereas there are no real restrictions on mixing fosphenytoin with standard IV solutions.

Fosphenytoin must be refrigerated; IV phenytoin does not need to be refrigerated. Whether this has important implications for the use of these

products in, for example, emergency settings, is an outstanding question (for example, would this make an important difference in whether or not these products can be readily available on crash carts, in emergency medical vehicles, etc.).

IV phenytoin is infused through a filter; fosphenytoin does not need to be infused through a filter.

The label for IV phenytoin contains dosing recommendations for all age groups, including infants. Fosphenytoin labeling does not provide dosing recommendations for pediatric patients. Although Pfizer did provide pharmacokinetic data in pediatric patients treated with fosphenytoin, the Agency concluded that the resulting free phenytoin levels were too variable to support adequate dosing recommendations. However, as noted earlier, the vast majority of pediatric patients who require IV therapy with either product are treated with fosphenytoin.

Fosphenytoin can be given intramuscularly (IM); phenytoin should not be given IM.

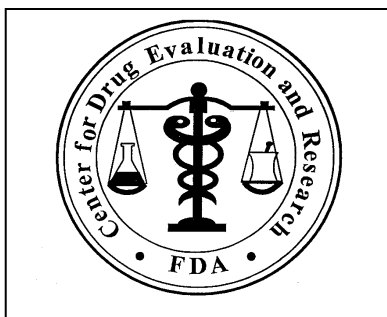
IV phenytoin is used off label for several indications, though, given the fact that the two products are bioequivalent, there should be no difference in the utility of both products.

There is a perception that one advantage of fosphenytoin compared to phenytoin is that it can be infused more rapidly. This is true, given that the maximum rate recommended for fosphenytoin is 150 mg PE/min, whereas the maximum rate of phenytoin infusion is 50 mg/min. However, these rates produce essentially identical free phenytoin levels for a given dose of either drug, so the effect of these two infusion rates (onset of action, etc.) would be expected to be the same.

One final point about the included reviews needs to be made.

Many of the reviews contain recommendations for various regulatory actions for both drugs. It is important for the Committee to understand that the Agency has taken no position on the recommendations included in these reviews, and no decisions about the issues we wish to discuss with the Committee have been made. Indeed, of course, we are coming to the Committee specifically to hear your views on these and related issues.

With this background, we are eager to hear the Committee's view of the comparison of these two products, and, especially, the Committee's view of whether or not, given these comparisons, the continued marketing of IV phenytoin is appropriate. I would like to thank you in advance for the work you will do in preparation for the meeting, and especially for your contributions at the meeting itself. I look forward to seeing you in November.



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Office of Surveillance and Epidemiology
Division of Drug Risk Evaluation

Date: October 4, 2010

To: Russell Katz, M.D., Director,
Division of Neuropharmaceutical Products

Through: Mark Avigan, M.D., C.M., Director
Division of Pharmacovigilance 1 (DPV1)
Office of Surveillance and Epidemiology (OSE)

From: Allen Brinker, M.D., M.S., Team Leader
Division of Pharmacovigilance 1

Subject: Covering memorandum for OSE reviews prepared for an Advisory Committee meeting planned for November 3, 2010 to discuss a number of safety concerns with IV administration of phenytoin and fosphenytoin, including Purple Glove Syndrome.

Drug Name: Cerebyx (Fosphenytoin Sodium) Injection
Phenytoin Sodium Injection

Application Type/Number: NDA 020450
ANDAs: 077481 / 078126 / 078137 / 078277 / 076886 / 077989
078158 / 078158 / 078417 / 078765 / 078052 / 078476 / 078736
089521 / 089744 / 040573 / 084307 / 040781

Applicant/sponsor: Eisai Inc., Bedford, Apotex Inc., Wockhardt, Pharmaforce, Teva Parenteral, Baxter Healthcare, Hospira, Sun Pharm Global, Hikma Farmaceutica, App Pharms, Akorn Strides, Strides Arcolab

OSE RCM #: 2010-571

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Introduction

This memorandum contains a collation of the conclusions and recommendations from four distinct OSE reviews¹⁻⁴ on IV phenytoin and fosphenytoin that are provided as background material to the Joint Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee (AC), planned for November 3, 2010. Per the Federal Register announcement, the AC will discuss a number of safety concerns with IV administration of phenytoin and fosphenytoin, including Purple Glove Syndrome. The memorandum includes recommendations for labeling changes for both products based on the reviews authored by DPV-1 and the Division of Medication Error Prevention and Analysis (DMEPA).

Purple Glove Syndrome

Clinical features consistent with purple glove syndrome (PGS) were first described as an adverse side effect of IV phenytoin therapy in the 1980s. The pathogenesis of PGS is unknown. The predominance of PGS related to IV phenytoin in the published literature postulates it is a unique feature of the formulation for IV phenytoin needed for solubilization of the active ingredient (basic pH, polyethylene glycol). However, its relationship to the vehicle, its pH, the active ingredient, or venous irritation has not been entirely elucidated. Surprisingly, there is a single literature report of PGS after oral administration of a large phenytoin overdose in a child. In contrast to IV phenytoin, the peer-reviewed literature, to date, has not identified cases of IV or IM fosphenytoin-associated PGS.

The most recent review¹ of PGS conducted by DPV-1 includes 43 cases of PGS in association with IV phenytoin. Two observational studies evaluating PGS in phenytoin-treated patients reported incidence rates of 1.7% and 5.9% in a routine hospital setting. Most cases included in these studies were generally mild and did not require additional hospitalization or specialized treatment. More serious outcomes, including skin necrosis and limb ischemia, have been reported and resulted in fasciotomy, skin grafting, or amputation. PGS currently appears within the **Precautions** section of the phenytoin label, under the **General** subsection, as follows:

Edema, discoloration, and pain of the distal limb (described as “purple glove syndrome”) have been reported following peripheral intravenous phenytoin sodium injection. This may or may not be associated with extravasation. Although resolution of symptoms may be spontaneous, skin necrosis and limb ischemia have occurred and required such interventions as fasciotomies, skin grafting, and amputation. Therefore, Phenytoin Sodium Injection should be administered as described above.

The most recent DPV-1 review¹ has identified five AERS cases consistent with PGS in association with fosphenytoin. The current product label for fosphenytoin does not mention PGS.

¹ Memorandum dated 4 October 2010. Andrew Fine and Jasmine Gatti to Russell Katz. Purple glove syndrome [in association with IV phenytoin and fosphenytoin].

A main regulatory focus of PGS and fosphenytoin has been on submission of spontaneous (AKA MedWatch) reports from the original NDA-holder for fosphenytoin, Pfizer. This concern was raised due to a divergent pattern of direct versus sponsor-submitted MedWatch reports for fosphenytoin. CDER's Office of Compliance recently investigated Pfizer's adverse drug event reporting practices. Notably, Pfizer recently stated, in their letter response to Office of Compliance, they have been 100% compliant with specialty reporting requirements for PGS since October 2009. However, DPV-1 remains circumspect about complete receipt and submission of PGS reports in association with fosphenytoin for the time period prior to October 2009.

Commentary: Purple glove syndrome and clinically overlapping events have been reported with both IV phenytoin and fosphenytoin. This conclusion is consistent with a previous review by OSE and the fosphenytoin sponsor. Although not definitive, based on literature findings to a large extent, it appears reasonable to conclude that PGS occurs more frequently with IV phenytoin than fosphenytoin. The data reviewed for both agents suggest that certain risk factors exist for PGS and typical outcomes are not serious in nature, though serious sequelae have been reported for phenytoin-associated PGS. The most recent review¹ also highlights inadequacies in current product labeling, specifically, a lack of critical PGS details (risk factors) within the phenytoin label and an absence PGS information altogether for fosphenytoin.

Drug Utilization

Over the recent past, sales of IV phenytoin have decreased while sales of fosphenytoin have remained generally constant.² Data available for analysis by the Agency show 2009 sales of IV phenytoin of ~3.0 million vials and sales of 2.3 million vials for fosphenytoin. The average price per vial for fosphenytoin sold to non-retail settings of care in 2004 was \$29.49. Following the appearance of generic fosphenytoin in late 2007, the average price per vial for fosphenytoin has decreased. In 2009, the average price per vial was \$2.59 for fosphenytoin and \$1.31 for IV phenytoin. It is notable that recently, with the marketing of generic fosphenytoin products, there has been a dramatic reduction of marketing of Cerebyx, the innovator fosphenytoin product manufactured by Pfizer. Whether possible short-falls in availability of generic fosphenytoin products will impact continuation in the rise of the proportion of IV fosphenytoin to IV phenytoin use, remains to be determined.

Although limited by the generalizability of the sample, analysis of inpatient hospital use of IV phenytoin and fosphenytoin in different age groups suggests no age strata, including neonates, infants and children in which there is selective use of only one of these products. Exclusive use of only one of these products was also not observed in any specific in-hospital setting such as ICUs, surgical and medical services, pediatric services, etc. Available in-patient discharge data did not permit analysis of outpatient settings including ERs, ambulatory clinics, etc.

² Memorandum dated 4 October 2010. Grace Chai to Russel Katz. IV phenytoin and fosphenytoin utilization review.

Commentary: Although the price for fosphenytoin has decreased since approval of generic versions and utilization of IV phenytoin has decreased over the same period, the utilization of fosphenytoin appears generally constant in the period 2004 – 2009. However, utilization of other agents used to treat status epilepticus, specifically midazolam, propofol, and most notably lorazepam appear to have increased. These agents appear to have taken up market share of IV phenytoin in the treatment of status epilepticus.

Selected Adverse Events Other Than Purple Glove Syndrome

In a review³ of adverse event profiles for both phenytoin and fosphenytoin, injection site reactions and skin and soft tissue disorders (e.g., dermatitis, skin discoloration, blisters) appear to be more frequently reported for IV phenytoin in comparison to fosphenytoin. This is expected based on the high pH of IV phenytoin and the propylene glycol component in its formulation. Among the most frequent adverse events reported for both drugs are cardiovascular events and medication errors.

The most important adverse clinical events caused by the IV use of phenytoin or fosphenytoin are cardiovascular collapse and/or central nervous system depression. Hypotension can occur when either drug is administered rapidly by the IV route. Per approved labeling for fosphenytoin, in premarketing clinical trials 0.3% of patients discontinued treatment due to hypotension and 0.2% of patients discontinued treatment due to bradycardia. Approved labeling for fosphenytoin also states that 7.7% of patients receiving fosphenytoin experienced treatment-emergent hypotension versus 9.1% of patients who receiving IV phenytoin. Despite earlier predictions, there is no convincing evidence of a substantial difference for risk of cardiovascular adverse events between IV phenytoin and IV/IM fosphenytoin.

Risk factors for serious cardiovascular complications of treatment with fosphenytoin and IV phenytoin include advanced age, rapid infusion rates, and known cardiac disease. However, the literature, the most recent case series³, and prior reviews of FDA's spontaneous reporting database provide evidence that serious cardiovascular events have been reported in younger patients, patients without significant cardiovascular risk factors, and at recommended doses and at labeled infusion rates.

Commentary: Side effect profiles include administration site/local reactions, cardiac disorders, and medication errors as the most prominent adverse events of IV phenytoin and fosphenytoin; local administration site reactions are much more common with IV phenytoin. Both IV phenytoin and IV or IM fosphenytoin appear able to induce serious cardiovascular events and hypotension at various doses and infusion rates and in a variety of patient populations. It is extremely difficult to quantify or compare the absolute rate of these serious events between the two agents based on spontaneous case reports.

³ Memorandum dated 4 October 2010. Jasmine Gatti and Andrew Fine to Russell Katz. Adverse effects and current clinical considerations for use of IV phenytoin versus fosphenytoin, excluding purple glove syndrome.

Though the initial marketing of fosphenytoin touted its potential for a lower incidence of cardiovascular adverse events, much of the literature – including approved labeling - suggests there is no easily discernable difference. Data included in the review³ suggest that some practitioners may still believe fosphenytoin to have a better cardiac profile and may not employ cardiac monitoring.

Medication Errors

OSE's Medication Error staff recently evaluated 494 cases of medication error involving fosphenytoin and phenytoin injection.⁴ Medication error reports of errors in dose, technique, frequency or, route of administration, administered drug, rate or duplication of infusion were evaluated for both fosphenytoin and phenytoin injection. Most of the types of errors retrieved occurred with both products. Causality for these errors is multifactorial and the contributing factors leading to these errors are somewhat different for each product. Product comparisons for incidence and comparative safety cannot be robustly estimated for these two agents based solely on spontaneous reports given the different factors that influence medication error reporting. Although some errors relate to practice-related issues such as errors in transcription, calculation, pump miss-programming, administration of multiple loading doses, etc., the majority are due to confusion as it relates to product labels and package labeling. Although, some product label and package labeling revisions have been made over the years, both products would greatly benefit from further revisions to their product labels and package labeling.

With interest in the outcome of death, the DMEPA review adjudicated 10 cases of death associated with fosphenytoin because of an error surrounding the total dose administered. Seven out of 10 of these individuals were aged < 3 years. In their review, DMEPA also adjudicated 6 cases of death associated with intravenous administration of phenytoin. These cases were attributed to errors of route (IV administration of oral suspension) and infusion rate errors. The majority of these cases were errors of route (5 of 6) and all were identified in patients aged > 16 years.

Commentary: There is a need to improve the overall consistency of the product labels and package labeling across these drug products. Furthermore, there is also a need to gain a better understanding as to the continued extent of confusion that remains with respect to the phenytoin equivalency nomenclature used for dosing fosphenytoin. These improvements can impact the occurrence of some of the errors associated with their use. The medication error data supports the need for additional label and labeling changes for both fosphenytoin and phenytoin injection in order to minimize confusion with respect to errors in rate of administration, product preparation, storage and administration, dose adjustments, and duplication of therapy.

⁴ Memorandum dated 1 October 2010. Anne Crandall to Russell Katz. Medication error review for Cerebyx (fosphenytoin sodium) injection and phenytoin sodium injection.

Global / Overall Assessment

In consideration of the conclusions advanced by the primary reviewers, there appears to be a difference in the risk for purple glove syndrome between IV phenytoin and fosphenytoin, supporting the labeling recommendations that have been advanced to address this issue.

While clinically significant purple glove syndrome appears to be a rare complication of therapy with these agents, serious cardiovascular events appear to occur much more frequently and represent a larger target for public health interest and intervention. As highlighted in the reviews, serious cardiovascular events in association with these agents are primarily linked to rates of intravenous infusion. Additionally, while selected patient populations (i.e., the elderly, individuals with underlying cardiac disease) appear to be at higher risk, adverse cardiovascular events have been reported in apparently healthy, younger individuals even at recommended infusion rates. Therefore, the labeling recommendations advanced to highlight and potentially prevent the adverse cardiovascular effects associated with IV phenytoin and fosphenytoin are justified.

Regulatory Recommendations by OSE

Product Labeling and Compliance issues

For Purple Glove Syndrome

- Label revision for phenytoin to elevate PGS to a specific Warning/Precaution under the Structured Product Labeling (SPL) format or to a specific Precaution with its own section under the current labeling format.
- Label revision to the Post-Marketing Section of the fosphenytoin label to state, “Reports of Purple Glove Syndrome (PGS) with fosphenytoin therapy have been identified.”
- All fosphenytoin sponsors, including Pfizer, should report all cases that include an adverse event in an extremity where fosphenytoin has been administered; these should be submitted as 15-day expedited reports, regardless of outcome and include follow-up information.
- Office of Compliance inspections of Pfizer’s foreign Adverse Drug Event (ADE) practices to ensure compliance with fosphenytoin special enhanced reporting requirements.

For Adverse Events Other Than Purple Glove Syndrome

- For IV phenytoin: Eliminate cardiac labeling from Adverse Reactions section and retain in the Warnings section only.
- For fosphenytoin and IV phenytoin: Labeling will continue to include “Cardiovascular Depression” and “Serious Cardiovascular Events and Fatalities” (with CAUTION in patients with hypotension and severe myocardial insufficiency).
- For fosphenytoin and IV phenytoin: Broaden Warnings labeling to include specific diagnoses of cardiac arrest, asystole, ventricular tachycardia, ventricular fibrillation, prolonged QT interval, junctional rhythm, sudden death, and pulseless electrical asystole as identified in the AERS database.

- For fosphenytoin and IV phenytoin: Broaden Warnings labeling to include specific language that serious cardiac events (as included immediately above) have been reported in healthy adults and children without underlying cardiac disease or co-morbidities, and occurrence at or below recommended doses, at or below recommended infusion rates and during and after infusions.
- For fosphenytoin: Update the Adverse Reaction table in the Clinical section with comprehensive data submitted from the integrated clinical trial adverse event profiles from Pfizer's 2008 systematic analysis. This data will more accurately reflect the rates of treatment-emergent adverse events for fatal, non-fatal serious and non-serious AE's.

Tracking of Fosphenytoin Marketing in US

- Marketing of fosphenytoin by individual generic manufacturers and innovator should be monitored and assessed. Sponsors should be surveyed for plans and issues surrounding the manufacture of these products to help determine future availability in the US pipeline.

Medication Errors Reduction / Elimination

Fosphenytoin

- Update the package insert to contain the following pertinent information:
 - Frequency of administration.
 - Update the Dosage and Administration section to include dosing recommendations in liver and renal failure and consider including the equation that can be used for phenytoin correction for altered albumin levels.
 - Detailed instructions for proper dilution and recommended ratio of drug to diluent.
 - A statement which informs practitioners of storage requirements after product dilution.
 - Dosing guidelines for pediatric patients.
 - Updated Drug Interaction section.

Phenytoin Sodium Injection

- Update the package insert to contain the following pertinent information:
 - Include a "Laboratory Test" section that includes the recommended phenytoin laboratory levels that should be used for monitoring (in conjunction with patient response) and a section devoted to phenytoin and albumin and include the equation that can be used for phenytoin correction for altered albumin levels.
 - Recommended diluent to be used for diluting phenytoin sodium injection.
 - Detailed instructions for proper dilution and recommended ratio of diluent and active drug.
 - Include rate of administration recommendations for pediatric patient population in the boxed warning.

- Fosphenytoin Container Labels and Carton Labeling
 - Revise either the 2 mL or 10 mL container labels to incorporate colors that are not used in the other volume, thereby allowing for improved visual differentiation between the 2 mL and 10 mL Cerebyx and fosphenytoin vials.
 - Revise the 2 mL container vials to ensure that the storage statement is displayed on immediate container label. This revision should be implemented by all manufacturers of Cerebyx and fosphenytoin.
 - The presentation of total drug content should be consistently presented in accordance with USP. The total drug content should be the most prominent and the mg per mL concentration should appear less prominent.
 - Include the statement “Dilute prior to administration” on the principal display panel of all container labels and carton labeling.
- Phenytoin Sodium Injection Container Label/Carton Labeling
 - Remove the ‘no infusion’ statement and replace it with the recommended rate of administration, “Maximum rate for adults should not exceed 50 mg/minute or 1-3 mg/kg/min in neonates” on the container labels and carton labeling.

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/s/

ALLEN D BRINKER

10/05/2010

This version replaces one entered on 4 Oct 2010 that was degraded in internal DARRTS conversion from Word to PDF.

MARK I AVIGAN

10/05/2010

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA 20-450

Sponsor: Pfizer

Drug: Cerebyx® (fosphenytoin sodium injection)

Formulation: IV and IM injection

Proposed Indication: Treatment of seizures

Material Submitted: Labeling supplement and response to request for additional information requested at June 30, 2008 meeting

Submission Date: April 2, 2009

Internal Meeting Date: Jan 25, 2010

Reviewer: Hristina Dimova, Ph.D.

Team Leader: Angela Men, M.D., Ph.D.

1. Background

This labeling supplement and supporting information are in response to a request by FDA (June 2008) to revise the Cerebyx label to address concerns about dosing errors. Additionally, the sponsor was asked to review all available information in order to determine whether there were sufficient data to propose appropriate dosing instructions for use of Cerebyx in pediatric patients.

Current Cerebyx Label:

Pediatrics: Cerebyx is not indicated for use in pediatric patients. Since pediatric pharmacokinetics data are limited, the kinetics of fosphenytoin in children are not well understood. Only limited pharmacokinetic data are available in children (N=8; age 5 to 10 years). In these patients with status epilepticus who received loading doses of Cerebyx, the plasma fosphenytoin, total phenytoin, and unbound phenytoin concentration-time profiles did not signal any major differences from those in adult patients with status epilepticus receiving comparable doses.

2. Summary of Fosphenytoin Pharmacokinetics

Fosphenytoin is a phosphate ester prodrug developed as an alternative to intravenous phenytoin for acute treatment of seizures. The anticonvulsant effects of fosphenytoin are attributable to phenytoin. Phenytoin therapeutic plasma concentration: total phenytoin plasma concentration >10 mg/L or unbound phenytoin plasma concentration >1 mg/L. Fosphenytoin is entirely eliminated through metabolism to phenytoin by blood and tissue phosphatases. The bioavailability of the derived phenytoin relative to intravenous phenytoin is approximately 100% following intravenous or intramuscular administration. The half-life for conversion of fosphenytoin to phenytoin ranges from 7–15 minutes. The pharmacokinetics of fosphenytoin following IV administration of Cerebyx, are complex, and when used in an emergency setting (eg, status epilepticus), differences in rate of availability of phenytoin could be critical. Studies have therefore empirically determined an infusion rate for Cerebyx that gives a rate and extent of phenytoin systemic availability similar to that of a 50 mg/min phenytoin sodium infusion. A dose of 15 to 20 mg PEsPE/kg of Cerebyx infused at 100 to 150 mg PEsPE/min yields plasma free phenytoin concentrations over time that approximate those achieved when an

equivalent dose of phenytoin sodium (eg, parenteral Dilantin®) is administered at 50 mg/min. Faster intravenous infusion rates and competitive displacement of derived phenytoin from plasma protein binding sites by fosphenytoin compensate for the expected conversion-related delay in appearance of phenytoin in the plasma. Plasma fosphenytoin concentrations following IM administration are lower but more sustained than those following IV administration due to the time required for absorption of fosphenytoin from the injection site.

Distribution: Phenytoin is highly bound to plasma proteins, primarily albumin, although to a lesser extent than fosphenytoin. In the absence of fosphenytoin, approximately 12% of total plasma phenytoin is unbound over the clinically relevant concentration range. However, fosphenytoin displaces phenytoin from plasma protein binding sites. This increases the fraction of phenytoin unbound (up to 30% unbound) during the period required for conversion of fosphenytoin to phenytoin (approximately 0.5 to 1 hour post-infusion).

Fosphenytoin is highly bound (93–98%) to plasma proteins. Saturable binding at higher plasma concentrations accounts for an increase in its distribution volume and clearance with increasing dose and infusion rate.

Earlier and higher unbound phenytoin plasma concentrations, and thus an increase in systemic adverse effects, may occur following intravenous fosphenytoin loading doses in patients with a decreased ability to bind fosphenytoin and phenytoin (renal or hepatic disease, hypoalbuminaemia, the elderly). Close monitoring and reduction in the infusion rate by 25–50% are recommended when intravenous loading doses of fosphenytoin are administered in these patients. The potential exists for drug-drug interactions when fosphenytoin is coadministered with other highly protein bound drugs.

Metabolism and Elimination: Phenytoin derived from administration of Cerebyx is extensively metabolized in the liver and excreted in urine primarily as 5-(p-hydroxyphenyl)-5-phenylhydantoin and its glucuronide; little unchanged phenytoin (1%–5% of the Cerebyx dose) is recovered in urine. Phenytoin hepatic metabolism is saturable, and following administration of single IV Cerebyx doses of 400 to 1200 mg PEsPE, total and unbound phenytoin AUC values increase disproportionately with dose. Mean total phenytoin half-life values (12.0 to 28.9 hr) following Cerebyx administration at these doses are similar to those after equal doses of parenteral Dilantin and tend to be greater at higher plasma phenytoin concentrations.

3. Summary of Fosphenytoin Pharmacokinetics in Children Provided by Pfizer (March 2009)

- Fosphenytoin (FPHT) pharmacokinetics in pediatric patients are generally consistent with those reported in adults
- In most cases, FPHT is readily converted to phenytoin (PHT) across ages ranging from premature neonates to adolescents. However, there are isolated instances of difficulty in achieving adequate PHT concentrations from FPHT, especially in infants and young children.
- Unexpected variability has been reported in PHT concentrations after FPHT.

- Pediatric malaria patients exhibit pharmacokinetic characteristics generally similar to those reported for pediatric patients without malaria except for FPHT lower bioavailability.

A review of metabolic factors which may contribute to FPHT and free PHT variability include the followings:

- Phosphatase mediated FPHT conversion to PHT. Phosphatase is present abundantly in the very young and not subject to inhibition. It should thus not be rate limiting in PHT production. Nonetheless, literature reports instances of failure to achieve adequate PHT levels after FPHT administration in young children.
- Metabolism of PHT by CYP2C9 and 2C19. CYP2C enzymes increase rapidly after birth, and may explain some variability in total and free PHT.
- Variability in concentration of the PHT binding proteins and/or competition for PHT and FPHT for binding sites. Albumin, the principal PHT binding protein, is reduced in the very young, has common binding sites for which FPHT and PHT compete, and thus may contribute to variations observed in free PHT.
- Additional variables affecting FPHT uptake after IM injection potentially influence PHT levels in the very young due to immature muscular and vascular anatomy.

3. Summary of NDA 20-450/SE5-003 Review

October 21, 1999 Memo

This supplement was submitted in fulfillment of a Phase 4 commitment made at the time of approval of the original NDA for fosphenytoin.

In this submission, the sponsor reported a study of i.v. and i.m. dosing of fosphenytoin (Study 982-28) in pediatric patients, including neonates (Birth-1 mon.), infants (1 mon.-2 yrs), children (2 -12 yrs) and adolescents (12-16 yrs). The sponsor was seeking approval for the use of fosphenytoin in pediatric population by comparing the conversion rate of fosphenytoin to phenytoin in pediatric patients to that of adults receiving similar dosing regimen (study 982- 16).

STUDY 982-28

113 pediatric patients were treated with fosphenytoin in an open, uncontrolled study, designed to accrue PK and safety data. A total of 91/113 (81%) were treated with IV drug; the rest were treated with IM fosphenytoin. About 2/3 of the IV treated patients (63/91) received maintenance therapy, whereas (6/24) of the IM patients received maintenance.

The approval of fosphenytoin in adults was based on showing that a dosing regimen of fosphenytoin could be determined that produced free phenytoin levels (the presumed active anti-seizure moiety) comparable to those produced when IV phenytoin was administered according to the approved phenytoin regimen. Given this, it would seem reasonable to base the approval of fosphenytoin in pediatric patients on the identification

of a dosing regimen in this population that produced free phenytoin levels comparable to those produced when IV phenytoin is given according to the approved dosing regimen for this population (IV phenytoin is approved, with accompanying dosing recommendations, for use in pediatric patients). [Comment: This could potentially be achieved via cross-study comparisons: IV phenytoin in pediatric patients vs. IV fosphenytoin in pediatric patients. However, our search in the FDA databases, DARRTS and published literature did not find any reliable PK data of IV phenytoin in pediatric patients.](#)

The sponsor has not empirically identified a dosing regimen that will reliably produce appropriate free phenytoin levels in pediatric patients.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW OF STUDY 982-28 (Oct 15, 1999)

Thus, the best way to address the approvability, in this reviewer's opinion, would be to compare free phenytoin (FPHT) level after fosphenytoin (FOS) administration in pediatric patients to that observed after administration of an equivalent dose of Dilantin in pediatric patients (phenytoin; the same approach as used in the original FOS NDA for adult use). However, in this submission, the sponsor compared the conversion half-life of FOS to phenytoin (PHT) in pediatrics to that of adults. Due to the limitation of study design, complex nature of the drug, and many unknown aspects of developmental changes in pediatric patients, FOS and PHT kinetics in pediatric populations can not be adequately assessed, and thus can not be properly compared to that in adults. Although the sponsor has demonstrated comparable range of conversion half-life of fosphenytoin to phenytoin in pediatric populations as that in adults, they have not provided adequate information to demonstrate comparable free PHT levels after FOS administration to those observed after an equivalent dose of Dilantin administration in pediatric populations. The sponsor is encouraged to conduct a thorough study to evaluate phenytoin kinetics at different developmental stage, by which the dosing regimen recommendation in each age group can be provided.

4. Summary of Published Literature

A search of the published literature related to fosphenytoin use in the pediatric population was performed by the reviewer and is summarized below.

Committee on Drugs: Drugs for Pediatric Emergencies¹

TABLE 1. Frequently Used Emergency Drugs

Adenosine	Diazoxide	Glucose	Meperidine	Phenylephrine
Albuterol	Digibind	Haloperidol	Methylprednisolone	Phenytoin
Atropine	Diphenhydramine	Insulin	Midazolam	Procainamide
Bicarbonate	Dopamine	Ipecac	Morphine sulfate	Propranolol
Calcium chloride	Dobutamine	Kayexalate	Naloxone	Prostaglandin E
Calcium gluconate	Epinephrine	Ketamine	Nitroprusside	Rocuronium
Charcoal	Fentanyl	Lidocaine	Oxygen	Succinylcholine
Dexamethasone	Fosphenytoin	Lorazepam	Pancuronium	Thiopental
Diazepam	Glucagon	Mannitol	Phenobarbital	Vecuronium

Fosphenytoin

Indication: Status epilepticus (same as phenytoin)

Dosage: ALWAYS IN PHENYTOIN EQUIVALENTS (PE) 10 to 20 mg PE/kg (same as phenytoin)

Route of administration: IM or IV: 1 to 3 mg PE/kg/min; maximum rate 150 mg PE/min

Note: Data are currently being collected on children less than 6 years of age.

WARNING: Rate of infusion should not exceed 3mg PE/kg/min. Heart rate should be monitored and the rate of infusion reduced if the heart rate decreases by 10 beats/minute (same as phenytoin).

Preparing for Pediatric Emergencies: Drugs to Consider²

Fosphenytoin

Indication: Status epilepticus

Dosage: Given in phenytoin equivalents (PE).

IV: 15–20 PE/kg, infused at a rate of 1–3 PE/kg per min (maximum rate: 150 PE per min).

IM: 15–20 PE/kg.

Notes: When given IV, itching is common and controllable by reducing the flow rate.

Lower risk of hypotension or cardiac effects than phenytoin.

Warning: Rate of infusion should not exceed 3 PE/kg per min. Monitor heart rate via ECG, and reduce the rate of infusion if heart rate decreases by 10 beats per min.

Expert Opin. Drug Metab. Toxicol. (2009)³

Clinical effectiveness, safety and tolerability of fosphenytoin in pediatric patients:

No significant differences in clinical efficacy have been demonstrated in patients from 5 to 18 years compared with adults aged 40 or less. There is limited experience in the administration of fosphenytoin to newborns and infants and concern has been raised regarding the conversion of the pro-drug to phenytoin. There are case reports in which difficulties in maintaining therapeutic serum phenytoin levels with i.v. fosphenytoin have been described despite increased doses^{3a}. Takeoka et al. (J Child Neurol 1998; 13:537-540).

In comparison with phenytoin preparations, which have a pH value of 11, fosphenytoin, a phosphorylated prodrug of phenytoin, has a pH value of only 8.6, which decreases the risk of cardiovascular and cutaneous side effects. The near-neutral pH value of fosphenytoin allows effective intravenous or intramuscular administration. A 1-mg phenytoin equivalent (PE) of fosphenytoin is converted to 1 mg of phenytoin in adults. We describe four infants whose seizures were treated with intravenous fosphenytoin. We had difficulty maintaining therapeutic serum phenytoin levels of 10 to 20 µg/mL on doses of 5 to 8 mgPE/kg/day, and many bolus doses of 5 to 10 mgPE/kg or maintenance doses of more than 10 mgPE/kg/day were given. Despite increased doses in three out of the four patients, a therapeutic serum phenytoin level was not maintained. From our experience, careful and individual dosing of fosphenytoin in this age group can be considered.

In another **case report**⁴, however, in two low-birth-weight infants, it was observed that fosphenytoin was converted adequately with varying effects on seizure control.

Ogutu, et al.⁵ have published the results from a study comparing the pharmacokinetics of phenytoin with fosphenytoin in children with severe malaria and status epilepticus. Children in the study were aged between 6 months and 13 years. Eleven children received i.v. phenytoin, sixteen children received i.v. fosphenytoin, and eleven children i.m. fosphenytoin.

Phenytoin (Faulding Pharmaceuticals plc., UK) was diluted with normal saline to a final concentration of 8 mg/ml and a loading dose of 18 mg/kg was infused over 20 min. A maintenance dose of 2.5 mg/kg infused over 5 min was administered 12 hourly for 48 h. Fosphenytoin sodium (Pro-Epanutin®; Parke-Davis, Eastleigh, UK) was also diluted with normal saline to a final concentration of 12.5 mg/ml before i.v. administration at a rate of 50 mg/min at the same dose expressed as phenytoin equivalents (PE).

Fosphenytoin sodium was administered undiluted i.m. as an injection into the anterior aspect of the thigh and the area was rubbed for 30 s. A loading dose of 18 mg/kg PE was used followed by a 12 hourly maintenance dose of 2.5 mg/kg PE.

After all routes of administration, plasma unbound phenytoin concentration of > 1 mg/ml was rapidly (in 5 – 20 min) attained. Mean (95% CI) steady-state free phenytoin concentrations were 2.1 (1.7, 2.4) for i.v. phenytoin, 1.5 (0.96, 2.1) for i.v. fosphenytoin and 1.4 (0.5, 2.4) for i.m. fosphenytoin and these were not statistically different. Median times (range) to peak plasma phenytoin concentrations following the loading dose were 0.08 (0.08 – 0.17), 0.37 (0.33 – 0.67) and 0.38 (0.17 – 2.0) h for i.v. fosphenytoin, i.v. phenytoin and i.m. fosphenytoin, respectively.

Unbound phenytoin concentrations within the therapeutic range (1–2 mg/ml) were achieved within 5–20 min after all the three routes of administration. Mean steady state unbound concentrations were maintained within this range for 48 h. Maximum plasma phenytoin concentrations were achieved most rapidly with i.v. fosphenytoin. There was no statistically significant difference in mean AUC(0,72 h) for total and unbound phenytoin between i.v. phenytoin and i.m. fosphenytoin. However, mean AUC(0,72 h) for phenytoin following i.v. fosphenytoin administration was significantly smaller compared with i.v. phenytoin.

CSF plasma phenytoin concentration ratio ranged from 0.12 to 0.53 (median = 0.28, n = 16). SE was controlled in 36% (4/11) of children following i.v. phenytoin, 44% (7/16) following i.v. fosphenytoin and 64% (7/11) following i.m. fosphenytoin administration. Cardiovascular parameters were not affected.

Pediatric Use of Intravenous and Intramuscular Phenytoin: Lessons Learned⁶

Intravenous administration of phenytoin caused burning at the infusion site and was associated with severe local cutaneous reactions following infiltration into surrounding tissue, leading to a recommendation that intravenous phenytoin be avoided in young children and the elderly. The propylene glycol solvent was linked to seizures, arrhythmia, asystole, and hepatic and renal damage. When administered intramuscularly, phenytoin is poorly absorbed and can cause hemorrhagic necrosis of the soft tissues at the injection site. Many of these side effects can be avoided in children with the use of fosphenytoin.

Treatment of Pediatric Epilepsy: Expert Opinion, 2005⁷

As initial therapy for neonatal status epilepticus, intravenous phenobarbital was treatment of choice, with intravenous lorazepam or fosphenytoin also first line.

As initial therapy for all types of pediatric status epilepticus, lorazepam was treatment of choice, with intravenous diazepam also first line.

For generalized tonic-clonic status epilepticus, rectal diazepam and fosphenytoin were also first line; for complex partial status epilepticus, fosphenytoin was also first line; and for absence status epilepticus, intravenous valproate was also first line.

Pellock, JM: Fosphenytoin use in children⁸

Fosphenytoin, a new phenytoin prodrug, can be safely administered through the IM route, and, because of the physical characteristics of its formulation, it offers advantages over phenytoin for IV administration. Clinical studies with IV and IM fosphenytoin demonstrate that the efficacy, safety, and pharmacokinetics of this drug are similar in 5- to 18-year-old children and in young adults. The safety and pharmacokinetic profile of IV and IM fosphenytoin in younger children and infants is currently being investigated.

5. Clinical Pharmacology Recommendations

On 12/18/98, the sponsor (Parke-Davis Pharmaceutical Research) submitted SE5-003 to NDA 20-450 for the use of fosphenytoin in pediatric patients. This supplement was submitted in fulfillment of a Phase 4 commitment made at the time of approval of the original NDA for fosphenytoin. In the Approval letter for the original NDA, dated 8/5/96, the sponsor committed to conduct a pharmacokinetic and safety study in appropriate pediatric populations. However, the letter did not describe the specific type of information deemed necessary to permit approval in children.

After reviewing the raw data of study 982-28 and the published literature, we conclude that the sponsor fulfilled the Phase 4 commitment. However, the provided information is insufficient to support inclusion of pediatric dosing information in the Cerebyx package insert.

The results from study 982-28 (pediatric patients) and study 982- 16 (adults) suggest that the conversion rate of fosphenytoin to phenytoin in pediatric patients is similar to that of adults receiving similar dosing regimen. However, comparison of free phenytoin plasma concentrations from study 982-28 (pediatric patients) and study 982- 16 (adults) is not appropriate since free phenytoin plasma concentrations after IV phenytoin administration in children are much more variable than free phenytoin plasma concentrations after IV phenytoin administration in adults and it is reasonable to assume that this will also apply to IV fosphenytoin administration as well. Therefore, the PK of IV phenytoin should be compared to IV fosphenytoin when both are administered to pediatric patients.

The results from the only published study comparing the pharmacokinetics of phenytoin with fosphenytoin in children⁵ should be interpreted with caution as the study was done in pediatric patients with severe malaria. In addition, the low number of pediatric patients does not allow any age-based comparisons.

Since fosphenytoin has been used for many years off-label in pediatric patients as initial therapy for pediatric status epilepticus (first line therapy⁷), efforts were made to include pediatric dosing information in the Cerebyx label based on cross-studies comparisons (IV phenytoin in pediatric patients vs. IV fosphenytoin in pediatric patients). However, our

search in the FDA databases, DARRTS and published literature did not find any PK data in pediatric patients treated with IV phenytoin.

Therefore, we recommend a new post marketing required (PMR) study to determine the PK of total and free phenytoin when IV phenytoin is administered in pediatric patients. The ultimate goal is to compare the PK and safety of IV fosphenytoin administration to IV phenytoin in pediatric populations. This will be done via cross-trial comparison with results from Study 982-28. Based on the results, a dosing regimen of fosphenytoin will be determined for pediatric patients. This dose will produce comparable free phenytoin levels to those who received IV phenytoin using the approved phenytoin regimen in pediatric patients.

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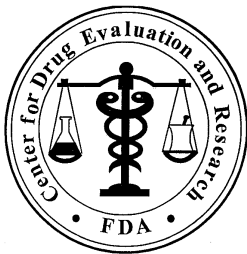
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/s/

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: October 4, 2010

To: Russell Katz, MD
Director
Division of Neurology Products
Office of New Drugs

Through: Laura Governale, Pharm.D., MBA
Drug Use Data Analyst Team Leader
Division of Epidemiology
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From: Grace Chai, Pharm.D.
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Office of Surveillance and Epidemiology

Subject: IV Phenytoin and Fosphenytoin Utilization Review

Drug Name(s): IV Phenytoin and Cerebyx®, Fosphenytoin

Application Type/Number: ANDA 40-573, 40-781, 84-307, 89-521, 89-744 and NDA 10-151;
and NDA 20-450, ANDA 76-866, 77-481, 77-989, 78-052, 78-126,
78-137, 78-158, 78-277, 78-417, 78-476, 78-765

Applicant/sponsor: Parke Davis, others

OSE RCM #: 2010-571

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EXECUTIVE SUMMARY

Sales and utilization data for IV phenytoin and fosphenytoin from years 2004 to 2009 were analyzed to assess the extent of use as well as differential use of these products in light of recent safety findings.

Sales data summary

- Sales of IV phenytoin decreased from 72% of the total IV phenytoin/fosphenytoin market (~5.3 million vials) to 56.5% (~3.0 million vials) while fosphenytoin sales increased from 28% (~2.1 million vials) to 43.5% of the total IV phenytoin/fosphenytoin market (~2.3 million vials) from year 2004 to 2009.
- The Average Price per Vial (EAAP) sold to non-retail settings of care was \$29.49 for fosphenytoin and \$1.92 for IV phenytoin in year 2004. However, with the approval of generic fosphenytoin in year 2007, the EAAP for fosphenytoin decreased to \$2.59 compared to IV phenytoin at \$1.31 in year 2009.
- In year 2009, the majority of fosphenytoin was sold by Hospira while the majority of phenytoin was sold by Westward. Eisai accounted for approximately 2.5% of the fosphenytoin market.

Inpatient hospital data summary

- Among IV medication billed on inpatient discharge records with the primary ICD-9 diagnosis code of “status epilepticus”, fosphenytoin increased to become the second most commonly billed IV medication in year 2009. IV lorazepam was the medication most commonly billed on discharge records with the ICD-9 code for “status epilepticus” from years 2004 to 2009.
- From year 2004 to year 2009, IV phenytoin use decreased while fosphenytoin use increased to account for the overall majority of use since year 2008, particularly in patients aged 17-64 years and 65+ years. However, fosphenytoin has consistently accounted for the majority of use in the pediatric population (72-85% of total use in patients aged 0-16 years) during years 2004 to 2009.
- The majority of use of both products was in patients aged 17-64 years (57% of fosphenytoin and 60% of IV phenytoin in year 2009). The pediatric population accounted for approximately 7% of fosphenytoin use and 2% of IV phenytoin use in year 2009.
- Within the inpatient hospital setting, the majority of IV phenytoin and fosphenytoin utilization was in the ICU and MED/SURG units.

1 INTRODUCTION

The Division of Neurology Products (DNP) is reviewing the use of fosphenytoin and IV phenytoin to determine the extent of use as well as differential use of these products in light of recent safety findings. IV phenytoin is thought to be associated with a higher risk of purple glove syndrome than fosphenytoin. In support of this review, the Division of Epidemiology has been requested to provide utilization data for IV phenytoin and fosphenytoin products by patient age from years 2004 to 2009.

2 BACKGROUND

IV phenytoin, marketed as Dilantin® Injection 50 mg/mL was approved year 1956. Generic IV phenytoin was approved in year 1975. Fosphenytoin, marketed as Cerebyx®, was approved in year 1996. The generic version of fosphenytoin appeared on the market in year 2007. The branded products, Dilantin and Cerebyx® are both manufactured by Parke Davis (now Pfizer); however, Parke Davis ceased marketing Dilantin Injection in year 1996. Only generic products of IV phenytoin remain on the market.

3 METHODS AND MATERIAL

3.1 DETERMINING SETTINGS OF CARE

IMS Health, IMS National Sales Perspectives™ data (see *Appendix 2* for full database description) was used to determine the primary setting(s) of utilization for IV phenytoin and fosphenytoin. During year 2009, the sales of these products by number of Eaches (bottles, vials, and packets) sold from the manufacturer into the various retail and non-retail channels of distribution revealed that non-retail settings accounted for approximately 99% of both products, with the majority sold to non-federal hospital settings (*Appendix 1: Table 1*). Thus, non-federal hospital inpatient discharge data was assessed to provide utilization patterns for IV phenytoin and fosphenytoin.

3.2 DATA SOURCES USED (SEE APPENDIX 2 FOR FULL DATABASE DESCRIPTION)

Proprietary drug utilization databases licensed by the Agency were used to conduct this analysis. The estimated number of vials (Eaches) distributed to wholesale distribution channels and the estimated cost per vial for IV phenytoin and fosphenytoin were obtained using the IMS Health, IMS National Sales Perspectives™ for years 2004 through 2009. In addition, we obtained sales data of both products by manufacturer for year 2009.

Inpatient hospital utilization data were obtained from the Premier RxMarket Advisor™ database from year 2004 to 2009. From this database, we obtained the number of inpatient discharges and unique patients by patient age (stratified by year 0-16, 17-64, and 65+ years). Analyses were conducted in the pediatric population by patient age in months and years (stratified by 0-1 month, 1-6 months, 6-24 months, 3-12 years, and 13-16 years) to further characterize pediatric use. Inpatient data was also analyzed by the location of the inpatient service where IV phenytoin and/or fosphenytoin were billed as well as the hospital characteristics of hospitals reporting use of either product. In addition, we obtained the number of discharges for drugs associated with the diagnosis code of “status epilepticus” ICD-9 code 345.3 from years 2004 through 2009.

4 RESULTS

4.1 SALES OF IV PHENYTOIN AND FOSPHENYTOIN

4.1.1 Sales distribution data by eaches and cost

Table 1 and Figure 1 in Appendix 1 show the total sales in vials (Eaches) of IV phenytoin and fosphenytoin from the manufacturer into the three major channels of distribution: retail, non-retail and mail-order. The average price of vials is also presented in this table. The sale of injectable forms of phenytoin decreased from 72% of the market share (~5.3 million vials) in year 2004 to 57% of the market share (~3 million vials) in year 2009. Fosphenytoin sales increased from 28% of the market share (~2.1 million vials) in year 2004 to 43.5% of the market share (~2.3 million vials) in year 2009.

Data on the average price per vial for year 2004 showed a large difference in cost between the two products. In year 2004, the average price per vial for IV phenytoin sold to non-retail settings of care was \$1.92 compared to fosphenytoin at \$29.49. However, with the approval of generic fosphenytoin in year 2007, the average price per vial for fosphenytoin purchased by these facilities fell to \$2.59 compared to IV phenytoin at \$1.31 in year 2009.

4.1.2 Sales distribution data by manufacturer

Figures 2 and 3 in Appendix 1 show the proportion of sales of IV phenytoin and fosphenytoin by manufacturer for year 2009. The majority of IV phenytoin was sold by Westward (~57% of the IV phenytoin market), followed by Baxter Pharmaceuticals (~26%) and Hospira (~17%) in year 2009. The majority of IV fosphenytoin was sold by Hospira (~78% of the fosphenytoin market), followed by Teva Parenteral (~14%) in year 2009. The vast majority of both IV phenytoin and fosphenytoin were sold as generics. Brand fosphenytoin, Cerebyx® sold by Eisai, Inc., decreased in sales from approximately 2.1 million vials (Eaches) sold in year 2005 down to 58,000 vials (Eaches) sold in year 2009, accounting for about 2.5% of the fosphenytoin market (data not shown).¹ Brand IV phenytoin, Dilantin®, is no longer manufactured.

4.2 INPATIENT HOSPITAL DISCHARGE DATA

4.2.1 IV Medications associated with ICD-9 code 345.3 for “Status Epilepticus”

Figure 4 in Appendix 1 shows the projected number of discharges for IV medications commonly associated with a hospital billing for “Status Epilepticus,” (ICD-9 code 345.3) for years 2004 to 2009. IV lorazepam was the most common IV medication billed on inpatient discharge records with the primary ICD-9 diagnosis code of “status epilepticus”, accounting for about 22,900 discharges among the selected IV medications in year 2009. The number of discharges billed for fosphenytoin with the diagnosis of “status epilepticus” increased over IV phenytoin from years 2007 to 2009 to become the second most commonly billed medication with this diagnosis code; in year 2009, discharges with the diagnosis of “status epilepticus” and fosphenytoin accounted for approximately ~13,800 discharges compared to 8,200 discharges for IV phenytoin.

4.2.2 Inpatient discharges and unique patients for IV phenytoin and fosphenytoin by patient age

Table 2 and 3, and Figure 5 in Appendix 1 shows the projected number of discharges and unique patients with a hospital billing for fosphenytoin and IV phenytoin from years 2004 to 2009. Over the study period, fosphenytoin use increased from approximately 42% (~197,000 discharges) to approximately 59% (~210,000 discharges) of the market share, while IV phenytoin use decreased from 58% (~275,000 discharges) to approximately 41% (~149,000 discharges) of the market share (*Table 2*). Trends in the projected number of unique patients reflected trends in discharges with nearly a 1-to-1 relationship between discharges and patients (*Table 3*).

Table 4 in Appendix 1 shows the actual (unprojected) number of inpatient discharges within the Premier network of hospitals with a billing for fosphenytoin and IV phenytoin by patient age from years 2004 to 2009. Among these products, patients aged 17-64 years accounted for the majority of discharges for both products (~57% of fosphenytoin and ~60% of IV phenytoin in year 2009), followed by patients aged 65 years of age and older (~37% of fosphenytoin and ~40% of IV phenytoin in year 2009).

¹ Source: IMS Health, IMS National Sales Perspectives™, Years 2004-2009, Extracted 05-10. File: 1005phen.xls

Use of fosphenytoin accounted for the majority of use in the pediatric population aged 0-16 years throughout the examined time of years 2004 to 2009. Pediatric patients aged 16 years and younger accounted for approximately 7% of fosphenytoin use and 2% of IV phenytoin use in year 2009. Of the pediatric population, the majority of discharges on fosphenytoin and IV phenytoin were for patients aged 3-12 years old, accounting for approximately 36% of pediatric fosphenytoin discharges and 30% of IV pediatric IV phenytoin discharges in year 2009. Patients aged 0-1 month accounted for about 6% of pediatric fosphenytoin discharges and 15% of IV phenytoin discharges in year 2009. Patients aged 1 month to 2 years accounted for about 28% of pediatric fosphenytoin discharges and 19% of pediatric IV phenytoin discharges in year 2009.

Figure 6 in Appendix 1 shows the trends of fosphenytoin and IV phenytoin use by patient ages from years 2004 to 2009. The majority of use shifted from IV phenytoin to fosphenytoin in patient age groups 17-64 years and 65+ years in year 2008 and 2009. However, fosphenytoin has consistently accounted for the majority of use in the pediatric population from year 2004 to 2009. Within the pediatric population (ages 0-16 years), there were 3-6 times more fosphenytoin use over IV phenytoin use over the entire study period.







5 DISCUSSION

Findings from this consult should be interpreted in the context of the known limitations of the databases used. We estimated that fosphenytoin and IV phenytoin is distributed primarily in non-federal inpatient hospital settings based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use. This analysis is limited to inpatient discharge data and does not capture ER, ambulance, or clinic data.

Analysis of sales and inpatient utilization data showed a decrease in IV phenytoin use and an increase in fosphenytoin use during the examined time. Analysis of the sales data also showed that the difference in cost between fosphenytoin and IV phenytoin dramatically narrowed following the approval of generic fosphenytoin in year 2007. This change in cost may have contributed to the shift to majority fosphenytoin utilization.

In the inpatient setting, IV lorazepam was the medication most commonly billed on discharges with the primary diagnosis of “status epilepticus” (ICD-9 code 345.3) during the examined time. Although IV benzodiazepines are considered first-line treatment for status epilepticus, consideration needs to be given for IV phenytoin loading that is often needed after the administration of a first-line medication in treatment facilities with no access to refrigeration.²

Fosphenytoin use increased to account for the majority of inpatient use in year 2008, primarily in patients 17 years and older. However, a correlation cannot be made regarding the *switching* of IV phenytoin use versus fosphenytoin use with these data at this time. Fosphenytoin has consistently accounted for the majority of use between the two products in the pediatric population (0-16 years), including the infant population, throughout the examined time.



² Rossetti, Andrea. Treatment Options in the Management of Status Epilepticus. *Current Treatment Options in Neurology*. 2010. 12:100-112.

Pediatric Limitations

Pediatric utilization (ages 0-1 month, 1-6 months, 6 months-2 years, 3-12 years, and 13-16 years) for fosphenytoin and IV phenytoin were provided as raw counts (unprojected patients/discharges) using hospitals from the Premier Hospital network and a subset of Premier's 37 pediatric hospitals. We are not able to make a reliable national estimate of inpatient drug use for pediatric patients with Premier data at this time. Although Premier Network hospitals appear representative of all U.S. acute short stay hospitals in general, it is not clear whether they are representative of pediatric inpatient care in the U.S. Any observed changes in raw counts do not necessarily represent national trends and should be interpreted with caution. Furthermore, these data are derived from hospital discharge billing data that do not have direct linkages between the drugs billed and the discharge diagnosis and procedure; therefore, indications for use cannot be directly correlated to the ICD-9 codes and the drugs billed during the hospital stay.

6 CONCLUSIONS

Preliminary analysis of inpatient use shows that there was a decrease in utilization from majority IV phenytoin use to majority fosphenytoin use in adult patients age 17 years and older. Although fosphenytoin use increased and IV phenytoin use decreased, in general, there has consistently been greater use of fosphenytoin over IV phenytoin use in the pediatric population during the examined time. Over the study period, the cost difference between IV phenytoin and fosphenytoin narrowed following the approval of generic fosphenytoin in year 2007, likely impacting use trends. [REDACTED]

The overall findings of this review illustrate a trend towards greater fosphenytoin use over IV phenytoin use. [REDACTED]

[REDACTED] Consideration needs to be given for the use of IV phenytoin in settings outside of the inpatient setting that may not have access to refrigeration and where phenytoin loading is warranted, and other niche uses. Although the impact of drug shortages of fosphenytoin was not included in this analysis, continued analysis of sales and use trends is recommended.

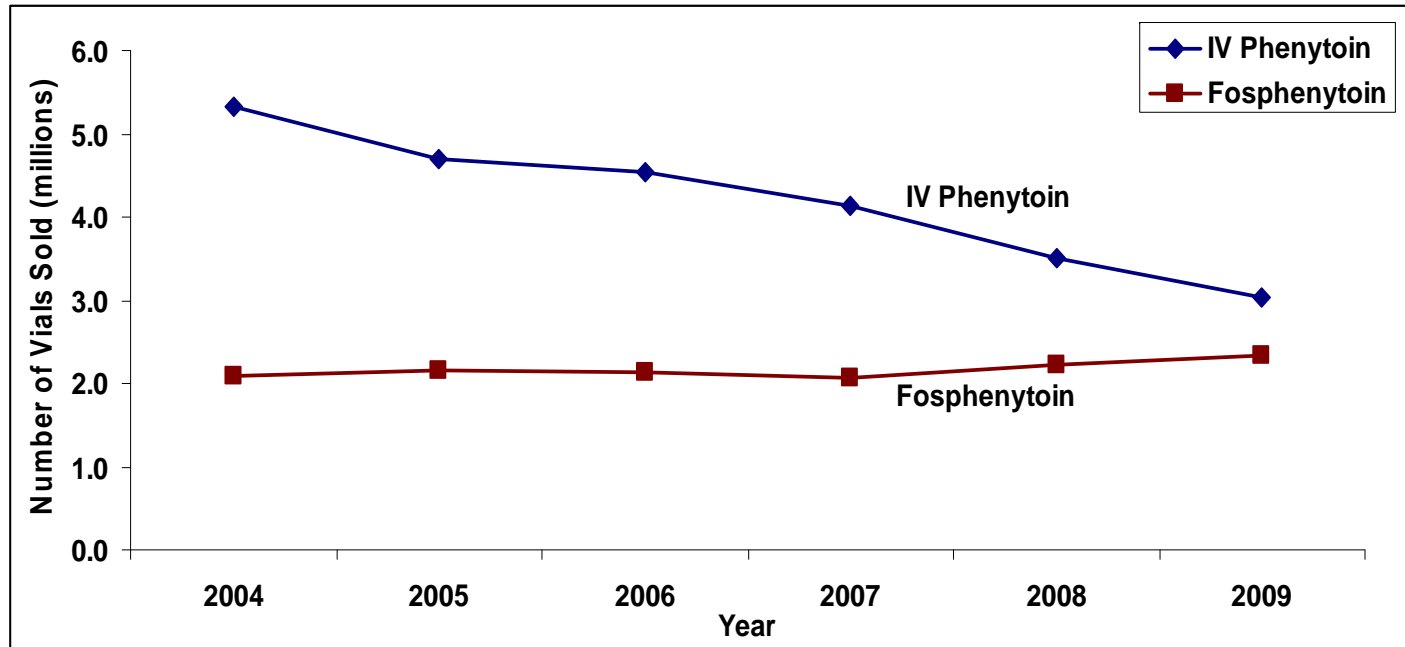
APPENDIX 1: TABLES AND FIGURES

Table 1: Sales and Average Price of Vials (Eaches) by Setting for Fosphenytoin and IV Phenytoin, Years 2004 – 2009

	Year 2004			Year 2005			Year 2006			Year 2007			Year 2008			Year 2009		
	Vials (N)000	Share %	Average Price/Vial (Dollars)	Vials (N)000	Share %	Average Price/Vial (Dollars)	Vials (N)000	Share %	Average Price/Vial (Dollars)	Vials (N)000	Share %	Average Price/Vial (Dollars)	Vials (N)000	Share %	Average Price/Vial (Dollars)	Vials (N)000	Share %	Average Price/Vial (Dollars)
TOTAL	7417.4	100%	--	6842.3	100%	--	6679.4	100%	--	6190.6	100%	--	5724.5	100%	--	5374.1	100%	--
FOSPHENYTOIN	2080.4	28.0%	\$29.49	2148.4	31.4%	\$31.45	2133.7	31.9%	\$33.45	2065.3	33.4%	\$25.07	2213.5	38.7%	\$4.05	2335.5	43.5%	\$2.61
NON-RETAIL	2071.1	100%	\$29.49	2142	100%	\$31.45	2128.2	100%	\$33.45	2060.3	100%	\$25.04	2206.3	100%	\$4.00	2330.8	100%	\$2.59
MAIL SERVICE	1.4	0.1%	\$23.61	0.1	0%	\$58.30	0.5	0%	\$46.32	0.1	0%	\$27.48	0.1	0%	\$35.29	0	0%	\$4.40
RETAIL	7.9	0.4%	\$28.50	6.3	0.3%	\$29.80	5.1	0.2%	\$31.60	5	0.2%	\$35.66	7	0.3%	\$19.15	4.7	0.2%	\$14.53
IV PHENYTOIN	5337	72.0%	\$1.92	4693.9	68.6%	\$1.88	4545.7	68.1%	\$1.74	4125.3	66.6%	\$1.58	3511	61.3%	\$1.56	3038.6	56.5%	\$1.31
NON-RETAIL	5301.7	99%	\$1.92	4630	99%	\$1.89	4503.8	99%	\$1.74	4099.4	99%	\$1.57	3473.6	99%	\$1.56	2988.8	98%	\$1.31
MAIL SERVICE	1.5	0%	\$2.55	1.1	0%	\$2.37	1.2	0%	\$2.28	2.5	0.1%	\$1.86	1.2	0%	\$1.86	1.8	0.1%	\$2.61
RETAIL	33.9	0.6%	\$2.16	62.8	1.3%	\$1.52	40.7	0.9%	\$1.43	23.3	0.6%	\$1.89	36.2	1%	\$1.67	48	1.6%	\$1.39

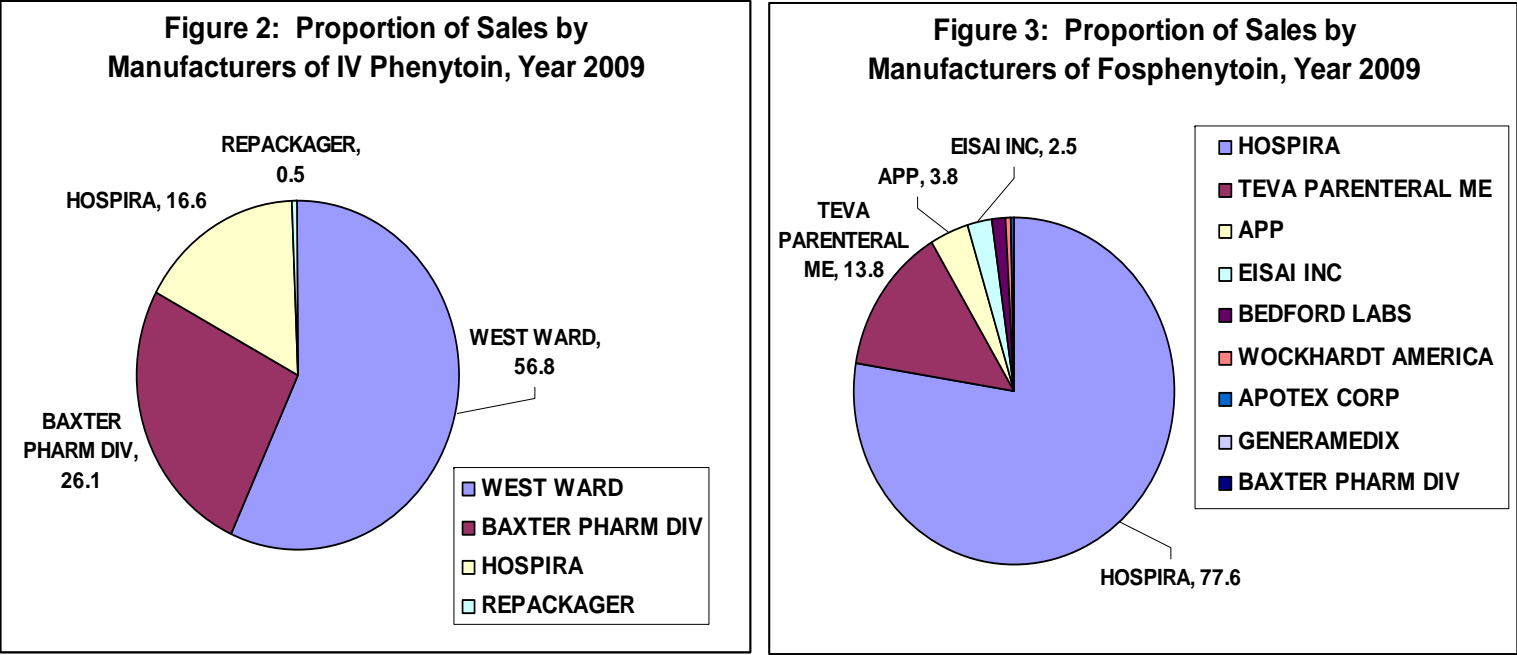
Source: IMS Health, IMS National Sales Perspectives™, Years 2004-2009, Extracted 12-09 and 04-10. Files: 0912fosp.xls and 1004fosp.xls

Figure 1: Number of Vials Sold of Fosphenytoin and IV Phenytoin, Years 2004 – 2009



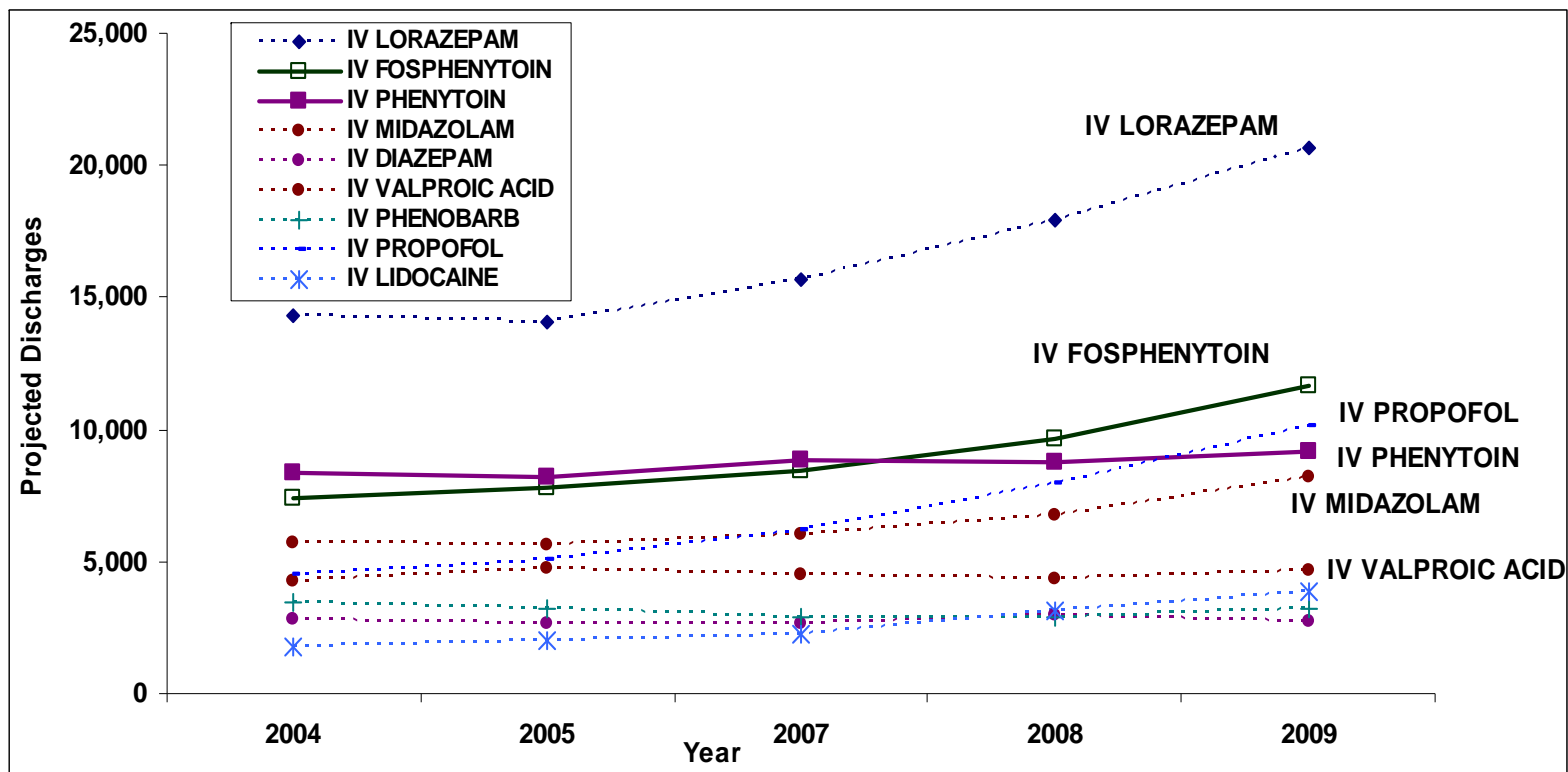
Source: IMS Health, IMS National Sales Perspectives™, Years 2004-2009, Extracted 12-09 and 04-10. Files: 0912fosp.xls and 1004fosp.xls

Figure 2 and 3: Proportion of Sales of Vials (Eaches) by Manufacturer for Fosphenytoin and IV Phenytoin, Year 2009



Source: IMS Health, IMS National Sales Perspectives™, Year 2009, Extracted 09-10. File: 1009fosp.xls

Figure 4: Projected Number of Discharges for IV Medications Associated with a Hospital Billing for “Status Epilepticus” ICD-9 code 345.3, Years 2004-2009



Source: Premier Healthcare Informatics, RxMarket Advisor™, years 2002-2009. Data extracted 8-09. File: Premier 2010-571 icd9 345.3 drugs y2004-2009.xls

Table 2: Projected Number of Discharges with a Hospital Billing for Fosphenytoin and IV Phenytoin, Year 2004 to 2009

	2004		2005		2006		2007		2008		2009	
	Projected Discharges (N)	Share %	Projected Discharges (N)	Share %	Projected Discharges (N)	Share %	Projected Discharges (N)	Share %	Projected Discharges (N)	Share %	Projected Discharges (N)	Share %
Total	472,551	100%	469,361	100%	443,168	100%	405,599	100%	383,826	100%	358,839	100%
Fosphenytoin	197,754	41.8%	206,154	43.9%	202,017	45.6%	192,514	47.5%	202,285	52.7%	210,150	58.6%
IV Phenytoin	274,797	58.2%	263,207	56.1%	241,151	54.4%	213,086	52.5%	181,541	47.3%	148,688	41.4%

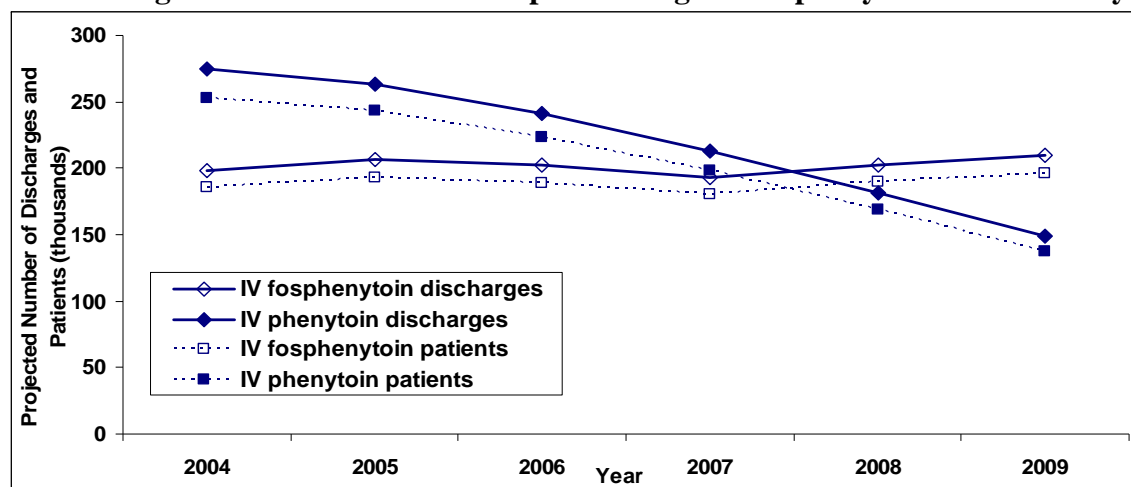
Source: Premier Healthcare Informatics, RxMarket Advisor™, years 2004-2009. Data extracted 3/2010. File: Premier 2007-1332 phenytoin and fos total discharges 2004-2009 mar2010.xls

Table 3: Projected Number of Unique Patients with a Hospital Billing for Fosphenytoin and IV Phenytoin, Year 2004 to 2009

	2004		2005		2006		2007		2008		2009	
	Projected Unique Patients (N)	Share %	Projected Unique Patients (N)	Share %	Projected Unique Patients (N)	Share %	Projected Unique Patients (N)	Share %	Projected Unique Patients (N)	Share %	Projected Unique Patients (N)	Share %
Total	438,591	100%	436,397	100%	411,628	100%	378,181	100%	358,359	100%	333,818	100%
Fosphenytoin	185,519	42.3%	193,170	44.3%	188,362	45.8%	180,234	47.7%	189,936	53.0%	196,249	58.8%
IV Phenytoin	253,072	57.7%	243,227	55.7%	223,265	54.2%	197,947	52.3%	168,423	47.0%	137,569	41.2%

Source: Premier Healthcare Informatics, RxMarket Advisor™, years 2004-2009. Data extracted 3/2010. File: Premier 2007-1332 phenytoin and fos total patients 2004-2009 mar2010.xls

Figure 5: Projected Number of Discharges and Patients with a Hospital Billing for Fosphenytoin and IV Phenytoin, Year 2004 to 2009



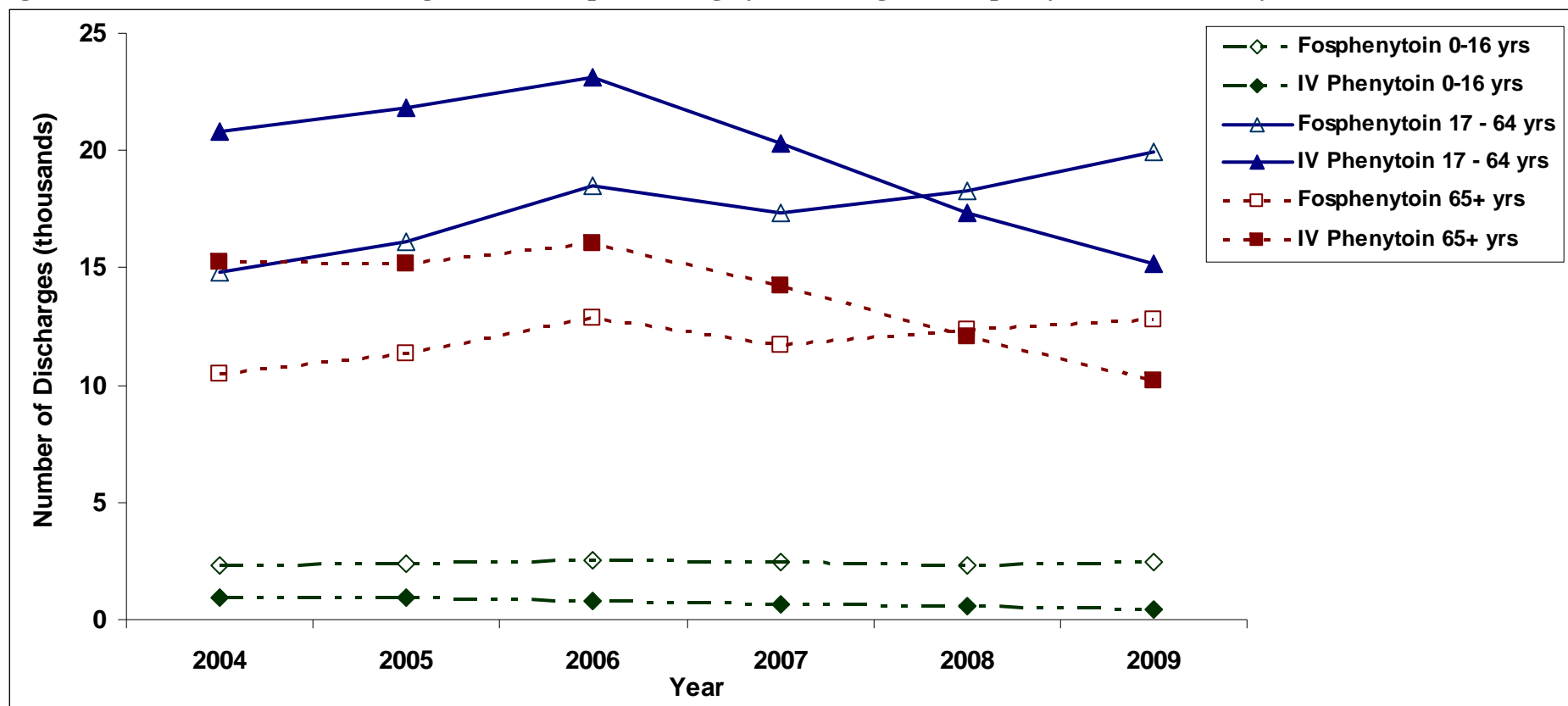
Source: Premier Healthcare Informatics, RxMarket Advisor™, years 2004-2009. Data extracted 3/2010. File: Premier 2007-1332 phenytoin and fos total discharges 2004-2009 mar2010.xls

Table 4: Actual Number of Discharges with a Hospital Billing for Fosphenytoin and IV Phenytoin by Patient Age, Year 2004 to 2009

	2004		2005		2006		2007		2008		2009	
Patient Age	Discharges (N)	Share %	Discharges (N)	Share %	Discharges (N)	Share %	Discharges (N)	Share %	Discharges (N)	Share %	Discharges (N)	Share %
Total	64,640	100%	67,796	100%	73,856	100%	66,598	100%	62,992	100%	61,025	100%
Fosphenytoin Total	27,637	42.8%	29,878	44.1%	33,878	45.9%	31,466	47.2%	32,970	52.3%	35,101	57.5%
0 - 16 years	2,346	8.5%	2,416	8.1%	2,557	7.5%	2,456	7.8%	2,333	7.1%	2,443	7.0%
0-1 month	267	11.4%	241	10.0%	179	7.0%	184	7.5%	172	7.4%	154	6.3%
1-6 months	252	10.7%	233	9.6%	216	8.4%	215	8.8%	242	10.4%	213	8.7%
6 months-2 years	366	15.6%	387	16.0%	402	15.7%	444	18.1%	464	19.9%	462	18.9%
3-12 years	862	36.7%	986	40.8%	1015	39.7%	879	35.8%	824	35.3%	888	36.3%
13-16 years	326	13.9%	351	14.5%	326	12.7%	336	13.7%	270	11.6%	287	11.7%
17 - 64 years	14,837	53.7%	16,117	53.9%	18,463	54.5%	17,312	55.0%	18,253	55.4%	19,969	56.9%
65+ years	10,454	37.8%	11,345	38.0%	12,858	38.0%	11,698	37.2%	12,384	37.6%	12,803	36.5%
IV Phenytoin Total	37,003	57.2%	37,918	55.9%	39,978	54.1%	35,132	52.8%	30,022	47.7%	25,526	41.8%
0 - 16 years	927	2.5%	932	2.5%	820	2.1%	645	1.8%	549	1.8%	438	1.7%
0-1 month	95	10.2%	124	13.3%	91	11.1%	86	13.3%	92	16.8%	66	15.1%
1-6 months	61	6.6%	75	8.0%	65	7.9%	40	6.2%	41	7.5%	24	5.5%
6 months-2 years	96	10.4%	94	10.1%	90	11.0%	77	11.9%	78	14.2%	59	13.5%
3-12 years	334	36.0%	293	31.4%	248	30.2%	201	31.2%	153	27.9%	129	29.5%
13-16 years	161	17.4%	174	18.7%	156	19.0%	111	17.2%	79	14.4%	74	16.9%
17 - 64 years	20,842	56.3%	21,792	57.5%	23,124	57.8%	20,278	57.7%	17,371	57.9%	15,208	59.6%
65+ years	15,234	41.2%	15,194	40.1%	16,034	40.1%	14,209	40.4%	12,102	40.3%	10,164	39.8%

Source: Premier Healthcare Informatics, RxMarket Advisor™, years 2004-2009. Data extracted 4-09. Files: CUSTOM iv phenytoin fosphenytoin by age.xlsx and Premier 2007-1332 phenytoin and fos discharges and pts 2004-2009 0-16, 17-64, 65+.xls

Figure 6: Actual Number of Discharges with a Hospital Billing by Patient Age for Fosphenytoin and IV Phenytoin, Years 2004-2009

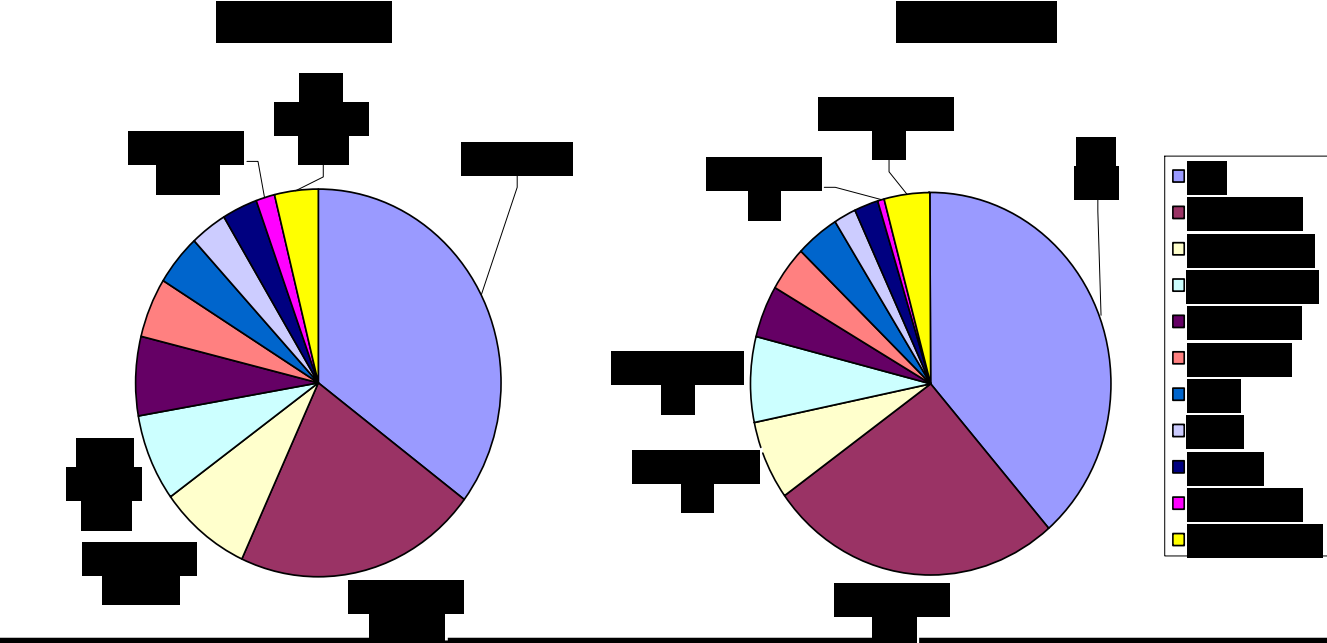
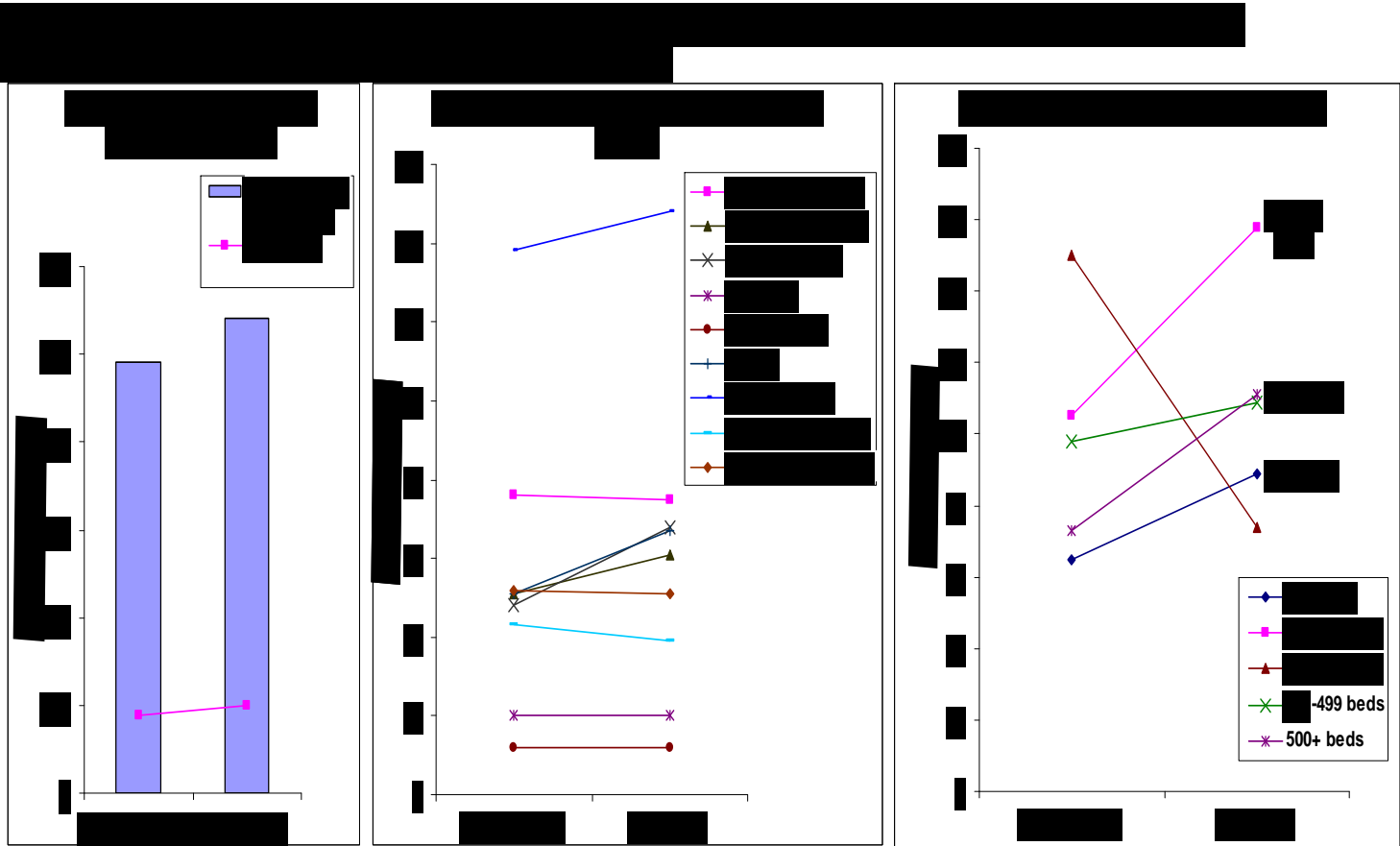


Source: Premier Healthcare Informatics, RxMarket Advisor™, years 2004-2009. Data extracted 4-09. Files: CUSTOM iv phenytoin fosphenytoin by age.xlsx and Premier 2007-1332 phenytoin and fos discharges and pts 2004-2009 0-16, 17-64, 65+.xls

Table 5: Actual Number of Unique Patients with a Hospital Billing for Fosphenytoin and IV Phenytoin by Patient Age, Year 2004 to 2009

	2004		2005		2006		2007		2008		2009	
Patient Age	Unique Patients (N)	Share %	Unique Patients (N)	Share %	Unique Patients (N)	Share %	Unique Patients (N)	Share %	Unique Patients (N)	Share %	Unique Patients (N)	Share %
Total	59,999	100%	62,983	100%	68,553	100%	61,875	100%	58,687	100%	56,645	100%
Fosphenytoin Total	25,911	43.2%	27,976	44.4%	31,593	46.1%	29,395	47.5%	30,918	52.7%	32,773	57.9%
0 - 16 years	2,194	8.5%	2,283	8.2%	2,380	7.5%	2,262	7.7%	2,174	7.0%	2,285	7.0%
0-1 month	266	12.1%	235	10.3%	179	7.5%	183	8.1%	171	7.9%	154	6.7%
1-6 months	242	11.0%	228	10.0%	210	8.8%	206	9.1%	234	10.8%	209	9.1%
6 months-2 years	347	15.8%	358	15.7%	373	15.7%	403	17.8%	428	19.7%	436	19.1%
3-12 years	791	36.1%	926	40.6%	934	39.2%	804	35.5%	758	34.9%	805	35.2%
13-16 years	310	14.1%	333	14.6%	305	12.8%	319	14.1%	263	12.1%	277	12.1%
17 - 64 years	13,884	53.6%	15,049	53.8%	17,190	54.4%	16,105	54.8%	17,078	55.2%	18,570	56.7%
65+ years	9,842	38.0%	10,652	38.1%	12,033	38.1%	11,030	37.5%	11,674	37.8%	12,029	36.7%
IV Phenytoin Total	34,067	56.8%	34,981	55.5%	36,943	53.9%	32,463	52.5%	27,754	47.3%	23,501	41.5%
0 - 16 years	902	2.6%	909	2.6%	797	2.2%	621	1.9%	529	1.9%	424	1.8%
0-1 month	94	10.4%	123	13.5%	88	11.0%	86	13.8%	91	17.2%	66	15.6%
1-6 months	59	6.5%	75	8.3%	63	7.9%	38	6.1%	41	7.8%	24	5.7%
6 months-2 years	94	10.4%	92	10.1%	88	11.0%	74	11.9%	74	14.0%	55	13.0%
3-12 years	318	35.3%	283	31.1%	242	30.4%	193	31.1%	145	27.4%	128	30.2%
13-16 years	159	17.6%	167	18.4%	153	19.2%	108	17.4%	78	14.7%	69	16.3%
17 - 64 years	19,173	56.3%	19,976	57.1%	21,248	57.5%	18,632	57.4%	16,016	57.7%	13,907	59.2%
65+ years	14,004	41.1%	14,114	40.3%	14,905	40.3%	13,225	40.7%	11,216	40.4%	9,430	40.1%

Source: Premier Healthcare Informatics, RxMarket Advisor™, years 2004-2009. Data extracted 4-09. Files: CUSTOM iv phenytoin fosphenytoin by age.xlsx and Premier 2007-1332 phenytoin and fos discharges and pts 2004-2009 0-16, 17-64, 65+.xls



APPENDIX 2: DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Premier RxMarket Advisor™

Premier's database is a large hospital drug utilization and financial database. Information is available from over 590 acute care and pediatric facilities and includes approximately 38 million inpatient records. On an annual basis, this constitutes roughly one out of every six inpatient discharges in the United States.³ Data are available from January 2000 through the present, but have a lag time of approximately 75 days. Premier's primary mission is to assist health care institutions improve clinical and operating performance in three strategic areas: group purchasing, supply chain and healthcare informatics. To that end, the Premier Informatics group developed this database in part to analyze utilization of resources to improve clinical efficiency.

The hospitals that contribute information to this database are a select sample of both Premier and U.S. institutions, and do not necessarily represent all hospitals in the U.S. Data are collected from this sample of participating hospitals with diverse characteristics based upon geographic location, bed size, population served, payors and teaching status. The data collected include demographic and pharmacy-billing information, as well as all diagnoses and procedures for every patient discharge. Preliminary comparisons between participating Premier hospital and patient characteristics and those of the probability sample of hospitals and patients selected for the National Hospital Discharge Survey (NHDS) proved to be very similar with regard to patient age, gender, length of stay, mortality, primary discharge diagnosis and primary procedure groups.⁴ Based upon these analyses, FDA believes that most estimates of national inpatient drug use based on Premier data appear to be reasonable, but strongly recommends making this determination on a drug-specific basis.

[REDACTED]

³ National Center of Health Statistics. Health United States, 2003.

⁴ Staffa JA, Gutierrez B, Kornegay C, et al. Outcome-based evaluation of a method for obtaining U.S. national estimates of inpatient drug utilization. *Pharmacoepidemiology Drug Safety* 2003;12: S173

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/s/

GRACE P CHAI

10/05/2010

LAURA A GOVERNALE

10/05/2010

Cleared for background package



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: November 26, 2008

To: Russell Katz, M.D., Director
Division of Neurological Products (DNP)

Through: Solomon Iyasu, MD, MPH, Director
Division of Epidemiology
Office of Surveillance and Epidemiology (OSE)

From: Kate Gelperin, MD, MPH
Division of Epidemiology, OSE

Subject: Purple Glove Syndrome

Drug Name(s): Phenytoin (Dilantin® Injection)
Fosphenytoin (Cerebyx®)

Application Type/Number: Dilantin® Injection N 10-151 (Mar 01, 1956)
Cerebyx® N 20-450 (Aug 05, 1996)

Applicant/sponsor: Parke Davis (now Pfizer)

OSE RCM #: 2007-1332

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

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EXECUTIVE SUMMARY

Intravenous phenytoin has been widely used for the treatment of seizures since FDA approval in 1956. Purple Glove Syndrome (PGS) is a unique adverse drug reaction first described and associated with intravenous phenytoin administration around the mid-1980s. For this review, PGS is defined as the progressive development of edema, discoloration, and pain in the limb after administration of intravenous phenytoin or fosphenytoin. The importance of careful adherence to proper administration techniques to avoid severe soft-tissue injury with intravenous phenytoin was emphasized in a 1988 publication which noted that over a 15 year period from 1969 to 1984 the FDA received 29 adverse drug reaction reports involving intravenous phenytoin including five patients who required amputations, four patients who required skin grafting, one patient who required fasciotomy, and five deaths. The FDA approval of fosphenytoin (a prodrug of phenytoin) in 1996 as a potentially safer and more convenient alternative has fostered a debate among clinicians regarding the relative merits of parenteral phenytoin versus fosphenytoin in patients who are actively seizing or who are unable to receive medications by mouth.

This review incorporates information from several sources including 1) Pfizer's responses to FDA queries regarding PGS; 2) previous FDA reviews of postmarketing spontaneous reports in AERS and drug utilization analyses; and 3) review of published medical literature.

Published Case Reports of Purple Glove Syndrome

Many well documented case reports of PGS associated with intravenous phenytoin administration have been published from around the world; however, no published case reports of PGS with fosphenytoin were identified.

Studies

Several observational studies relevant to PGS have been published. Incidence estimates of PGS associated with intravenous phenytoin administration ranged from zero to 5.9%, a rate which is perhaps consistent with a worst case "real life" scenario, since company sponsored clinical trials did not identify any cases of PGS. An incidence of 25.2% was found in a prospective observational study which encompassed a broader assessment of subacute local cutaneous reactions with phenytoin (mild to moderate in intensity). No cases of PGS with fosphenytoin were identified in any published studies.

Drug Utilization

IMS and Premier drug utilization data show that both phenytoin and fosphenytoin are widely used in the US and several other countries worldwide, with recent overall annual utilization of parenteral phenytoin approximately twice that of fosphenytoin, based on sales data covering the past three years.

Postmarketing Spontaneous Reports of Purple Glove Syndrome

Challenges were identified by both the sponsor and the FDA to completely identify all spontaneous reports consistent with purple glove syndrome (PGS), largely because there was no pertinent MedDRA coded term available for PGS until May 2003. To address

this limitation, string searches of case narratives were done, followed by individual case review. Although much effort went into conducting these searches of postmarketing spontaneous reports from FDA and Pfizer safety databases, ascertainment of pertinent cases was not complete. For this reason, the calculation of reporting rates using spontaneous reports as a numerator is unlikely to provide meaningful information.

FDA and Pfizer safety analysts identified several spontaneous postmarketing reports which were considered possibly or probably consistent with PGS related to fosphenytoin administration. All were reported by US hospital pharmacists, but lacked clinical confirmation from attending physicians or nursing staff who had cared for the patients. No medical records have been obtained for these cases, and documentation of clinical signs and symptoms, treatment, and outcome of the adverse events is lacking. No reports of possible PGS with fosphenytoin were identified from countries other than the US, despite the fact that IMS data show fosphenytoin sales in France, Canada, and Sweden, all of which are countries with sophisticated pharmacovigilance systems. The few poorly documented spontaneous reports identified so far do not provide an adequate basis to make conclusions about the risk of PGS with fosphenytoin, and do not provide sufficient useful clinical information to warrant a change to the fosphenytoin product labeling at this time.

Recommendations

After discussion with colleagues in the Division of Pharmacovigilance 1 who wrote a previous review of this issue, OSE recommends that no changes regarding purple glove syndrome be made to the fosphenytoin label at this time, but that more effort should be focused in obtaining complete clinical information about any potential cases that may be consistent with purple glove syndrome during fosphenytoin administration. The goal of careful follow-up is to provide meaningful clinical information that can inform a label revision in the future, if warranted.

We recommend that Pfizer be requested to develop and implement an effective plan to obtain complete and clinically meaningful information, such as hospital discharge summaries or copies of consultant's reports, for any new cases consistent with PGS or other severe local cutaneous reactions associated with fosphenytoin. In addition, expedited 15-day reporting is recommended for all US and foreign reports of PGS with fosphenytoin. We also recommend that Pfizer be asked to communicate pro-actively with responsible pharmacovigilance staff in the worldwide affiliate company offices located in countries where fosphenytoin is sold to assure that reports of serious unexpected adverse drug reactions are promptly reported to Health Authorities, including FDA.

It may also be desirable to review and update the Precautions section in the phenytoin USPI to more clearly describe the modifiable risk factors for patients developing PGS due to intravenous administration of phenytoin, as well as to consider an appropriate communication strategy for health professionals to minimize these risks.

OSE recommends follow-up with the FDA Office of Compliance to ensure the adequacy of Pfizer's postmarketing pharmacovigilance practices to identify any potential serious unexpected safety issues. After follow-up with the Office of Compliance has been completed, the issue of appropriate labeling to address possible occurrence and severity of soft tissue injury after fosphenytoin administration should be revisited.

1 BACKGROUND

1.1 INTRODUCTION

Although intravenous phenytoin has been widely used for the treatment of seizures since FDA approval in 1956, Purple Glove Syndrome^{1 2} (PGS) was not recognized or described in published literature until after 1980 and was not discussed in medical textbooks until the mid-1990s.³ Guidelines for proper administration techniques to avoid complications of intravenous phenytoin (such as burning at the administration site, hypotension or arrhythmias associated with rapid infusion rate) were published in JAMA in 1983.⁴

In 1987 the Dilantin injection USPI was updated with a Precaution describing “rare instances of amputation” associated with severe administration site reactions.⁵

The importance of careful adherence to proper administration techniques to avoid severe soft-tissue injury with intravenous phenytoin was further emphasized in a 1988 publication in Archives of Internal Medicine (co-authored by epidemiologists from the CDC Epidemiology Program Office and the FDA Division of Epidemiology and Surveillance).⁶ The authors noted that “over a 15 year period from 1969 to 1984 the FDA received 29 adverse drug reaction reports involving IV phenytoin” including “five patients who had required amputations, four patients who had required skin grafting, one patient who had required fasciotomy, and five patients who had died.”⁷

The FDA approval of fosphenytoin (a prodrug of phenytoin) in 1996 as a potentially safer and more convenient alternative has fostered a debate among clinicians regarding the relative merits of parenteral phenytoin vs. fosphenytoin in patients who are actively seizing or who are unable to receive medications by mouth.

Potential advantages of fosphenytoin over intravenous phenytoin include:

- Route of administration includes IV or IM
- Faster speed of administration is possible (however, conversion from prodrug to phenytoin takes time and no evidence exists of faster penetration into the CNS)

¹ For this review, purple glove syndrome is defined as the progressive development of edema, discoloration, and pain in the limb after administration of intravenous phenytoin (or fosphenytoin), consistent with the definition used by O'Brien et al (1998).

² O'Brien TJ, Cascino GD, So EL, Hanna DR. Incidence and clinical consequence of the purple glove syndrome in patients receiving intravenous phenytoin. *Neurology*. 1998 Oct;51(4):1034-9.

³ Browne TR. Intravenous phenytoin: cheap but not necessarily a bargain. *Neurology* 1998;51(4):942-3.

⁴ Earnest MP, Marx JA, Drury LR. Complications of intravenous phenytoin for acute treatment of seizures. Recommendations for usage. *JAMA*. 1983 Feb 11;249(6):762-5.

⁵ Phelan K, Pamer CA. Purple Glove Syndrome. DPV I Review. OSE RCM #2007-1332. July 9, 2008.

⁶ Spengler RF, Arrowsmith JB, Kilarski DJ, Buchanan C, Von Behren L, Graham DR. Severe soft-tissue injury following intravenous infusion of phenytoin. Patient and drug administration risk factors. *Arch Intern Med*. 1988 Jun; 148(6):1329-33.

⁷ Spengler RF, et al. 1988. *op.cit*, page 1329.

- Filter not needed
- Improved local tolerance

Disadvantages included higher cost of fosphenytoin and a high rate of occurrence of paresthesias with burning and itching, although these side effects are not considered to be clinically serious and symptoms usually resolve soon after the infusion is stopped. Cardiovascular side effects have been reported with intravenous administration of both drugs, and the anticipated lower potential for cardiac toxicity with fosphenytoin is now considered questionable.⁸ Perhaps the safety issue of greatest concern with fosphenytoin is the occurrence of fatal drug administration errors, especially in children.⁹

1.2 PRODUCT LABELING

1.2.1 FOSPHENYTOIN

Current approved USPI for Cerebyx (fosphenytoin) includes the following Precaution:

Sensory Disturbances

Severe burning, itching, and/or paresthesia were reported by 7 of 16 normal volunteers administered IV Cerebyx at a dose of 1200 mg PE at the maximum rate of administration (150 mg PE/min). The severe sensory disturbance lasted from 3 to 50 minutes in 6 of these subjects and for 14 hours in the seventh subject. In some cases, milder sensory disturbances persisted for as long as 24 hours. The location of the discomfort varied among subjects with the groin mentioned most frequently as an area of discomfort. In a separate cohort of 16 normal volunteers (taken from 2 other studies) who were administered IV Cerebyx at a dose of 1200 mg PE at the maximum rate of administration (150 mg PE/min), none experienced severe disturbances, but most experienced mild to moderate itching or tingling. Patients administered Cerebyx at doses of 20 mg PE/kg at 150 mg PE/min are expected to experience discomfort of some degree. The occurrence and intensity of the discomfort can be lessened by slowing or temporarily stopping the infusion. The effect of continuing infusion unaltered in the presence of these sensations is unknown. No permanent sequelae have been reported thus far.

There is no mention of purple glove syndrome in the current Cerebyx (fosphenytoin) USPI.

1.2.2 PHENYTOIN

Current approved USPI for Dilantin (phenytoin) includes the following Precaution:

Phenytoin Sodium Injection should be injected slowly (not exceeding 50 mg per minute in adults), directly into a large vein through a large-gauge needle or intravenous catheter. Each injection of intravenous Phenytoin Sodium Injection should be followed by an injection of sterile saline

⁸ Adams BD, Buckley NH, Kim JY, Tipps LB. Fosphenytoin may cause hemodynamically unstable bradycardias. J Emerg Med. 2006 Jan; 30(1):75-9.

⁹ Taylor K, Paparella S. Fatal errors with CEREBYX. J Emerg Nurs. 2008 Oct;34(5):460-1.

through the same needle or intravenous catheter to avoid local venous irritation due to the alkalinity of the solution. Continuous infusion should be avoided.

Soft tissue irritation and inflammation has occurred at the site of injection with and without extravasation of intravenous phenytoin. Soft tissue irritation may vary from slight tenderness to extensive necrosis, sloughing, and in rare instances has led to amputation. Improper administration including subcutaneous or perivascular injection should be avoided to prevent the possibility of the above.

Edema, discoloration and pain of the distal limb (described as “purple glove syndrome”) have been reported following peripheral intravenous phenytoin sodium injection. This may or may not be associated with extravasation. Although resolution of symptoms may be spontaneous, skin necrosis and limb ischemia have occurred and required such interventions as fasciotomies, skin grafting and amputation. Therefore, Phenytoin Sodium Injection should be administered as described above.

2 METHODS AND MATERIALS

2.1 INTRODUCTION

This review incorporates information from several sources:

- Pfizer’s Responses to FDA Queries regarding Purple Glove Syndrome and Cerebyx® (fosphenytoin sodium): Systematic Analysis of Association between Purple Glove Syndrome and Fosphenytoin¹⁰ which includes sections on the following topics:
 - Analysis of cases in Pfizer’s postmarketing safety database;
 - Analysis of adverse event data from clinical studies in humans, including Clinical Study Reports for 982-15 and 982-21;
 - Drug utilization data (IMS) and Pfizer’s estimate of reporting rates;
 - Literature search;
 - Reports of animal studies.
- Previous FDA/CDER/OSE reviews¹¹
 - Analysis of cases from FDA AERS postmarketing safety database;
 - Drug utilization data.
- Searches using FDA Biosciences Library resources were also done for this review.

2.2 CASE REPORTS OF PURPLE GLOVE SYNDROME

¹⁰ Pfizer responses to FDA queries regarding Purple Glove Syndrome safety experience: initial response August 4, 2008; follow-up response (revised) October 16, 2008.

¹¹ Phelan K, Pamer CA. OSE RCM #2007-1332. July 9, 2008.

2.2.1 Fosphenytoin

- **Published Case Reports of PGS with Fosphenytoin**

A literature search was performed using PubMed to identify published case reports of PGS or other severe injection site reactions with fosphenytoin.

- **Spontaneous Case Reports of PGS with Fosphenytoin: FDA AERS Safety Database Searches**

A search of the FDA AERS safety database was conducted by FDA staff on April 16, 2008 to identify case reports of PGS or severe injection site reactions with fosphenytoin.

- **Spontaneous Case Reports of PGS with Fosphenytoin: Sponsor's Safety Database Searches**

At the request of FDA DNP, the Sponsor conducted a search of their proprietary postmarketing safety database to identify case reports of PGS with fosphenytoin.

2.2.2 Phenytoin

- **Published Case Reports of PGS with Phenytoin**

A literature search was performed using PubMed to identify published case reports of PGS or severe injection site reactions with phenytoin.

- **Spontaneous Case Reports of PGS with Phenytoin: FDA AERS Safety Database Searches**

A search of the FDA AERS safety database was conducted on April 17, 2008 by FDA staff to identify selected case reports of PGS with phenytoin.

- **Spontaneous Case Reports of PGS with Phenytoin: Sponsor's Safety Database Searches**

At the request of FDA DNP, the Sponsor conducted a search of their proprietary postmarketing safety database to identify case reports of PGS with phenytoin.

2.3 BRIEF REVIEW OF OTHER PUBLISHED LITERATURE

2.3.1 PUBLISHED OBSERVATIONAL STUDIES

A literature review was performed using PubMed to identify published observational studies relevant to the occurrence of PGS or injection site reactions with phenytoin or fosphenytoin.

2.3.2 PUBLISHED PHARMACOECONOMIC STUDIES

A literature review was performed using PubMed to identify pharmacoeconomic studies relevant to the benefit risk balance of parenteral phenytoin versus fosphenytoin.

2.3.3 REVIEW ARTICLES AND TREATMENT GUIDELINES: STATUS EPILEPTICUS

A literature review was performed using PubMed to identify recent published treatment guidelines or reviews pertaining to expert opinion of the role of parenteral phenytoin and/or fosphenytoin in the emergency treatment of seizures, especially status epilepticus.

2.4 CLINICAL TRIALS CONDUCTED BY SPONSOR

The Sponsor conducted a search and analysis of adverse event data from clinical studies in humans. Clinical Study Reports were provided for two of these studies (982-15 and 982-21) which included global assessments of injury and irritation at the infusion site specified per protocol.

2.5 DRUG UTILIZATION

Drug utilization of parenteral phenytoin and fosphenytoin (US only) was analyzed by FDA staff using IMS Health and Premier databases.¹² In addition, the Sponsor provided an analysis of phenytoin and fosphenytoin utilization (both US and foreign) using IMS data.

3 RESULTS

3.1 CASE REPORTS OF PURPLE GLOVE SYNDROME

3.1.1 Fosphenytoin

3.1.1.1 Published Case Reports of PGS with Fosphenytoin

No published case reports of PGS or other severe injection site reactions with fosphenytoin were identified in searches conducted for this review.

3.1.1.2 Spontaneous Case Reports of PGS with Fosphenytoin: FDA AERS Safety Database Search Results

A search of the FDA AERS safety database on April 16, 2008 identified four (4) cases of possible PGS and four (4) cases of severe injection site reactions with fosphenytoin from an overall total of 575 reports for this drug.¹³ Narrative summaries of these cases are presented in Appendix 1.

3.1.1.3 Spontaneous Case Reports of PGS with Fosphenytoin: Sponsor's Postmarketing Safety Database Search Results

The Sponsor identified eight (8) potential case reports of PGS with fosphenytoin, of which five (5) cases were considered by the Sponsor to be possibly or probably consistent with a diagnosis of PGS. Narrative summaries of each of these cases are presented in Appendix 2.

¹² Phelan K, Pamer CA. OSE RCM #2007-1332. July 9, 2008. *op.cit.*

¹³ *Ibid.*

3.1.2 Phenytoin

3.1.2.1 Published Case Reports of PGS with Phenytoin

Many well documented case reports of PGS associated with intravenous phenytoin administration were identified in searches conducted for this review. Since 1983 numerous case reports describing reactions to parenteral phenytoin have been published from around the world, including the United States,^{14 15 16 17 18 19 20} Germany,²¹ Japan,²² and India.²⁴

A single published case report describing PGS after oral administration of phenytoin (overdose in a child) was identified.²⁵

A bibliography of the published case reports of PGS with phenytoin (listed in reverse chronological order) is provided in Appendix 3.

3.1.2.2 Spontaneous Case Reports of PGS with Phenytoin: FDA AERS Safety Database Search Results

A search of the FDA AERS safety database on April 17, 2008 identified 33 cases of possible PGS from an overall total of 18,060 reports in which phenytoin was identified as a suspect drug.²⁶

¹⁴ Chokshi R, Openshaw J, Mehta NN, Mohler E 3rd. Purple glove syndrome following intravenous phenytoin administration. *Vasc Med*. 2007 Feb; 12(1):29-31.

¹⁵ Kirsch S, Bayard M, Darraj K. Distal upper extremity edema and discoloration. *Am Fam Physician*. 2007 Mar 15;75(6):889-91.

¹⁶ Earnest MP. 1983 *op.cit*.

¹⁷ Hanna DR. Purple glove syndrome: a complication of intravenous phenytoin. *J Neurosci Nurs*. 1992 Dec;24(6):340-5.

¹⁸ Hayes AG, Chesney TM. Necrosis of the hand after extravasation of intravenously administered phenytoin. *J Am Acad Dermatol*. 1993 Feb;28(2 Pt 2):360-3.

¹⁹ Bhattacharjee P, Glusac EJ. Early histopathologic changes in purple glove syndrome. *J Cutan Pathol*. 2004 Aug;31(7):513-5.

²⁰ Helfaer MA, Ware C. Purple glove syndrome. *J Neurosurg Anesthesiol*. 1994 Jan;6(1):48-9.

²¹ Cadenbach A, Röttger K, Müller MK. Purple glove syndrome. Severe soft tissue reaction following phenytoin infusion. *Dtsch Med Wochenschr*. 1998 Mar 13;123(11):318-22.

²² Sonohata M, Asami A, Tsunoda K, Hotokebuchi T. Purple glove syndrome associated with intravenous phenytoin administration in a patient with severe mental and motor retardation. *J Orthop Sci*. 2006 Jul;11(4):409-11.

²³ Endoh T, Miyake S. [A case of purple glove syndrome following a intravenous infusion of phenytoin] *No To Hattatsu*. 2001 Sep;33(5):442-4.

²⁴ Mahajan RP, Batra YK, Rajeev S. Intravenous phenytoin and percutaneous arterial cannulation: the purple-glove syndrome. *Eur J Anaesthesiol*. 2007 Oct; 24(10):900-1.

²⁵ Yoshikawa H, Abe T, Oda Y. Purple glove syndrome caused by oral administration of phenytoin. *J Child Neurol*. 2000 Nov;15(11):762.

²⁶ Phelan K, Pamer CA. OSE RCM #2007-1332. July 9, 2008. *op.cit*.

The earliest case of PGS identified in this search was received by FDA in 1998 for an adverse reaction that occurred in 1996, suggesting there are inherent limitations of search capabilities spanning the fifty year period of phenytoin availability. Although PGS may not have been widely recognized or reported prior to 1998, it is likely that the unavailability of a pertinent MedDRA code prior to 2003 impedes identification of potential relevant cases in the AERS database. These search strategy limitations for PGS with phenytoin were also pointed out by the FDA reviewer who stated that “the object of this phenytoin case review is to characterize, not to quantify, the cases because PGS is a recognized adverse reaction to phenytoin.”²⁷

The incidence of PGS with intravenous phenytoin administration has been shown in two prospective observational studies to range from 1.7%²⁸ to 5.9%,²⁹ a rate which is perhaps consistent with a worst case “real life” scenario, since company sponsored clinical trials of parenteral phenytoin and fosphenytoin did not identify any cases of PGS. Nonetheless, it seems clear that searches of the AERS data substantially underestimate the true number of PGS cases with phenytoin. For this reason, the calculation of reporting rates using AERS spontaneous reports as a numerator are unlikely to provide meaningful information.

3.1.2.3 Spontaneous Case Reports of PGS with Phenytoin: Sponsor’s Postmarketing Safety Database Search Results

The Sponsor identified 132 potential case reports of PGS with phenytoin, of which 112 cases were considered by the Sponsor to be possibly or probably consistent with a diagnosis of PGS. The earliest company receipt date for postmarketing reports of PGS with phenytoin was identified as the year 1983. The majority of cases were from the US, but there were a few cases identified by the Sponsor as possible or probable PGS which originated from France (1), UK (1), Sweden (1), Germany (1), Jamaica (1), Canada (1), and India (1).

3.2 BRIEF REVIEW OF OTHER PUBLISHED LITERATURE

3.2.1 PUBLISHED OBSERVATIONAL STUDIES

Several observational studies relevant to PGS have been published. Results have varied, probably depending on prospective versus retrospective study design, the patient population studied and the clinical definition of PGS used by the study investigators. An annotated bibliography is included in Appendix 4.

Case-Control Study

In 1988, Centers for Disease Control epidemiologists reported that between April 1982 through June 1984, 11 patients in a single hospital experienced 17 episodes of limb

²⁷ *Ibid.* page 16.

²⁸ Burneo JG, Anandan JV, Barkley GL. A prospective study of the incidence of the purple glove syndrome. *Epilepsia*. 2001 Sep;42(9):1156-9.

²⁹ O’Brien TJ, Cascino GD, So EL, Hanna DR. Incidence and clinical consequence of the purple glove syndrome in patients receiving intravenous phenytoin. *Neurology*. 1998 Oct;51(4):1034-9.

edema and discoloration after the intravenous (IV) administration of phenytoin sodium (Dilantin). One patient required a below-the-elbow amputation; all other patients recovered. No single drug lot was implicated. A case-control study was performed using three controls for each case; controls received IV infusions of phenytoin and were hospitalized close in time to the case patients. Compared with controls, patients with reactions were more often female and elderly and had underlying cardiovascular disease. Affected patients also received phenytoin through an IV catheter smaller than 20 gauge (50% vs 6%), at a rate greater than 25 mg/min (63% vs 19%), and in two or more IV infusions of phenytoin given "IV push" at the same site (81% vs 24%). The authors concluded that "high-risk patients require careful monitoring and stricter guidelines for the IV administration of phenytoin."³⁰

Retrospective Observational Study

In 1998, O'Brien et al conducted a study at the Mayo Clinic in Minnesota to determine the incidence, risk factors, and long-term sequelae of purple glove syndrome (PGS) in hospital patients receiving IV phenytoin. The pharmacologic records of the Mayo Foundation hospitals were reviewed to identify 179 consecutive patients who had IV phenytoin ordered during a 3-month period. Their hospital records were then reviewed to confirm IV phenytoin treatment, the frequency of PGS (defined as the progressive development of edema, discoloration, and pain in the limb after administration of IV phenytoin), and the outcome of PGS. A total of 152 patients received IV phenytoin, and nine (5.9%) developed PGS. PGS patients received a greater median initial dose of phenytoin, total 24-hour dose, and total number of doses (all $p < 0.05$). In addition, the median age of the PGS patients was older, their infusion was more often given for acute seizures, it was less likely to be administered in the operating room, and the length of their hospital stay was longer (all $p < 0.05$). One patient required surgical therapy, and all other patients resolved within 3 weeks with conservative management. The authors concluded that PGS is not rare, and that elderly patients and individuals receiving large, multiple doses are particularly at risk. They recommended that this iatrogenic complication may be preventable by substituting fosphenytoin for IV phenytoin.³¹

Prospective Observational Studies

In 2001, Burneo et al published the results of a prospective study of 179 consecutive administrations of intravenous phenytoin at a single institution (Henry Ford Hospital in Detroit, MI) which found that the incidence of PGS was 1.7%. This complication involved two patients who recovered without prolonged hospitalization or surgical intervention. Most patients received an initial loading dose (intravenous) followed by oral doses. The administration of phenytoin at that institution was standardized and managed by the Pharmacy Department, where parenteral phenytoin was packaged in normal saline and administered via IVPB at a rate not to exceed 20 mg/min, using an electronic

³⁰ Spengler RF, Arrowsmith JB, Kilarski DJ, Buchanan C, Von Behren L, Graham DR. Severe soft-tissue injury following intravenous infusion of phenytoin. Patient and drug administration risk factors. *Arch Intern Med.* 1988 Jun;148(6):1329-33. Comment in: *Arch Intern Med.* 1989 Aug;149(8):1905.

³¹ O'Brien TJ, Cascino GD, So EL, Hanna DR. Incidence and clinical consequence of the purple glove syndrome in patients receiving intravenous phenytoin. *Neurology.* 1998 Oct;51(4):1034-9. Comment in: *Neurology.* 1998 Oct;51(4):942-3. *Neurology.* 1999 Oct 22;53(7):1611-2.

infusion control device and a 0.22µm in-line filter, based on the manufacturer's recommendations.³²

Also in 2001, O'Brien et al (Australian Centre for Clinical Neuropharmacology) published the results of a prospective evaluation of the occurrence of subacute local cutaneous reactions (LCR) in patients receiving IV phenytoin over a 12-month period at a general hospital in Australia. LCR were detected in 29 of 115 patients (25.2%; 22 mild and seven moderate). All resolved within 3 weeks. Patients with LCR were older (median 68 versus 54.5 years, $p = 0.004$), were more likely to be in a general ward (86% versus 66%, $p = 0.04$), and had larger catheters (median 16 G versus 18 G, $p = 0.05$). The authors conclude that LCR are common in routine hospital practice, but are generally mild and benign.³³

Prospective Randomized Studies

In 2004, Swadron et al published the results of a randomized study designed to compare three phenytoin-loading techniques³⁴ which was conducted at the Department of Emergency Medicine, Keck School of Medicine, in California. Patients with subtherapeutic phenytoin concentrations who presented within 48 hours of a seizure were randomized to receive either 20 mg/kg of oral phenytoin, divided in maximum doses of 400 mg every two hours, 18 mg/kg of intravenous phenytoin at an initial infusion rate of 50 mg/min, or 18 mg/kg (phenytoin equivalents) of intravenous fosphenytoin at an initial infusion rate of 150 mg/min. A total of 45 patients were enrolled: 16 in the oral group, 14 in the intravenous phenytoin group, and 15 in the intravenous fosphenytoin group. The times required to reach therapeutic drug concentrations were 5.62 hours, 0.24 hours, and 0.21 hours, respectively. A total of 17, 27, and 32 adverse drug events were observed in the oral, intravenous phenytoin, and intravenous fosphenytoin groups, respectively, with significantly fewer events in the oral group ($p = 0.02$, $p = 0.01$). No significant difference was found between the numbers of necessary adjustments to the infusions in the two IV groups. The average time to safe emergency department discharge was significantly shorter for the IV groups compared with the oral group ($p < 0.001$). The authors concluded that oral loading has fewer adverse drug events than either IV loading method, but its use may be limited when therapeutic concentrations are required quickly. Although intravenous fosphenytoin loading is faster, from an adverse-drug event perspective, no advantage of intravenous fosphenytoin over intravenous phenytoin was apparent.

³² Burneo JG, Anandan JV, Barkley GL. A prospective study of the incidence of the purple glove syndrome. *Epilepsia*. 2001 Sep;42(9):1156-9.

³³ O'Brien TJ, Meara FM, Matthews H, Vajda FJ. Prospective study of local cutaneous reactions in patients receiving IV phenytoin. *Neurology*. 2001 Oct 23;57(8):1508-10. Comment in: *Neurology*. 2002 Apr 9;58(7):1134; author reply 1134.

³⁴ Swadron SP, Rudis MI, Azimian K, Beringer P, Fort D, Orlinsky M. A comparison of phenytoin-loading techniques in the emergency department. *Acad Emerg Med*. 2004 Mar;11(3):244-52.

Coplin et al³⁵ evaluated adverse events and length-of-stay during routine emergency department use in an open-label randomized study of phenytoin or fosphenytoin in 256 Emergency Department patients prescribed 279 parenteral doses of a phenytoin-equivalent. All phenytoin was administered intravenously, and fosphenytoin was given intravenously or intramuscularly (physician preference). Adverse events and Emergency Department length-of-stay were recorded; re-presentation to the Emergency Department within three months was reviewed for evidence of the purple glove syndrome. Seventy-seven patients received phenytoin and 202 fosphenytoin; 28 (10.0%) received intramuscular fosphenytoin. The mean phenytoin-equivalent dose was similar between the groups. Eighteen patients required reduction in infusion rates because of an adverse event (phenytoin = 6.5%, fosphenytoin = 6.4%; OR 0.9, 95% CI 0.4 2.6; $p = 1.0$). Adverse events occurred with similar frequency (phenytoin 9.1%, fosphenytoin 15.8%; OR 0.7, 95% CI 0.3 1.4; $p = 0.3$). The most common events were: pruritis, pain on infusion, and paresthesias. One patient developed hypotension (fosphenytoin); there were no other serious adverse events, including phlebitis. Median Emergency Department length-of-stay was 6.7 h for phenytoin and 5.7 h for fosphenytoin ($p = 0.6$). The authors concluded that these results do not support formulary conversion from phenytoin to fosphenytoin in routine Emergency Department use, based on the incidence of adverse events or Emergency Department length-of-stay.

Summary

A wide range of incidence estimates were found in studies of PGS associated with intravenous phenytoin administration, ranging from zero to 5.9% for PGS defined as the “progressive development of edema, discoloration, and pain in the limb” after intravenous administration.³⁶ A much higher incidence of 25.2% was found in a prospective study which encompassed a broader assessment of subacute local cutaneous reactions (LCR) which were considered to be mild to moderate in intensity, and all of which resolved within three weeks.³⁷ No cases of PGS with fosphenytoin were identified in any of these studies.

3.2.2 PUBLISHED PHARMACOECONOMIC STUDIES

Two pharmacoeconomic analyses in hospital Emergency Departments concluded that parenteral phenytoin is a more cost effective choice than fosphenytoin.^{38 39} One publication, a randomized study of 45 patients admitted to the hospital Emergency

³⁵ Coplin WM, Rhoney DH, Rebuck JA, Clements EA, Cochran MS, O'Neil BJ. Randomized evaluation of adverse events and length-of-stay with routine emergency department use of phenytoin or fosphenytoin. *Neurol Res.* 2002 Dec;24(8):842-8.

³⁶ O'Brien TJ et al. 1998. *op cit.*

³⁷ O'Brien TJ et al. 2001. *op cit.*

³⁸ Touchette DR, Rhoney DH. Cost-minimization analysis of phenytoin and fosphenytoin in the emergency department. *Pharmacotherapy.* 2000 Aug;20(8):908-16.

³⁹ Rudis MI, Touchette DR, Swadron SP, Chiu AP, Orlinsky M. Cost-effectiveness of oral phenytoin, intravenous phenytoin, and intravenous fosphenytoin in the emergency department. *Ann Emerg Med.* 2004 Mar;43(3):386-97.

Department after a seizure, concluded that oral phenytoin is “the most cost-effective loading method in most settings”, but intravenous phenytoin is preferred” and “it is unlikely that intravenous fosphenytoin is justifiable in any setting.”⁴⁰ Based on their study results, Rudis et al recommend that “oral phenytoin loading be considered in cases in which patients do not otherwise require monitoring” and that fosphenytoin use be “restricted to status epilepticus or cases in which the time required to load must be kept to the absolute minimum (e.g., patient going immediately to the operating room).”⁴¹

In contrast, a pharmacoeconomic study⁴² sponsored by Parke-Davis found that the “average cost to treat patients with fosphenytoin was lower than the cost to treat similar patients with phenytoin based on the frequency of adverse events” and “the resources (human and material) consumed.”

A study of “inappropriate fosphenytoin use” in a hospital Emergency Department⁴³ was conducted at Vanderbilt University in Tennessee with the objective of evaluating how often intravenous fosphenytoin is used when oral phenytoin loading is possible. The authors conducted a retrospective chart review of all patients receiving IV fosphenytoin in their emergency department. From February 1997 to June 1999, 55 patients received IV fosphenytoin. Thirty patients were felt to have received fosphenytoin appropriately. The remaining 25 patients could have been loaded orally with phenytoin. The authors concluded that, at their institution, fosphenytoin administration was inappropriate almost half the time since oral phenytoin loading is less expensive and safe.

Overall, results of these pharmacoeconomic analyses are inconsistent, and appear to depend on methods used and patient populations studied.

3.2.3 REVIEW ARTICLES AND TREATMENT GUIDELINES: STATUS EPILEPTICUS

A review article published in 2000 in the journal *Drug Safety* compared fosphenytoin and phenytoin for the treatment of patients with tonic-clonic status epilepticus (TCSE). The authors were very clear in their endorsement of fosphenytoin as a clinically superior choice over parenteral phenytoin as a second line agent after a benzodiazepine:

Because of its efficacy, absence of sedation or respiratory suppression, intravenous phenytoin has largely replaced phenobarbital (phenobarbitone) as the second agent of choice (following the administration of a benzodiazepine) in the treatment of TCSE. While the efficacy of phenytoin in the treatment of acute seizures and TCSE is well established, the parenteral formulation of phenytoin has several inherent shortcomings which compromise its tolerability and limit the rate of administration. Intravenous phenytoin has been associated with fatal haemodynamic

⁴⁰ Rudis MI, Touchette DR, Swadron SP, Chiu AP, Orlinsky M. Cost-effectiveness of oral phenytoin, intravenous phenytoin, and intravenous fosphenytoin in the emergency department. *Ann Emerg Med.* 2004 Mar;43(3):386-97.

⁴¹ *Ibid*, page 397.

⁴² Marchetti A, Magar R, Fischer J, Sloan E, Fischer P. A pharmacoeconomic evaluation of intravenous fosphenytoin (Cerebyx) versus intravenous phenytoin (Dilantin) in hospital emergency departments. *Clin Ther.* 1996 Sep-Oct;18(5):953-66.

⁴³ Johnson J, Wrenn K. Inappropriate fosphenytoin use in the ED. *Am J Emerg Med.* 2001 Jul;19(4):293-4.

complications and serious reactions at the injection site including skin necrosis and amputation of extremities. All other factors being equal, there is no doubt that fosphenytoin is better tolerated and can be delivered faster than intravenous phenytoin, two measures that clearly improve outcome in patients with TCSE. The tolerability of intramuscular fosphenytoin also extends its use to clinical situations where prompt administration of a nondepressing anticonvulsant is indicated but secure intravenous access and cardiac monitoring are not available, such as treatment of seizures by rescue squads in the field and serial seizures in the institutionalised, elderly and other patients with intractable epilepsy.⁴⁴

Consistent with this view, recommendations for the management of status epilepticus from a well known medical text book (ACP Medicine 2008) in a chapter written by neurologists from the University of Texas Health Sciences Center at Houston, favor the use of fosphenytoin (over phenytoin) as part of the standard treatment algorithm.⁴⁵

Fischer et al⁴⁶ reviewed the comparative advantages of fosphenytoin as an alternative to intravenous phenytoin for acute treatment of seizures. Advantages include more convenient and rapid intravenous administration, availability for intramuscular injection, and low potential for adverse local reactions at injection sites. Drawbacks include the occurrence of transient paresthesias and pruritis at rapid infusion rates, and cost.

Most published guidelines in recent years recommend phenytoin or fosphenytoin as second line therapy in status epilepticus if seizures persist after first line therapy (benzodiazepines); of note, several reviews state a preference of fosphenytoin over phenytoin in treatment algorithms for status epilepticus, including publications from the US,⁴⁷ Germany,⁴⁸ and Finland,⁴⁹ but not the UK.⁵⁰

Kälviäinen et al, who state no conflict of interest, recommend that “intravenous fosphenytoin is preferred over phenytoin because of its water solubility and normal pH, allowing more rapid administration and less infusion-related adverse effects.”

A differing perspective from the UK was described in the British Medical Journal in 2005 by Dr Matthew Walker of the Institute of Neurology and the National Hospital for Neurology and Neurosurgery, London. He recommended that “phenytoin should be given in established status epilepticus as an adjunct to a benzodiazepine.” Although he

⁴⁴ DeToledo JC, Ramsey RE. Fosphenytoin and phenytoin in patients with status epilepticus: improved tolerability versus increased costs. *Drug Saf.* 2000 Jun; 22(6):459-66.

⁴⁵ ACP Medicine 2008. WebMD Corporation. Slater JD, Kalamangalam GP. Chapter XII: Epilepsy. Posted 30 July 2008. Available at <http://online.statref.com/document.aspx?fxid=48&docid=2012>.

⁴⁶ Fischer JH, Patel TV, Fischer PA. Fosphenytoin: clinical pharmacokinetics and comparative advantages in the acute treatment of seizures. *Clin Pharmacokinet.* 2003;42(1):33-58.

⁴⁷ Arif H, Hirsch LJ. Treatment of status epilepticus. *Semin Neurol* 2008; 28: 342-354.

⁴⁸ Rosenow F, Knake S. Review: Recent and future advances in the treatment of status epilepticus. *Therapeutic Advances in Neurological Disorders* 2008; 1; 25; available at: <http://tan.sagepub.com/cgi/content/abstract/1/1/25>.

⁴⁹ Kälviäinen R, Eriksson K, Parviainen I. Refractory generalised convulsive status epilepticus: a guide to treatment. *CNS Drugs.* 2005; 19(9):759-68. Review.

⁵⁰ Walker M. Status epilepticus: an evidence based guide. *BMJ.* 2005 Sep 24; 331(7518):673-7.

acknowledged that fosphenytoin “reduces the small risk of purple glove syndrome”, he expressed the view that “a prospective study found an incidence of purple glove syndrome of 1.7%, which probably does not justify the widespread use of fosphenytoin (a water soluble prodrug of phenytoin that does not cause purple glove syndrome).”⁵¹

Clinically meaningful benefits of intravenous phenytoin in the treatment of community onset childhood convulsive status epilepticus were described in a prospective, population based study in the UK.⁵² Treatment with intravenous phenytoin (n=32) as a second-line therapy was associated with a 9 times (95% CI 3–27) greater likelihood of seizure termination than was treatment with rectal paraldehyde (n=42). Although the current UK treatment guidelines for status epilepticus recommend that rectal paraldehyde should be used after benzodiazepine therapy has failed, this observational study showed that current UK practice differs: approximately half of the children received phenytoin. The authors commented that absence of fosphenytoin use in their study population might be related to “its exclusion from the APLS and NICE (National Institute for Health and Clinical Excellence) guidelines.”

There is no discussion of fosphenytoin in a recent (2008) Cochrane review of pediatric convulsive status epilepticus treatment.⁵³

3.3 CLINICAL TRIALS CONDUCTED BY SPONSOR

No cases of PGS were identified by Pfizer from clinical trials with parenteral phenytoin and fosphenytoin.

3.4 DRUG UTILIZATION

FDA analysis of US hospital use of phenytoin and fosphenytoin for the years 2000 through mid-2007 showed drug utilization levels for parenteral phenytoin were roughly twice that of fosphenytoin.

Overall, fosphenytoin parenteral was associated with a projected total number of 1,260,460 unique patients from January 2000 through June 2007, compared with phenytoin parenteral which was associated with a projected total number of 1,864,878 unique patients during the same time period. Table 3, reproduced below from the FDA review, provides the data for fosphenytoin in yearly and cumulative totals.⁵⁴

⁵¹ Walker M. 2005. *op.cit*, page 675.

⁵² Chin RF, Neville BG, Peckham C, Wade A, Bedford H, Scott RC. Treatment of community-onset, childhood convulsive status epilepticus: a prospective, population-based study. *Lancet Neurol.* 2008 Aug;7(8):696-703. Epub 2008 Jul 2. Erratum in: *Lancet Neurol.* 2008 Sep;7(9):771.

⁵³ Appleton R, Macleod S, Martland T. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. *Cochrane Database Syst Rev.* 2008 Jul 16;(3):CD001905. Review.

⁵⁴ Phelan K, Pamer CA. OSE RCM #2007-1332. July 9, 2008. Source: Premier Data extracted September 2007. File: Fosphenytoin parenteral by year.xls.

Table 3: Fosphenytoin parenteral projected U.S. hospital discharges and unique patients for years 2000 through June 2007

	Year	Projected Discharges	Projected Unique Patients
Total		1,337,809	1,260,460
FOSPHENYTOIN PARENTERAL	2000	147,941	139,926
	2001	151,769	143,644
	2002	172,674	163,004
	2003	179,731	170,040
	2004	195,717	183,719
	2005	204,432	191,704
	2006	193,418	180,417
	2007 Q1 & Q2	92,128	88,006
Source: Premier Data extracted September 2007. File: Fosphenytoin parenteral by year.xls.			

The Sponsor's analysis of US drug use levels (Source of data: IMS Health) for a recent three year time period was consistent with this pattern of roughly twice as many units of parenteral phenytoin sold compared to fosphenytoin (as shown in Table 4 below, reproduced from Sponsor's report, page 15).

Table 4. Units of fosphenytoin and injectable phenytoin sold in the United States
(Source of data: IMS Health)

Drug	Units of drug sold		
	Moving Annual Total from April 1 2005 to March 31 2006	Moving Annual Total from April 1 2006 to March 31 2007	Moving Annual Total from April 1 2007 to March 31 2008
Cerebyx	2,245,000	2,230,000	938,000
Non-Pfizer fosphenytoin	0	0	1,236,000
Pfizer injectable phenytoin	0	0	0
Generic injectable phenytoin	4,926,000	4,664,000	4,190,000

A similar proportion of international phenytoin vs fosphenytoin drug use, with parenteral phenytoin units of drug sold roughly twice that of fosphenytoin, as shown in Table 5 below (reproduced from the Sponsor's report, page 16). Countries other than the US which were identified in the Sponsor's report as markets for fosphenytoin include India (non-Pfizer), France, Finland, Canada, and Sweden.

Table 5. Units of fosphenytoin and injectable phenytoin sold outside the United States (Source of data: IMS Health)

Drug	Units of drug sold		
	Moving Annual Total from April 1 2005 to March 31 2006	Moving Annual Total from April 1 2006 to March 31 2007	Moving Annual Total from April 1 2007 to March 31 2008
Pfizer fosphenytoin	93,000	95,000	95,000
Non-Pfizer fosphenytoin	437,000	495,000	655,000
Pfizer injectable phenytoin	1,419,000	1,301,000	1,259,000
Non-Pfizer injectable phenytoin	9,782,000	10,559,000	11,011,000

In summary, information on utilization of parenteral phenytoin and fosphenytoin in recent years shows that both drugs are widely used in the US and several other countries worldwide, with overall approximately twice as much utilization of parenteral phenytoin compared to fosphenytoin, based on sales data.

4 DISCUSSION

4.1 Phenytoin

Challenges were identified by both the sponsor and the FDA to completely identify all spontaneous reports consistent with purple glove syndrome (PGS), largely because there was no pertinent MedDRA coded term available for PGS until May 2003. To address this limitation, string searches of case narratives were undertaken by safety analysts, followed by individual case review. Although much effort went into conducting these searches of postmarketing spontaneous reports from FDA and Pfizer safety databases, it is clear that ascertainment of pertinent cases was not complete. For perspective, it should be noted that both searches were apparently unable to ascertain and retrieve the 29 cases noted by Spengler et al in their 1988 publication describing phenytoin adverse drug reaction reports received by FDA over a fifteen year period which included five amputations, four cases with skin grafting, one case requiring fasciotomy, and five deaths.⁵⁵

Results of published observational studies indicate that, at least in some settings, the incidence of purple glove syndrome associated with intravenous phenytoin administration can be in the range of 1.7%⁵⁶ to 5.9%.⁵⁷ In contrast, company sponsored clinical trials

⁵⁵ Spengler RF, et al. 1988. *op.cit*, page 1329.

⁵⁶ Burneo JG, Anandan JV, Barkley GL. A prospective study of the incidence of the purple glove syndrome. *Epilepsia*. 2001 Sep;42(9):1156-9.

of parenteral phenytoin did not identify any cases of PGS, which may reflect the beneficial effects of optimal management of risk factors in a clinical trial setting, such as patient selection and infusion administration practices.

4.2 Fosphenytoin

FDA and Pfizer safety analysts identified four (4) spontaneous postmarketing reports which were considered possibly or probably consistent with purple glove syndrome (PGS) associated with intravenous fosphenytoin administration. All were reported by US hospital pharmacists (from Tennessee, Florida, Oregon, and Indiana), but lacked clinical confirmation from attending physicians or nursing staff who had cared for the patients. No medical records have been obtained for these cases, and documentation of clinical signs and symptoms, treatment, and outcome of the adverse events is lacking. No information was provided about the infusion site, rate of administration, or other medications that may have been administered through the same intravenous line.

It is also striking that no similar reports of possible PGS have been received from countries other than the US, despite the fact that IMS data show fosphenytoin sales in France, Canada, and Sweden, all of which are countries with sophisticated pharmacovigilance systems.

In a previous FDA review⁵⁸ the safety analyst expressed concern that, based on her experience, an unusually high number of AERS reports had been received directly from consumers rather than from the manufacturer of fosphenytoin (56% of total AERS cases).

In this current review, an additional potential compliance related issue is noted in that there are very few fosphenytoin reports in the AERS database originating from non-US countries. The top five non-US countries identified in the Sponsor's report as markets for fosphenytoin include India (non-Pfizer), France, Finland, Canada, and Sweden.

The total number of fosphenytoin reports in AERS originating from each of these countries is: India (0), France (62), Finland (2), Canada (0) and Sweden (6), out of a total number of 508 cases in the AERS database which include fosphenytoin as a suspect drug (regardless of event or country of origin).

We agree with the previous FDA OSE review which recommended follow-up with the FDA Office of Compliance to determine whether under-reporting of serious, unexpected adverse events could be occurring with fosphenytoin.

5 CONCLUSION

Based on available information including numerous published case reports, postmarketing spontaneous reports, and several published observational studies, it seems reasonable to conclude that purple glove syndrome (PGS) is a serious complication of intravenous phenytoin administration that may occur in up to 2 to 6% of patients,

⁵⁷ O'Brien TJ, Cascino GD, So EL, Hanna DR. Incidence and clinical consequence of the purple glove syndrome in patients receiving intravenous phenytoin. *Neurology*. 1998 Oct;51(4):1034-9.

⁵⁸ Phelan K, Pamer C. 2008. *op cit*.

depending on risk factors such as rate of infusion, needle or catheter gauge, and patient age.

In contrast, no published case reports have been identified describing PGS with fosphenytoin, and no cases have been identified in clinical trials or observational studies. A few poorly documented postmarketing spontaneous reports have been identified, all reported by US hospital pharmacists, but in every case lacking in meaningful clinical details that would enable assessment of the diagnosis, treatment, and clinical course of the adverse events. Unfortunately, such poorly documented cases may in fact contain erroneous information about the correct suspect drug received by the patient and/or the correct diagnosis of the patient's condition. Hospital medical records have not been received for any of these cases. We conclude that these few poorly documented reports do not provide an adequate basis to make conclusions about the risk of PGS with fosphenytoin, and do not provide sufficient useful clinical information to warrant a change to the fosphenytoin product labeling at this time. It is possible that the Sponsor's postmarketing pharmacovigilance practices, which should ensure ascertainment and follow-up of spontaneous reports, have not been adequate to detect and characterize a signal for PGS with fosphenytoin if in fact there is one.

6 RECOMMENDATIONS

After discussion with colleagues in the Division of Pharmacovigilance 1 who wrote a previous review of this issue, OSE recommends that no changes regarding purple glove syndrome be made to the fosphenytoin label at this time, but that more effort should be focused in obtaining complete clinical information about any potential cases that may be consistent with purple glove syndrome during fosphenytoin administration. The goal of careful follow-up is to provide meaningful clinical information that can inform a label revision in the future, if warranted. We recommend that Pfizer be requested to develop and implement an effective plan to obtain complete and clinically meaningful information, such as hospital discharge summaries or copies of consultant's reports, for any new cases consistent with PGS or other severe local cutaneous reactions associated with fosphenytoin. In addition, expedited 15-day reporting is recommended for all US and foreign reports of PGS with fosphenytoin. We also recommend that Pfizer be asked to communicate pro-actively with responsible pharmacovigilance staff in the worldwide affiliate company offices located in countries where fosphenytoin is sold to assure that reports of serious unexpected adverse drug reactions are promptly reported to Health Authorities, including FDA.

It may also be desirable to review and update the Precautions section in the phenytoin USPI to more clearly describe the modifiable risk factors for patients developing PGS due to intravenous administration of phenytoin, as well as to consider an appropriate communication strategy for health professionals to minimize these risks.

OSE recommends follow-up with the FDA Office of Compliance to ensure the adequacy of Pfizer's postmarketing pharmacovigilance practices to identify any potential serious unexpected safety issues. After follow-up with the Office of Compliance has been completed, the issue of appropriate labeling to address possible occurrence and severity of soft tissue injury after fosphenytoin administration should be revisited.

7 APPENDICES

7.1 APPENDIX 1

Narrative Summaries of Eight (8) Spontaneous Reports of PGS or Severe Local Cutaneous Reactions (LCR) with Fosphenytoin Identified in Searches of the FDA AERS Safety Database:

1. ISR 3942116-X: A pharmacist (b) (6) reported that a one-day-old male developed extravasation after fosphenytoin 100mg/2mL (single dose) was administered on June 25, 2002 through a “peripheral vein.” The IV was stopped and Silvadene cream was applied to the lesion on the foot. No other information was provided.
2. ISR 4223551-1: A pharmacist (b) (6) reported that a physician notified her of a patient (age and gender not stated) who developed extravasation after receiving Cerebyx sometime prior to Oct 17, 2003. No other information was provided. This was considered an important medical event.
3. ISR 4618759-7: A pharmacist (b) (6) reported that a patient (age and gender not stated) experienced extravasation with redness and swelling at the site while receiving Cerebyx sometime prior to March 12, 2005. Cerebyx was stopped due to the events. This was considered an important medical event.
4. ISR 5113338-X: A pharmacist (b) (6) reported that a 34-year-old male developed a “red, hard, swollen and painful” arm extending from the “elbow to the fingertips” within 30 minutes after receiving Cerebyx 1 gm intravenous infusion in normal saline on Sept 6, 2006. The line had been started by EMS in the field. Cerebyx was administered at the hospital. While administering the IV infusion, “the drug infiltrated into the arms and extravasation occurred.” Medical history, concomitant medications, treatment and outcome of the events were not reported. This was considered an important medical event. *(Note: this is the same case as #7 in Appendix 2, Mfr Report #2006111007).*
5. ISR 5484058-7 (dup 5406600-4): A pharmacist (b) (6) reported that a 72 year-old-male with a history of liver disease developed “blisters on the right hand and dorsal forearm” and “purplish discoloration which darkened” after receiving 500 mg Cerebyx on July 11, 2007, followed by 100 mg eight hours later, for the treatment of subdural hematoma, subarachnoid hemorrhage and convulsions. The fingers were not affected. A wound consultant examined the patient on (b) (6). Treatment included debridement and hyperbaric treatment. Subsequent medication included IV Keppra which may have been administered through the same line. This was a Direct report and was classified as serious (required hospitalization). The patient’s chart included a notation of “PGS?” but no other information. The wound was reported to be “healing”. *(Note: this is the same case as #8 in Appendix 2, Mfr Report #2007062067).*
6. ISR 4121846-3: A pharmacist (b) (6) reported that an unknown patient was given fosphenytoin via intravenous infusion and developed discoloration of the skin which he referred to as “black glove syndrome” when the IV infiltrated. No other information was provided. *(Note: this is the same case as #6 in Appendix 2, Mfr Report #2002052928).*
7. ISR 3566977-1: A pharmacy student (b) (6) reported that a patient who was hospitalized for depression and psychosis developed purple glove syndrome, considered medically significant, after receiving intravenous fosphenytoin 600 mg on 20SEPT1999 after unspecified testing. Fosphenytoin was discontinued the same day. On 22SEPT1999

the patient developed purple glove syndrome. The patient recovered. Concomitant medications included lorazepam, phenytoin, potassium, fluvastatin, levothyroxine, citalopram, terbinafine, dexamethasone, carbamazepine, pentoxifylline, tocopherol, selenium, quetiapine, rofecoxib, sertraline, Myadec, and warfarin. No other information was provided. (*Note: this is the same case as #2 in Appendix 2, Mfr Report #001-0982-990045*).

8. ISR 3311714-9: A pharmacist (b) (6) reported that a 73-year-old male with a diagnosis of stroke and hypertension developed “a swollen arm from his wrist to elbow, with seven to eight blisters containing fluid” after receiving fosphenytoin 1.5 gm on (b) (6) for prophylactic treatment of seizures, followed by 100 mg fosphenytoin in D5NS with 20 mEq KCl every 8 hours, and “other unspecified medications”. Fosphenytoin was discontinued on (b) (6) when the arm swelling was noted. It was “unclear if infiltration occurred.” The pharmacist later reported that “the patient also experienced second degree burns to his right arm.” Treatment included Silvadene to the affected area. Concomitant medications included midazolam, furosemide, and mannitol. CT scan showed large intraparenchymal hematoma. Subsequent therapy included intravenous phenytoin. The patient was discharged to a nursing facility on (b) (6). His right arm was reported to be “healing slowly at that time.” No additional information was provided. (*Note: this is the same as Case #1 in Appendix 2, Mfr Report #001-0982-980025*).

7.2 APPENDIX 2

Narrative Summaries of Eight (8) Spontaneous Reports of Possible PGS with Fosphenytoin Identified by Sponsor in Searches of Pfizer Proprietary Postmarketing Safety Database:

1. Mfr Report #001-0982-980025: A pharmacist (b) (6) reported that a 73 year-old male with a diagnosis of stroke and hypertension developed “a swollen arm from his wrist to elbow, with seven to eight blisters containing fluid” after receiving fosphenytoin 1.5 gm on (b) (6) for prophylactic treatment of seizures, followed by 100 mg fosphenytoin in D5NS with 20 mEq KCl every 8 hours, and “other unspecified medications”. Fosphenytoin was discontinued on (b) (6) when the arm swelling was noted. It was “unclear if infiltration occurred.” The pharmacist later reported that “the patient also experienced second degree burns to his right arm.” Treatment included Silvadene to the affected area. Concomitant medications included midazolam, furosemide, and mannitol. CT scan showed large intraparenchymal hematoma. Subsequent therapy included intravenous phenytoin. The patient was discharged to a nursing facility on (b) (6). His right arm was reported to be “healing slowly at that time.” No additional information was provided. *(Note: this is the same case as #8 in Appendix 1, ISR 3311714-9 from FDA AERS database.)*
2. Mfr Report #001-0982-990045: A pharmacy student (b) (6) reported that an 83-year-old female who had been admitted to the hospital for “depression and psychosis” developed purple glove syndrome, considered medically significant, after receiving a single 600 mg dose of intravenous fosphenytoin on 20SEPT1999 after unspecified “testing” was done. Purple glove syndrome developed on 22SEPT1999. Concomitant medications included lorazepam, phenytoin, potassium chloride, fluvastatin, levothyroxine, citalopram, terbinafine, dexamethasone, carbamazepine, pentoxifylline, tocopherol, selenium, quetiapine, rofecoxib, sertraline, and warfarin. The patient was reported to recover, but no information was provided about the patient’s symptoms or appearance of the injection site, the treatment administered, or the time to resolution of the events. No other information was provided. *(Note this is the same case as #7 in Appendix 1, ISR 3566977-1, from FDA AERS database.)*
3. Mfr Report #001-0982-M0000027: A pharmacist (b) (6), (b) (6) reported that an adult patient (gender not reported) developed extravasation after a single dose of fosphenytoin 100 mg via intravenous piggyback on 20SEPT2000. The extravasation was characterized by “erythema, flushed, irritation, and pain.” Indication for treatment, medical history, and concomitant medications were not reported. The patient left the hospital against medical advice, and the outcome is not known. No additional information was provided.
4. Mfr Report #001-0982-M0000038: A pharmacist (b) (6) reported that a patient (age and gender not known) developed a “possible phlebitis” while receiving fosphenytoin in the Intensive Care Unit. The indication for therapy and dose were not reported. On 7DEC2000 the patient’s “IV infiltrated” during fosphenytoin administration. The next day the patient’s “skin was red and warm and looked like phlebitis”. Concomitant medications included nitroprusside. No additional information was provided.
5. Mfr Report #001-0982-M0100021: A pharmacist (b) (6), (b) (6) reported that a patient (age and gender not stated) developed “purple glove syndrome which was characterized by bruising up the hand similar to what occurs with intravenous Dilantin (phenytoin)” after receiving a dose of fosphenytoin. On follow up

the pharmacist stated that “upon further investigation there was no adverse event to report” and the “nurse manager states the patient had other non-Cerebyx related clinical problems.”

6. Mfr Report #2002052928: A pharmacist (b) (6) reported that an unknown patient (age and gender not stated) developed “discoloration of the skin” and “black glove syndrome” after infiltration of the patient’s intravenous line during administration of fosphenytoin (dose and indication not stated). No other information was provided. *(Note: this is the same case as #6 in Appendix 1, ISR 4121846-3, from FDA AERS database.)*
7. Mfr Report #2006111007: A pharmacist (b) (6) reported via a sales rep that a 34-year-old male experienced seizures on 6SEPT2006 and was taken via ambulance to the hospital. An intravenous line was started by EMS and fosphenytoin 1 gm was administered intravenously when he reached the hospital. The “drug infiltrated into the arms and extravasation occurred. The whole area from elbow to fingertips turned red, hard, swollen and painful. This happened in a span of 30 minutes.” Treatment and outcome of the events was not known. No additional information was provided. *(Note: this is the same case as #4 in Appendix 1, ISR 5113338-X, from FDA AERS database.)*
8. Mfr Report #2007062067: A pharmacist (b) (6) reported that a 72-year-old male experienced “purple glow syndrome” or “purple glove syndrome” and his “hands were purple which spread to midway of his arms, he developed 3 blisters (2 in hands and one in midway of his arm) which burst later” after receiving fosphenytoin 100 mg intravenous injection three times daily starting on 11JUL2007 (indication not stated). On 12JUL2007 he was given a bolus of 500 mg fosphenytoin. Fosphenytoin was discontinued on 13JUL2007 due to adverse events. The patient was reported to be recovering. Medical history, concomitant medications, and treatment of the events were not reported. No additional information was provided. *(Note: this is the same case as #5 in Appendix 1, ISR 5484058-7, dup 5406600-4, from FDA AERS database.)*

7.3 APPENDIX 3

Published Case Reports of Purple Glove Syndrome with Phenytoin (*listed in reverse chronological order*):

- Mahajan RP, Batra YK, Rajeev S. Intravenous phenytoin and percutaneous arterial cannulation: the purple-glove syndrome. *Eur J Anaesthesiol.* 2007 Oct; 24(10):900-1.
- Kirsch S, Bayard M, Darraj K. Distal upper extremity edema and discoloration. *Am Fam Physician.* 2007 Mar 15; 75(6):889-91.
- Chokshi R, Openshaw J, Mehta NN, Mohler E 3rd. Purple glove syndrome following intravenous phenytoin administration. *Vasc Med.* 2007 Feb; 12(1):29-31.
- Sonohata M, Asami A, Tsunoda K, Hotokebuchi T. Purple glove syndrome associated with intravenous phenytoin administration in a patient with severe mental and motor retardation. *J Orthop Sci.* 2006 Jul; 11(4):409-11.
- Bhattacharjee P, Glusac EJ. Early histopathologic changes in purple glove syndrome. *J Cutan Pathol.* 2004 Aug; 31(7):513-5.
- Endoh T, Miyake S. [A case of purple glove syndrome following an intravenous infusion of phenytoin] *No To Hattatsu.* 2001 Sep; 33(5):442-4.
- Yoshikawa H, Abe T, Oda Y. Purple glove syndrome caused by oral administration of phenytoin. *J Child Neurol.* 2000 Nov; 15(11):762.
- Cadenbach A, Röttger K, Müller MK. Purple glove syndrome. Severe soft tissue reaction following phenytoin infusion. *Dtsch Med Wochenschr.* 1998 Mar 13; 123(11):318-22.
- Helfaer MA, Ware C. Purple glove syndrome. *J Neurosurg Anesthesiol.* 1994 Jan; 6(1):48-9.
- Hayes AG, Chesney TM. Necrosis of the hand after extravasation of intravenously administered phenytoin. *J Am Acad Dermatol.* 1993 Feb; 28(2 Pt 2):360-3.
- Hanna DR. Purple glove syndrome: a complication of intravenous phenytoin. *J Neurosci Nurs.* 1992 Dec; 24(6):340-5.
- Spengler RF, Arrowsmith JB, Kilarski DJ, Buchanan C, Von Behren L, Graham DR. Severe soft-tissue injury following intravenous infusion of phenytoin. Patient and drug administration risk factors. *Arch Intern Med.* 1988 Jun; 148(6):1329-33. Comment in: *Arch Intern Med.* 1989 Aug; 149(8):1905.
- Earnest MP, Marx JA, Drury LR. Complications of intravenous phenytoin for acute treatment of seizures. Recommendations for usage. *JAMA.* 1983 Feb 11; 249(6):762-5.

7.4 APPENDIX 4

Published Observational Studies of Phenytoin and Fosphenytoin (*listed in reverse chronological order*)

- Swadron SP, Rudis MI, Azimian K, Beringer P, Fort D, Orlinsky M. A comparison of phenytoin-loading techniques in the emergency department. *Acad Emerg Med.* 2004 Mar; 11(3):244-52.
 - Dept of Emergency Medicine, Keck School of Medicine, UCLA
 - OBJECTIVES: To compare the effectiveness of three phenytoin-loading techniques. METHODS: Patients with subtherapeutic phenytoin concentrations who presented within 48 hours of a seizure were randomized to receive either 20 mg/kg of oral phenytoin (PO), divided in maximum doses of 400 mg every two hours, 18 mg/kg of intravenous phenytoin (IVP) at an initial infusion rate of 50 mg/min, or 18 mg/kg (phenytoin equivalents) of intravenous fosphenytoin (IVF) at an initial infusion rate of 150 mg/min. RESULTS: A total of 45 patients were enrolled: 16 in the PO group, 14 in the IVP group, and 15 in the IVF group. The times required to reach therapeutic drug concentrations were (mean +/- standard deviation [SD]) 5.62 +/- 0.28 hours, 0.24 +/- 0.3 hours, and 0.21 +/- 0.28 hours, respectively. A total of 17, 27, and 32 adverse drug events were observed in the PO, IVP, and IVF groups, respectively, with significantly fewer events in the PO group ($p = 0.02$, $p = 0.01$). No significant difference was found between the numbers of necessary adjustments to the infusions in the two IV groups. The average time to safe emergency department discharge was significantly shorter for the IV groups compared with the PO group ($p < 0.001$). CONCLUSIONS: Oral loading has fewer adverse drug events than either IV loading method, but its use may be limited when therapeutic concentrations are required quickly. Although IVF loading is faster, from an adverse-drug event perspective, no advantage of IVF over IVP was apparent.
- Appleton RE, Gill A. Adverse events associated with intravenous phenytoin in children: a prospective study. *Seizure.* 2003 Sep; 12(6):369-72.
 - Dept of Neurology and Dept of Pharmacy, Royal Liverpool Children's Hospital, UK
 - A prospective study was undertaken to assess the type and frequency of adverse side-effects following the use of intravenous phenytoin in children. Twenty-two children received a total of 100 doses over a 10-month period. Six patients (27%) experienced one or more side-effects, including extravasation of the drug, hypotension and cardiac arrhythmia. No patient developed skin necrosis, including the 'purple glove syndrome'. Recovery from all adverse side-effects was spontaneous and complete. It is possible that some or all of these side-effects may have been caused by an excessive rate of infusion of phenytoin or the saline 'flush' following administration of the drug. The overall frequency of side-effects was perhaps less than expected.
- Coplin WM, Rhoney DH, Rebuck JA, Clements EA, Cochran MS, O'Neil BJ. Randomized evaluation of adverse events and length-of-stay with routine emergency department use of phenytoin or fosphenytoin. *Neurol Res.* 2002 Dec; 24(8):842-8.
 - Dept of Neurology, Dept of Neurological Surgery, Dept of Emergency Medicine, Dept of Pharmacy, Detroit Medical Center, Detroit, MI
 - Intravenous phenytoin has come under increased scrutiny with the introduction of the prodrug, fosphenytoin. We evaluated adverse events and length-of-stay using parenteral the two drugs in routine emergency department use. Open-label randomization of phenytoin or fosphenytoin in 256 Emergency Department patients

prescribed 279 parenteral doses of a phenytoin-equivalent. All phenytoin was administered intravenously, and fosphenytoin was given intravenously or intramuscularly (physician preference). Adverse events and Emergency Department length-of-stay were recorded; re-presentation to the Emergency Department within three months was reviewed for evidence of the purple glove syndrome. Nonparametric statistics were used to analyze the data. Seventy-seven patients received phenytoin and 202 fosphenytoin; 28 (10.0%) received intramuscular fosphenytoin. The mean phenytoin-equivalent dose was similar between the groups. Eighteen patients required reduction in infusion rates because of an adverse event (phenytoin = 6.5%, fosphenytoin = 6.4%; OR 0.9, 95% CI 0.4 2.6; $p = 1.0$). Adverse events occurred with similar frequency (phenytoin 9.1%, fosphenytoin 15.8%; OR 0.7, 95% CI 0.3 1.4; $p = 0.3$). The most common events were: pruritis, pain on infusion, and paresthesias. One patient developed hypotension (fosphenytoin); there were no other serious adverse events, including phlebitis. Median Emergency Department length-of-stay was 6.7 h for phenytoin and 5.7 h for fosphenytoin ($p = 0.6$). In routine Emergency Department use, our data do not support formulary conversion from phenytoin to fosphenytoin, based on the incidence of adverse events or Emergency Department length-of-stay.

- O'Brien TJ, Meara FM, Matthews H, Vajda FJ. Prospective study of local cutaneous reactions in patients receiving IV phenytoin. *Neurology*. 2001 Oct 23; 57(8):1508-10. Comment in: *Neurology*. 2002 Apr 9; 58(7):1134; author reply 1134.
 - Australian Centre for Clinical Neuropharmacology, Pharmacy Dept, and Dept of Medicine, University of Melbourne, Australia.
 - The authors prospectively examined the occurrence of subacute local cutaneous reactions (LCR) in patients receiving IV phenytoin over a 12-month period at a general hospital. LCR were detected in 29 of 115 patients (25.2%; 22 mild and seven moderate). All resolved within 3 weeks. Patients with LCR were older (median 68 versus 54.5 years, $p = 0.004$), were more likely to be in a general ward (86% versus 66%, $p = 0.04$), and had larger catheters (median 16 G versus 18 G, $p = 0.05$). The authors conclude that LCR are common in routine hospital practice, but are generally mild and benign.
- Burneo JG, Anandan JV, Barkley GL. A prospective study of the incidence of the purple glove syndrome. *Epilepsia*. 2001 Sep; 42(9):1156-9.
 - UAB Epilepsy Center, Univ of Alabama; Dept of Pharmacy, and Dept of Neurology, Henry Ford Health System and Case Western Reserve Univ, Detroit, MI
 - PURPOSE: Phenytoin (PHT) has been widely used intravenously for the treatment of seizures since 1956, and for many years, it has been considered first-line therapy for status epilepticus. It is routinely administered intravenously in emergency departments and hospitals for patients who have had isolated seizures and for many patients undergoing neurosurgical procedures who are unable to receive oral medication. Adverse reactions from PHT have been widely studied for years, but in the past decade, new adverse reactions have been identified. One of these adverse reactions is the purple glove syndrome (PGS), characterized by edema, discoloration, and pain distal to the site of i.v. administration of PHT. Because there have been no prospective reports of the incidence of PGS, the objective of the study was to report the incidence of this syndrome. METHODS: We enrolled 179 consecutive exposures to i.v. PHT at Henry Ford Hospital. Distal portions of the upper extremities were examined and digitally photographed by one of the authors (J.G.B.). The photos were blindly evaluated by the third author (G.L.B.) for PGS. Demographic and pertinent

medical history was recorded for all patients, and outcome for those who experienced PGS was recorded. Associations between PGS, demographic, and medical history information were assessed. RESULTS: In only three of the 179 exposures did PGS develop. In both patients, the severity of the clinical picture was mild and did not require prolonged hospitalization or specialized treatment. CONCLUSIONS: PGS is an infrequent and mild adverse effect of i.v. PHT administration.

- Johnson J, Wrenn K. Inappropriate fosphenytoin use in the ED. *Am J Emerg Med.* 2001 Jul; 19(4):293-4.
 - Dept of Emergency Medicine, Vanderbilt Univ, Nashville, TN
 - The objective of the study was to evaluate how often intravenous (IV) fosphenytoin is used when oral phenytoin loading is possible. The methods included a retrospective chart review of all patients receiving IV fosphenytoin in the emergency department. We prospectively derived criteria that identify patients with seizures who could receive oral fosphenytoin loading (awake on arrival, alert, no emesis, and lack of endotracheal intubation, repeated seizures, or status epilepticus after arrival). The setting of the study was at an urban, university hospital emergency department with an annual census of 55,000 patients. The outcomes included the number of patients receiving IV fosphenytoin who could have received oral phenytoin loading. From February 1997 to June 1999, 55 patients received IV fosphenytoin. Thirty of these patients (55%, 95% confidence interval 41%-68%) were felt to have received fosphenytoin appropriately. The remaining 25 (45%, 95% confidence interval 32%-59%) patients could have been loaded orally with phenytoin. In a single institution, fosphenytoin administration is inappropriate almost half the time. Oral phenytoin loading is less expensive and safe.
- O'Brien TJ, Cascino GD, So EL, Hanna DR. Incidence and clinical consequence of the purple glove syndrome in patients receiving intravenous phenytoin. *Neurology.* 1998 Oct; 51(4):1034-9. Comment in: *Neurology.* 1998 Oct; 51(4):942-3. *Neurology.* 1999 Oct 22; 53(7):1611-2.
 - Dept of Neurology, Mayo Clinic, Rochester, MN
 - OBJECTIVE: To determine the incidence, risk factors, and long-term sequelae of the purple glove syndrome (PGS) in hospital patients receiving IV phenytoin. BACKGROUND: PGS is a poorly understood, potentially serious local complication of IV phenytoin administration characterized by progressive distal limb edema, discoloration, and pain. METHODS: The pharmacologic records of the Mayo Foundation hospitals were reviewed to identify 179 consecutive patients who had IV phenytoin ordered during a 3-month period. Their hospital records were then reviewed to confirm IV phenytoin treatment, the frequency of PGS (defined as the progressive development of edema, discoloration, and pain in the limb after administration of IV phenytoin), and the outcome of PGS. RESULTS: A total of 152 patients received IV phenytoin, and nine (5.9%) developed PGS. PGS patients received a greater median initial dose of phenytoin, total 24-hour dose, and total number of doses (all $p < 0.05$). In addition, the median age of the PGS patients was older, their infusion was more often given for acute seizures, it was less likely to be administered in the operating room, and the length of their hospital stay was longer (all $p < 0.05$). One patient required surgical therapy, and all other patients resolved within 3 weeks with conservative management. CONCLUSIONS: PGS is not rare and elderly patients and individuals receiving large, multiple doses are particularly at risk. This iatrogenic complication may be preventable by substituting fosphenytoin for IV phenytoin.

- Boucher BA, Feler CA, Dean JC, Michie DD, Tipton BK, Smith KR Jr, Kramer RE, Young B, Parks BR Jr, Kugler AR. The safety, tolerability, and pharmacokinetics of fosphenytoin after intramuscular and intravenous administration in neurosurgery patients. *Pharmacotherapy*. 1996 Jul-Aug; 16(4):638-45.
 - Department of Clinical Pharmacy, University of Tennessee, Memphis, USA.
 - STUDY OBJECTIVE: To evaluate the safety, tolerability, and pharmacokinetic profile of fosphenytoin, a water-soluble phenytoin prodrug, after intramuscular and intravenous administration. DESIGN: Open-label study of intramuscular administration, and double-blind, randomized study of intravenous administration. SETTING: Six and ten hospitals throughout the United States for the intramuscular and intravenous multicenter studies, respectively. PATIENTS: Neurosurgical patients who required anticonvulsant prophylaxis or treatment. INTERVENTIONS: In the intramuscular study, 118 patients received loading doses ranging from 480-1500 mg phenytoin equivalents (PE) and daily maintenance doses ranging from 130-1250 mg PE for 3-14 days. In the intravenous study, 88 patients received fosphenytoin and 28 received phenytoin sodium for 3-14 days. RESULTS: Intramuscular fosphenytoin was safe and well tolerated, with no irritation found for 99% of all injection site evaluations. Adverse events associated with the drug occurred in 9% of patients, commonly those typical of the parent drug. For intravenous treatment, the frequency of mild irritation at the infusion site was significantly lower in the fosphenytoin group (6%) than in the phenytoin group (25%, $p < 0.05$). Reductions in infusion rates were required in 17% and 36% of fosphenytoin and phenytoin recipients, respectively. No significant difference was observed relative to adverse events or seizure frequency between the groups. CONCLUSION: Fosphenytoin can be administered intramuscularly and intravenously in neurosurgical patients to achieve and maintain therapeutic phenytoin concentrations for up to 14 days. Both routes are safe and well tolerated. Intravenous fosphenytoin is significantly better tolerated than intravenous phenytoin sodium in this patient subset.
- Spengler RF, Arrowsmith JB, Kilarski DJ, Buchanan C, Von Behren L, Graham DR. Severe soft-tissue injury following intravenous infusion of phenytoin. Patient and drug administration risk factors. *Arch Intern Med*. 1988 Jun; 148(6):1329-33. Comment in: *Arch Intern Med*. 1989 Aug; 149(8):1905.
 - Epidemiology Program Office, Centers for Disease Control, Atlanta
 - From April 8, 1982, through June 1984, 11 patients in a single hospital experienced 17 episodes of limb edema and discoloration after the intravenous (IV) administration of phenytoin sodium (Dilantin). One patient required a below-the-elbow amputation; all other patients recovered. No single drug lot was implicated. A case-control study was performed using three controls for each case; controls received IV infusions of phenytoin and were hospitalized close in time to the case patients. Compared with controls, patients with reactions were more often female and elderly and had underlying cardiovascular disease. Affected patients also received phenytoin through an IV catheter smaller than 20 gauge (50% vs 6%), at a rate greater than 25 mg/min (63% vs 19%), and in two or more IV infusions of phenytoin given "IV push" at the same site (81% vs 24%). High-risk patients require careful monitoring and stricter guidelines for the IV administration of phenytoin.

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/s/

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: October 4, 2010

To: Russell Katz, M.D., Director
Division of Neurology Products (DNP)

Through: Mark Avigan, M.D., C.M., Director
Cindy Kortepeter, Pharm.D., Safety Evaluator Team Leader
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Division of Pharmacovigilance I (DPV I)

From: Andrew Fine, Pharm.D., Safety Evaluator
Jasmine Gatti, M.D., Medical Officer
Division of Pharmacovigilance 1 (DPV1)

Subject: Purple Glove Syndrome (PGS)

Drug Name(s): Cerebyx (Fosphenytoin)
Dilantin (Phenytoin)

Application Type/Number: NDA 020450 ANDA 089521
ANDA 077481 ANDA 089744
ANDA 078126 ANDA 040573
ANDA 078137 ANDA 084307
ANDA 078277 ANDA 040781
ANDA 076886
ANDA 077989
ANDA 078158
ANDA 078417
ANDA 078765
ANDA 078052
ANDA 078476
ANDA 078736

Applicant/sponsor: Eisai Inc., Bedford, Apotex Inc., Wockhardt, Pharmforce,
Teva Parenteral, Baxter Healthcare, Hospira, Sun Pharma
Global, Hikma Farmaceutica, App Pharms, Akorn Strides,
Strides Arcolab

OSE RCM #: 2010-571

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EXECUTIVE SUMMARY

This review evaluates the medical literature, sponsor-submitted post-marketing data, and post-marketing reports in the Adverse Event Reporting System (AERS) for an association of Purple Glove Syndrome (PGS) with fosphenytoin and with intravenous (IV) phenytoin. Purple Glove Syndrome is characterized by the development of progressive distal limb edema, discoloration, and pain following peripheral administration of IV phenytoin, and possibly associated with phenytoin's chemically related pro-drug fosphenytoin. Risk factors for PGS include: large IV doses, infusion rate >25 mg/min, advanced age, infusing through a small vein, and underlying vascular disease. Complications from PGS are typically minor (with spontaneous recovery), but serious interventions (surgical revisions and amputations) have been reported.

The Division of Neurology Products (DNP) and the Office of Surveillance and Epidemiology (OSE) are jointly evaluating the safety profiles, including PGS, of IV phenytoin and fosphenytoin. Along with a companion OSE review also conducted by the Division of Pharmacovigilance (DPV-I), this review will aid the joint efforts of the Peripheral and Central Nervous System Drugs and the Drug Safety and Risk Management Advisory Committee members in determining what and whether regulatory decisions regarding intravenous (IV) phenytoin and/or fosphenytoin are warranted.

Several well-documented case reports of PGS associated with IV phenytoin are found in the literature, while no such reports exist for fosphenytoin. Additionally, observational and randomized studies evaluating IV phenytoin-associated PGS identify incidence rates from zero to 5.9%, describe risk factors for PGS, and report minor phenotypes. No such studies exist in the literature for PGS resulting from fosphenytoin administration.

Forty-three (43) AERS cases of PGS associated with IV phenytoin are included in this review, and in most circumstances confirm risk factors and typical outcomes (minor clinical adverse events) defined in the literature; although serious clinical outcomes (amputation) have been reported. This review also includes five (5) cases of PGS associated with fosphenytoin (4 cases from AERS and 1 unique case submitted by the sponsor), and describe a similar course of events as seen in the phenytoin cohort. Considering comparable market share (fosphenytoin currently has a slight edge), and discrepancies in PGS reporting with fosphenytoin (lack of compliance with specialty reporting requirements and potential of misclassification of cases), one cannot definitively conclude, based on AERS data, that the drugs appear to differ in the rate or severity of PGS events. However, the lack of fosphenytoin-specific information in the medical literature suggests that PGS is likely to occur more frequently with IV phenytoin than with fosphenytoin.

Based on the data included in this review, DPV-1 recommends the following actions:

- Revisions to the IV phenytoin label to include risk factors for Purple Glove Syndrome.
- Elevating PGS to a specific Warning/Precaution under the Structured Product Labeling (SPL) format or to a specific Precaution with its own section under the current labeling format for IV phenytoin.
- Label revision to the Post-marketing section of the fosphenytoin label to state, “Reports of Purple Glove Syndrome (PGS) with fosphenytoin therapy have been identified.”
- Pharmacology/Toxicology reviews to shed light on a possible mechanism of Purple Glove Syndrome.
- All fosphenytoin sponsors, including Pfizer, should report all cases that include an adverse event in an extremity where fosphenytoin has been administered; these should be submitted as 15-day expedited reports, regardless of outcome and include follow-up information.
- Office of Compliance inspections of Pfizer’s foreign Adverse Drug Event (ADE) practices to ensure compliance with fosphenytoin special enhanced reporting requirements.

BACKGROUND

1.1 INTRODUCTION

This review of fosphenytoin or phenytoin-associated Purple Glove Syndrome (PGS) evaluates three main data streams: the Adverse Event Reporting System (AERS) data, sponsor-submitted post-marketing data, and the medical literature. The Division of Neurology Products (DNP) and the Office of Surveillance and Epidemiology (OSE) are jointly evaluating the safety profiles, including PGS, of intravenous (IV) phenytoin and fosphenytoin. Along with other OSE reviews¹, and notably a companion DPV-I document,² this review will aid the joint efforts of the Peripheral and Central Nervous System Drugs and the Drug Safety and Risk Management Advisory Committee members in determining what and whether regulatory decisions regarding intravenous phenytoin and/or fosphenytoin are warranted.

By evaluating AERS data, sponsor data, and the medical literature, this review is designed to: 1) determine if PGS occurs with fosphenytoin, and 2) describe the characteristics of phenytoin PGS cases.

This review also serves as an updated analysis to two previous OSE drug safety reviews that evaluated cases of PGS in association with IV phenytoin or fosphenytoin (Section 1.2.1).^{3,4} Synopses of the prior OSE safety reviews are incorporated into this document.

Purple Glove Syndrome is the development of progressive distal limb edema, discoloration, and pain following peripheral IV administration of phenytoin.⁵ Specifically PGS occurs in three stages: 1) dark-purple discoloration around the IV-site 2-12 hours after infusion; 2) increasing edema and discoloration spreading distally 12-24 hours post-infusion; 3) gradual resolution over days to weeks. With a prevalence ranging from zero to 5.9% (based on retrospective and prospective observational studies and randomized studies), the exact mechanism for PGS is poorly understood, but descriptions range from an interstitial tissue reaction to extravasation.^{5,6,7} If detected early, this reaction can resolve spontaneously with minimum sequelae, but severe outcomes (skin

¹ Conducted by DPV-I, the Division of Medication Errors and Prevention (DMEPA), and the Division of Epidemiology (DEPI). OSE RCM# 2010-571. October 2010.

² Gatti JC, Fine A. Adverse effects and current clinical considerations for use of phenytoin versus fosphenytoin, excluding Purple Glove Syndrome. OSE RCM# 2010-571. 4 October 2010.

³ Phelan K, Pamer CA. Purple Glove Syndrome. OSE RCM# 2007-1332. 9 July 2008.

⁴ Gelperin K. Purple Glove Syndrome. OSE RCM#2007-1332. 26 November 2008

⁵ O'Brien TJ, Cascino GD, So EL, Hanna DR. Incidence and clinical consequences of the purple glove syndrome in patients receiving intravenous phenytoin. *Neurology* 1998; 51:1034-39.

⁶ Burneo JG, Anandan JV, Barkley GL. A prospective study of the incidence of the purple glove syndrome. *Epilepsia* 2001;42: 1156-59.

⁷ Coplin WM, Rhoney DH, Rebuck JA, Clements EA, Cochran MS, O'Neil BJ. Randomized evaluation of adverse events and length-of-stay with routine emergency department use of phenytoin or fosphenytoin. *Neurol Res.* 2002 Dec;24(8):842-8.

necrosis, ischemia), have resulted in fasciotomies, skin grafting, and limb amputations. Risk factors for PGS include advanced age, repeated dosing, acute seizure use, and large doses. Additionally, administering the anti-epileptic agent through larger veins, infusing at a rate less than 25 mg/min, and following an infusion with a normal saline flush can help prevent PGS.^{8,9} Treatment for PGS is often supportive in nature and includes limb elevation, compression, massage, and gentle heat.

1.2 REGULATORY HISTORY (PURPLE GLOVE SYNDROME)

Phenytoin (Dilantin) injection was approved in 1956 as an anticonvulsant. Fosphenytoin, the phenytoin pro-drug was approved in 1996 to treat epilepsy. Soon after Fosphenytoin approval, Parke-Davis discontinued marketing of their Dilantin injection in 1997. Currently, Baxter's IV phenytoin is the reference listed drug in the orange book. A comparison chart of phenytoin and fosphenytoin drug properties is located below in Table 1.

Table 1: Drug Properties: Intravenous Phenytoin versus Injectable Fosphenytoin¹⁰		
Characteristic	Phenytoin	Fosphenytoin ¹¹
pH	weak organic acid, alkaline pH 12	pH 8.6 to 9
Chemical properties	vehicle of ethanol and propylene glycol added to its carrier sodium hydroxide to enhance its solubility	phosphate ester pro-drug of phenytoin ¹²
Solubility, compatibility with parenteral fluids	<ul style="list-style-type: none"> cannot be mixed with IV fluids 	<ul style="list-style-type: none"> water soluble and compatible with most standard IV fluids, including dextrose.
Local Skin Effects	<ul style="list-style-type: none"> irritating to the skin tissue necrosis if extravasation 	<ul style="list-style-type: none"> designed to diminish the complications of i.v. phenytoin less local irritation
Mode of Administration	PO/IV	IV/IM
Doses (for Status Epilepticus in adults only)	Load IV: 10-15 mg/kg (or 250 mg,) over 10 mins. at max rate 50 mg/min, Maintain 100mg q 6-8 hr.	Load: IV 15-20 mg/kg PE (phenytoin equivalents: 1.5 mg fosphenytoin=1 mg phenytoin) over 5-7 mins. at max rate 50-150 mg/min. Maintain 4-6 mg PE/kg/day. IM dose: single day dose at 1-2 sites

Additionally, Purple Glove Syndrome was not noted in clinical trials for IV phenytoin or fosphenytoin; however clinical features (progressive pain, edema, and discoloration) may

⁸ Chokshi R, Openshaw J, Mehta NN, Mohler III E. Purple glove syndrome following intravenous phenytoin administration. *Vascular Medicine* 2007; 12:29-31.

⁹ Spengler RF, Arrowsmith JB, Kilarski DJ, Buchanan C, Von Behren L, Graham DR. Severe soft-tissue injury following intravenous infusion of phenytoin. Patient and drug administration risk factors. *Arch Intern Med.* 1988 Jun; 148(6):1329-33. Comment in: *Arch Intern Med.* 1989 Aug; 149(8):1905.

¹⁰ Gatti JC, Fine A. Adverse effects and current clinical considerations for use of phenytoin versus fosphenytoin, excluding Purple Glove Syndrome. OSE RCM# 2010-571. 4 October 2010.

¹¹ Eriksson K, Keranen T, Kalviainen R, Fosphenytoin. *Expert Opinion Drug Metab Toxicol.* 2009; 5 (6); 695-701

¹² Pro-drug=disodium phosphate ester of 3-hydroxymethyl- 5,5-diphenylhydantoin

have occurred without recognizing a diagnosis of PGS. In one trial that compared infusion-site effects between the two agents, pain and burning were reported at the infusion site for phenytoin, whereas systemic burning, pruritus, and paresthesias were reported after fosphenytoin administration.¹³

1.2.1 Prior Office of Surveillance and Epidemiology (OSE) Reviews

In 2008, two separate reviews of PGS were conducted by the Office of Surveillance and Epidemiology (OSE). The first review evaluated the AERS database for cases of PGS associated with phenytoin or fosphenytoin usage.¹⁴ The review included 4 possible cases of PGS with fosphenytoin, and 33 possible PGS cases with phenytoin (see Section 3.1). The review's conclusion stated, "these cases suggest PGS and clinically similar cutaneous lesions can occur with or without extravasation after intravenous administration of either phenytoin or fosphenytoin. AERS data do not clarify whether the drugs differ in the rate or severity of such events." Although the review included drug use data, reporting rates, which were not computed, are of questionable utility because there is a large gap (40 years) between approvals of the two agents. Such a difference in marketing time is often accompanied by different levels of spontaneous reporting.

The second OSE review, discussed the fosphenytoin sponsor's response to FDA queries (see Section 1.2.2, 2.3, and 3.2) regarding PGS, post-marketing data included in the aforementioned review (see Section 3.1), and the medical literature (see Section 3.3).¹⁵ According to the reviewer, many well documented published case reports and observational studies were found associating phenytoin with PGS. In contrast to the presence of literature reports surrounding IV phenytoin, no reports of fosphenytoin-associated PGS were identified in the medical literature.

1.2.2 Fosphenytoin: Sponsor's Assessment of Purple Glove Syndrome

In July 2008, Pfizer submitted its own systematic analysis of fosphenytoin-associated PGS.¹⁶ Using diagnostic categories, Pfizer identified eight cases (3 probable, 2 possible, 3 unlikely) of PGS in their database that were associated with fosphenytoin (also see Section 3.2). Many of the cases lacked essential clinical details, but according to Pfizer, their safety database "provided evidence of an association between fosphenytoin and PGS." Given the lack of comparative data in the literature and clinical trials and the inherent limitations of spontaneously reported adverse events, the sponsor also concluded that the relative incidence or reporting rates (based on drug utilization data) between the two drugs cannot be obtained. The DNP clinical review¹⁷ of the OSE documents and

¹³ Cerebyx-fosphenytoin sodium injection, solution. Parke-Davis Div of Warner Lambert LLC. Rev August 2001.

¹⁴ Phelan K, Pamer CA. Purple Glove Syndrome. OSE RCM# 2007-1332. 9 July 2008.

¹⁵ Gelperin K. Purple Glove Syndrome. OSE RCM#2007-1332. 26 November 2008.

¹⁶ General Correspondence-Analysis of Association between Purple Glove Syndrome with Fosphenytoin. Pfizer, Inc. 22 July 2008.

¹⁷ Marc Stone, MD, former Medical Officer in the Division of Neurology, FDA; completed 10/29/08.

sponsor submission, which concurred with the conclusion of the AERS review¹⁸ and sponsor submission, is located in Appendix A.

In February 2009, Pfizer submitted responses to three requests by DNP pertaining to the reporting of possible PGS with fosphenytoin (details in Appendix B).¹⁹ Highlights of DNP's requests include Pfizer's development and implementation of necessary policies and procedures pertaining to spontaneous reports suggestive of PGS. Pfizer intends to use the literature definition of PGS (see Section 1.1), with the trigger for potential cases being all fosphenytoin cases that contain any reference to any adverse event in the extremity where fosphenytoin was administered, to identify and expedite reporting of possible and probable cases to FDA. Of note, this initial filter (any adverse event in the extremity where fosphenytoin was administered) is a different modality used in Pfizer's July 2008 submission (Section 2.3 and Appendix C), but PGS's diagnostic categorization criteria is the same (Appendix D).

1.2.3 Fosphenytoin: Sponsor and the Office of Compliance

In the previously cited OSE AERS review²⁰, an assessment revealed that the majority of reports for fosphenytoin were direct reports, rather than manufacturer submitted reports. Overall, about 6% of all reports in the AERS database are sent directly to FDA and about 94% come through the manufacturer.²¹ However, between 1997 and 2008, 56% of all reports for fosphenytoin were direct reports. This observation brought into question the Adverse Drug Event (ADE) reporting practices of Pfizer (fosphenytoin's sponsor). In June 2009, the Office of Compliance (OC) initiated an investigation of Pfizer's New York Offices, and noted 11 observations pertaining to Adverse Event Reporting. Particularly, one observation addressed the implementation of specialty reporting requirements for three products, one being Cerebyx (fosphenytoin). Pfizer responded to the inspection observations (FDA Form 483) on September 9, 2009. Subsequently, in May 2010, the Office of Compliance issued an enforcement letter pertaining to their 2009 inspection and the Pfizer response with specific mention of fosphenytoin (See Appendix E).²² Based on this letter, Pfizer failed to adequately implement procedures for specialty reporting requirements for PGS as requested by DNP in December of 2008 for PGS.

Pfizer submitted a formal response to the OC enforcement letter on June 28, 2010.²³ Pfizer developed a Safety Job Aid, effective October 1, 2009, to document the handling of specialty reporting requirements for fosphenytoin. According to the sponsor, they have been 100% compliant with specialty reporting requirements between February and May 2010. Also, the necessary follow-up activities portion of the requirement has been undertaken since October 2009. Pfizer states, "no reports of PGS or local cutaneous

¹⁸ Phelan K, Pamer CA. Purple Glove Syndrome. OSE RCM# 2007-1332. 9 July 2008.

¹⁹ General Correspondence-Response to letter about purple glove syndrome. 13 February 2009.

²⁰ Phelan K, Pamer CA. Purple Glove Syndrome. OSE RCM# 2007-1332. 9 July 2008.

²¹ Roger Goetsch, OSE Regulatory Director.

²² Warning Letter NYK 2010-19. Pfizer, Inc. May 26 2010.

²³ Pfizer response to Pfizer Warning Letter NYL 2010-19. 28 June 2010.

reactions suggestive of PGS have been received since the implementation of SJA200-[Special Individual Case Safety Report Regulatory Commitments] in October 2009.” In addition to Pfizer’s response, the sponsor met with Compliance in August 2010 to further discuss ADE reporting issues.

1.3 PRODUCT LABELING (RELEVANT TO PURPLE GLOVE SYNDROME)

1.3.1 Phenytoin²⁴

PRECAUTIONS

General

Edema, discoloration, and pain of the distal limb (described as “purple glove syndrome”) have been reported following peripheral intravenous phenytoin sodium injection. This may or may not be associated with extravasation. Although resolution of symptoms may be spontaneous, skin necrosis and limb ischemia have occurred and required such interventions as fasciotomies, skin grafting, and amputation. Therefore, Phenytoin Sodium Injection should be administered as described above.

1.3.2 Fosphenytoin²⁵

Current product labeling does not mention Purple Glove Syndrome.

2 METHODS AND MATERIALS

2.1 INTRODUCTION

This section describes data sources utilized to identify and compare the relationship between phenytoin as well as between fosphenytoin and the development of Purple Glove Syndrome (PGS). Three primary resources were utilized. First the Adverse Event Reporting System (AERS) was used to search for cases of PGS with phenytoin OR with fosphenytoin use. Second, a sponsor (Pfizer) safety submission of PGS with fosphenytoin use was utilized to explore additional cases of PGS with Fosphenytoin. Third, the medical literature was searched for representation of PGS associated with IV phenytoin or fosphenytoin. Drug utilization data is also included to assess market share of each agent.

²⁴ Phenytoin Sodium injection, solution. Baxter Healthcare Corporation.

²⁵ Cerebyx-fosphenytoin sodium injection, solution. Parke-Davis Div of Warner Lambert LLC. Rev August 2001.

2.2 AERS SELECTION OF CASES

The AERS database was searched for possible cases of Purple Glove Syndrome (PGS) in association with phenytoin and fosphenytoin. The focus of this search was to capture additional cases of PGS since the previous AERS review discussed in Section 1.2.1 was completed, and to provide a cumulative total. The following search strategy was applied to IV phenytoin AND fosphenytoin:

- Each drug was searched using the lone MedDRA PT, “Purple Glove Syndrome.”
- All cases were text searched in an effort to identify additional cases of purple glove syndrome or other local infusion-related reactions that could be suggestive of PGS.
 - The following text search terms were used: “blu” (to capture blue or bluish), purple, finger, hand, foot, dusky, color (to capture discoloration), glove, “amputat” (to capture amputate or amputation), gangrene, skin, swollen, swell, edema, pain, lesion, infusion.
- ONLY eligible cases received between April 17, 2008 and June 8, 2010 were included.²⁶

Relevant cases of PGS were then analyzed to determine if cases met the following criteria:

1. Diagnosis of Purple Glove Syndrome
OR
2. Temporal relationship between drug administration and onset of symptoms + Bluish or purplish discoloration AND edema or pain at limb distal to injection + No alternative explanations for reported event.

This case definition is consistent with the one used in the previous OSE AERS review.²⁷ The PGS criteria used prior required, “cases reporting discoloration and another sign of PGS, such as edema, in a limb beginning after fosphenytoin or phenytoin administration and providing no alternative explanation.” Cases identified from the previous AERS review are also included in this analysis.

2.2.1 Fosphenytoin

On June 8, 2010, AERS was searched for cases of PGS with fosphenytoin. Only cases received between April 17, 2008 and June 8, 2010 were included in this updated analysis. Using the preferred term “Purple Glove Syndrome,” AERS was searched and retrieved zero relevant cases. The 63 fosphenytoin reports in AERS during this time frame were then text searched (see Section 2.2) to determine if any of the cases mention infusion-related or local reactions suggestive of PGS. Newly identified cases were then combined

²⁶ AERS cut-off date for prior OSE PGS review was April 17, 2008, therefore (to avoid duplicates) only relevant cases received after this date were included.

²⁷ Phelan K, Pamer CA. Purple Glove Syndrome. OSE RCM# 2007-1332. 9 July 2008.

with data (cases submitted to FDA prior to April 17, 2008) from the prior AERS analysis,²⁷ thus creating a cumulative case series.

2.2.2 Phenytoin

On June 8, 2010, AERS was searched for cases of PGS with phenytoin. During the April 17, 2008 and June 8, 2010 time frame, 1842 (172 for intravenous phenytoin) total²⁸ phenytoin reports were retrieved from AERS, and 11 were coded for PGS. The 172 IV reports were then text searched (see Section 2.2) to determine if any of the cases mention infusion-related or local reactions suggestive of PGS. Newly identified cases were then combined with data (cases submitted to FDA prior to April 17, 2008) from the prior AERS analysis, thus creating a cumulative case series.

2.3 SPONSOR SUBMISSION

This section details Pfizer's submission (introduced in Section 1.2.2) of an analysis of PGS with fosphenytoin.²⁹ The sponsor analysis was based on a review of Pfizer's safety database, usage data, clinical trial data, animal studies, and the literature. Of note, Pfizer's safety database contains cases of adverse events (AEs) reported spontaneously to Pfizer, cases reported from health authorities, cases published in the medical literature, and cases of serious AEs reported from clinical studies and Pfizer-sponsored marketing programs (solicited cases) regardless of causality. These events are reviewed by Pfizer on an ongoing basis.

In an effort to identify and analyze relevant cases, Pfizer's database was searched for all fosphenytoin **and** phenytoin cases reported worldwide from the international birth date (first international market approval) through 30 May 2008. This multiple step approach, described by Pfizer, is located in Appendix F.

2.4 LITERATURE SEARCH

This section details two literature searches. First, as included in a previous OSE review³⁰, PubMed was searched to identify published case reports and observational studies relevant to the occurrence of PGS with phenytoin or fosphenytoin. Additionally, on August 27, 2010, PubMed and Web of Science (from 1999 to 2010) and EMBASE (all years) were searched using the terms "purple glove syndrome," and "purple glove syndrome with phenytoin OR fosphenytoin." Case reports or studies not included in the initial OSE review were analyzed.

²⁸ All dosage forms.

²⁹ Response to FDA Query Regarding Purple Glove Syndrome and Cerebyx® (Fosphenytoin sodium). Systematic Analysis of Association between Purple Glove Syndrome and Fosphenytoin. Pfizer Global Pharmaceuticals. 22 July 2008.

³⁰ Gelperin K. Purple Glove Syndrome. OSE RCM#2007-1332. 26 November 2008.

2.5 DRUG UTILIZATION DATA

Drug Utilization data for IV phenytoin and fosphenytoin was provided by the Division of Epidemiology/Drug use analyst. The main source of information is Premier RxMarket Advisor™, which uses data derived from billing claims for patients who were admitted to and discharged from U.S. acute care hospitals, including patients who are admitted through emergency rooms. Two separate utilization reviews provide usage data for both agents from 2000-2009.^{31,32}

3 RESULTS

This section provides the results from three main data streams. First, AERS data for Purple Glove Syndrome in association with phenytoin or fosphenytoin is presented. Next, this section lists the results from Pfizer's submission of post-marketing reports of PGS with fosphenytoin. Finally, this section incorporates literature case reports and studies involving PGS with IV phenytoin OR fosphenytoin. Drug utilization data is also included in this section.

3.1 ADVERSE EVENTS CASES

3.1.1 FOSPHENYTOIN AND PURPLE GLOVE SYNDROME

On June 8, 2010, AERS was searched for cases of PGS with fosphenytoin between April 17, 2008 and June 8, 2010. Using the preferred term, "Purple Glove Syndrome," no relevant cases were identified and included in this review as possible cases.

In an effort to identify potential cases of PGS in AERS that were not MedDRA-coded as "Purple Glove Syndrome," an extensive narrative text search (see Section 2.2) was applied to all 63 fosphenytoin cases in AERS during the pre-specified time frame. Four cases³³ were identified as infusion-related reactions and further analyzed to determine if the event described is consistent with Purple Glove Syndrome. Three of these reports describe hypersensitivity (itching, shortness of breath, rash) following IV administration of fosphenytoin without any signs or symptoms of PGS. The remaining report described tingling that was temporally related to administration of other drugs (Xanax and Lortab), and not associated with PGS. Resultantly, AERS did not identify any cases of PGS following fosphenytoin use during the specified time frame.

Using the same search criteria, the 2008 AERS³⁴ review identified four possible cases of Purple Glove Syndrome. Combining the results from the prior review and this update,

³¹ Phelan K, Pamer CA. Purple Glove Syndrome. OSE RCM# 2007-1332. 9 July 2008.

³² Chai G. IV Phenytoin and Fosphenytoin Utilization Review. OSE RCM# 2010-571. 17 May 2010.

³³ ISR #'s 5715583, 5841149, 6005561, 6075640

³⁴ Phelan K, Pamer CA. Purple Glove Syndrome. OSE RCM# 2007-1332. 9 July 2008.

Table 2 below summarizes all known AERS cases of possible PGS associated with fosphenytoin.

Table 2. Characteristics of AERS Cases of Possible Purple Glove Syndrome Associated with Fosphenytoin Submitted between Fosphenytoin Approval in 1996 and June 2010. (N=4)

Characteristic (number of cases providing information)	Value (number of cases reporting each value)
Country (4)	U.S. (4)
Year FDA Received Report (4)	1999, 2003, 2006, 2007
Report type (4)	Direct (2), Periodic (1), Expedited (1)
Gender (3)	Male (2), Female (1)
Age (3)	34, 72, 83
Relevant medical history (1)	Patient taking hydrochlorothiazide, lisinopril, furosemide, carvedilol
Adverse event date (3)	1999, 2006, 2007
Reported local adverse event (4)	<ul style="list-style-type: none"> • hand dark purple, erythema, edema, pain, PGS (1) • skin discoloration, “black glove syndrome,” extravasation (1) • purplish discoloration, blisters, skin sloughing on hand and forearm but not fingers, PGS (1) • elbow to fingertips red, hard, swollen, painful, extravasation (1)
Treatment of adverse event (2)	<ul style="list-style-type: none"> • Debridement and hyperbaric treatment (1) • X-ray hand to rule out fracture (1)
Time from start of fosphenytoin to development of signs (3)	<ul style="list-style-type: none"> • 30 minutes (1) • 2 days (2)
Outcome (2)	<ul style="list-style-type: none"> • Improving at 5 days (1) • Improving at 2 weeks (1)
Fosphenytoin Indication (3)	Seizures (3)
Setting of fosphenytoin use (1)	Emergency room
Fosphenytoin dose (3)	<ul style="list-style-type: none"> • Single doses: 600mg (1), 1000mg (1) • Multiple Doses: 500mg, 100mg, 500mg over 2 days (1)
Administration method (3)	<ul style="list-style-type: none"> • IV push (1) • IV infusion (1) • IV nos* (1)
Extravasation information (2)	Extravasation reported (2)

*nos = not otherwise specified.

These four possible cases of PGS with fosphenytoin were identified in the original OSE review, and the best case summaries (n=2) of this series are described below. Complete narrative summaries for all (n=4) cases can be found in Appendix G (Numbers 1-4).

ISR# 3566977-1, U.S., Direct, 1999 (duplicate: ISR# 3381912-7, MFR# 001-0982-990045, U.S., Periodic, 1999.)

An 83-year-old female received one 600 mg dose of fosphenytoin by IV push to treat seizures. The injection site was not reported. The patient's oral phenytoin had been held that morning for "ECT." Two days later, nursing staff verbally noted a bruise and, the next day, an x-ray of the hand was taken to rule out fracture. The hand was dark purple with erythema, edema, and pain. Four days after discoloration was first noted, "neurology" diagnosed purple glove syndrome. Five days after discoloration was first noted, the color was improving on the top of the hand. Concomitant illness was major depression with psychotic features. Concomitant medications included lorazepam IV, phenytoin, triamterene/hydrochlorothiazide, terbinafine, pentoxifylline, fluvastatin, levothyroxine, warfarin, celecoxib, carbamazepine, sertraline, and quetiapine.

ISR# 5484058-7 (OSE follow-up) and ISR# 5406600-4, MFR# US-Pfizer Inc-2007062067, U.S., expedited, 2007

A 72-year-old male was hospitalized with syncope, subdural hematoma, convulsions, subarachnoid hemorrhage, and incoherence. He received 500 mg IV fosphenytoin. Eight hours later, he received 100 mg IV fosphenytoin and, the next day, he received 500 mg IV fosphenytoin. The injection site was "probably" in the right arm. Fosphenytoin was switched to IV levetiracetam because of insufficient phenytoin levels. Three or four days after the third dose of fosphenytoin, purplish discoloration and blisters on the patient's right hand were noted by nurses; although, restraints and a bandage over the IV site may have hidden earlier signs. The fingers were unaffected. The blisters opened and the skin sloughed. The area was debrided and treated hyperbarically and was healing 30 days after onset. "PGS?" appears in the patient's chart, but no diagnosis was given for the event. The patient had a history of liver disease and regular medications were hydrochlorothiazide, carvedilol, lisinopril, furosemide, and levothyroxine. The patient's regular medications included no anticonvulsants.

Additionally, when analyzing cases of Purple Glove Syndrome due to fosphenytoin administration, the author identified four (4) cases of serious local cutaneous reactions causally related to fosphenytoin. These cases describe local reactions ranging from phlebitis (n=1), to swollen arms and blisters (n=1), extravasation (n=1), to necrosis (n=2). Although these cases did not meet the pre-defined case criteria for Purple Glove Syndrome³⁵, their clinical details were appropriately included in the review. Complete narrative summaries of these four (4) local reactions are also found in Appendix G (Numbers 5-8).

3.1.2 PHENYTOIN AND PURPLE GLOVE SYNDROME

On June 8, 2010, an AERS search was conducted, using Purple Glove Syndrome as a preferred term, which resulted in 11 potential cases received between April 17, 2008 and June 8, 2010. After accounting for duplicates and excluding cases in which the diagnosis

³⁵ (Diagnosis of Purple Glove Syndrome) OR (Temporal relationship between drug administration and onset of symptoms + Bluish or purplish discoloration AND edema or pain at limb distal to injection + No alternative explanations for reported event.)

of PGS could not be confirmed, a total of 9 cases were identified as meeting the case definition from Section 2.2. Also, the 172 IV phenytoin reports identified in AERS were text searched according to methods described in Section 2.2, yielding one (1) additional case³⁶ for inclusion. The previous AERS review³⁷ identified 33 possible cases of Purple Glove Syndrome with phenytoin use between market approval and April 16, 2008. Combining the original analysis (n=33) with this update (n=10), 43 cases fit the case definition of PGS. Table 3 summarizes these cases.

Table 3. Characteristics of AERS Cases of Purple Glove Syndrome Associated with IV Phenytoin Submitted between the establishment of FDA’s Post-marketing Database and June 2010 (N=43)

Characteristic (number of cases providing information)	Value (number of cases reporting each value)
Country (43)	U.S. (34), Foreign (9)
Year FDA Received Report (43)	1998 (5), 1999 (4), 2000 (7), 2001 (5), 2002 (3), 2003 (2), 2004 (2), 2006 (3), 2007 (1), 2008 (3), 2009 (7), 2010 (1)
Report type (43) (Not mutually exclusive)	Direct (13), Periodic (7), Expedited (17), Literature (8)
Gender (41)	Male (19), Female (22)
Age (37)	<ul style="list-style-type: none"> • Range: 3 – 88 years • Mean: 54 years • Median: 59 years
Relevant medical history (15) (Not mutually exclusive)	<ul style="list-style-type: none"> • Hypertension (7) • Stroke/CVA/cerebral aneurysm (5) • Vasculitis (1) • Peripheral artery disease (2) • Arterial insufficiency (1) • Cardiomegaly (1) • Congestive heart failure (1) • Cardiac arrest (1) • Hyperlipidemia (1) • Diabetes (2)
Reported local adverse event (43) (not mutually exclusive)	<ul style="list-style-type: none"> • Purple Glove/hand Syndrome (25) • Discoloration (purple, blue, black, or unspecified) (27) • Suspected/looks like purple glove syndrome (3) • Edema/swelling (23) • Redness/erythema (9) • Pain/tenderness (9) • Blistering (5)

³⁶ ISR 6186190

³⁷ Phelan K, Pamer CA. Purple Glove Syndrome. OSE RCM# 2007-1332. 9 July 2008.

	<ul style="list-style-type: none"> • Necrosis (3) • Cellulitis (3) • Cold finger(s) or thumb (3) • Local warmth (2) • Cutaneous flushing along vein and petechiae around (1) • Injection site (1) • Bullous lesions (1) • Rash (1) • Reduce range of motion (1) • Ecchymosis of right hand, not necrotic. (1) • Mild limb ischemia (1) • Hand weakness (1) • Brisk capillary refill (1) • Lack of capillary refill (1) • High resistance to flow in radial and ulnar arteries and small thrombus in left radial artery (1)
Treatment of adverse event (21) (Not mutually exclusive)	<ul style="list-style-type: none"> • Elevation (15) • Warmth (7) • Massage/physical therapy (2) • Cooling (1) • Monitor radial pulse (1) • Rule out occlusion (1) • Surgical revision/consult (2) • Hyperbaric treatments (1) • Fasciotomy (1) • Rule out broken bones (1) • Lymph drainage (1) • Debridement and skin graft (1) • Fasciotomy considered (1) • Drugs: antibiotic (4), anti-inflammatory drugs (2), neostigmine (1), hydrocortisone (1), diphenhydramine (1), heparin (1), hyaluronidase (1), brachial plexus block with bupivacaine (1)
Time from start of phenytoin to development of signs (24)	<p>Range: during IV to 6 days</p> <p>Median: 12 hours</p>
Outcome (26)	<ul style="list-style-type: none"> • Recovered (15) • Improving at time of report (5) • Ongoing at time of death by other cause (2) • Amputation (1) • Resolved with unspecified sequelae caused by hemodynamic instability and resulting vasoconstriction (1) • Hospitalization (1)

	<ul style="list-style-type: none"> • Compartment Syndrome (1) 	
Time to resolution (9)	Range: 12 hours to 3 months	
Indication for phenytoin use (29)	<ul style="list-style-type: none"> • Seizures NOS* (20) • Status Epilepticus (3) • Acute Seizure (2) • Seizure Prophylaxis (4) 	
Setting of phenytoin use (20)	Emergency room (5), Intensive care unit (3), hospital (12)	
Phenytoin dose (mg/day on first day-may include loading dose) (28)	Range: 200 mg to 1230 mg Mean: 635 mg Median: 800 mg	<u>Labeled dosage</u> *status epilepticus: 10 to 15 mg/kg then 100 mg every 6 to 8 hours *neurosurgery seizure prophylaxis: 100 to 200 mg every 4 hours
Administration rate (7)	15 mg/min (1) 17 mg/min (1) <20 mg/min (1)	25 mg/min (2) 33 mg/min (1) <50 mg/min (1)
Number of IV doses (26)	one (17) two or more (9)	
Needle Gauge (5)	18 gauge (1), 20 gauge (4)	
Vehicle (9)	Normal saline (8) 5% Dextrose and half-normal saline (1)	
Saline Flush (3) (not mutually exclusive)	Before phenytoin administration (2) After phenytoin administration (2)	

*NOS = not otherwise specified.

Forty-three cases were identified in AERS, 33 from the previous AERS review, and 10 from the current AERS update. The best case summaries (n=3) of the recent series, the single case of amputation (from the previous AERS review), and two additional best case representatives from the previous AERS review are detailed in Appendix H.

3.2 SPONSOR SUBMISSION

On July 22, 2008, Pfizer submitted an analysis that evaluated spontaneous safety reports, usage data, clinical trial data, animal data, and the literature in an effort to determine if an association exists between fosphenytoin and the development of PGS. The search strategy applied to the sponsors' safety database, outlined in Section 2.3 and Appendix F, was applied to fosphenytoin AND phenytoin. The search yielded 266 cases (251 phenytoin and 16 fosphenytoin³⁸) that required closer analysis. Of these 266 cases, 126 were excluded, and the sponsor diagnostically categorized (based on the described local reaction) the resultant 140 cases (132 phenytoin and 8 fosphenytoin) as probable, possible, or unlikely Purple Glove Syndrome. Categorization criteria implemented by the sponsor is explained in Appendix D.

³⁸ One report listed fosphenytoin AND phenytoin as causative products.

The detailed categorization of the 132 phenytoin cases is not described in this review because the primary purpose of Pfizer's submission was to identify cases of PGS in conjunction with fosphenytoin administration. Appendix I describes the 8 categorized cases (Probable (4), Possible (1), Unlikely (3), all domestic) of PGS with fosphenytoin use.

Based on Appendix I, five cases are classified as probable or possible. Four of these cases (Case numbers 1-4 in Appendix I) were identified in AERS and included in Section 3.1.1 and Appendix G (case numbers 1-4), thus yielding one new case. This new case (Case #5, Appendix I) is therefore included in this review. The three remaining "unlikely" PGS cases describe infusion-related reactions, "extravasation characterized by erythema, flushed, irritation, and pain" AND "possible phlebitis," respectively (see Appendix I for case details).

3.3 LITERATURE SEARCH

This section includes literature results (case reports, observational studies) for Purple Glove Syndrome (PGS) associated with IV phenytoin or fosphenytoin administration. Included in this section, as mentioned in Section 2.4, are literature results from a prior OSE review³⁹ and updated literature findings published after the completion of the prior review.

3.3.1 Published Case Reports of Purple Glove Syndrome

The original review identified several well documented published case reports of PGS with IV phenytoin and no published reports of PGS or other severe injection site reactions with fosphenytoin. Full references of these findings are located in Appendix J.

The updated literature search was conducted on August 27, 2010 and identified three (3) additional case reports of PGS with IV phenytoin use and none for fosphenytoin. The characteristics of these three case reports^{40,41,42,43} and the collection identified in the previous OSE review are described in Appendix K. Notably, this collection includes a single published case of PGS following oral administration (overdose in a child) of phenytoin.⁴⁴

³⁹ Gelperin K. Purple Glove Syndrome. OSE RCM#2007-1332. 26 November 2008.

⁴⁰ Warnecke I, et. al. Purple Glove Syndrome: a case report. *Handchir Mikrochir Plast chir.* 2010 Aug; 42(4): 260-2. (abstract only currently available, undergoing copyright clearance).

⁴¹ Keane M.G., Shirazi H., Marsh P. and Khushal A. Purple Glove Syndrome following intravenous phenytoin infusion. *British Journal of Surgery* 2009 96:1065.

⁴² Santoshi J, et al. Purple Glove Syndrome: a case report. *Hand surgeons and physicians be aware. Journal of Plastic, Reconstructive and Aesthetic Surgery.* 2009; XX: 1-3.

⁴³ Singh G, Cherian V, Thomas B. Low-concentration, continuous brachial plexus block in the management of Purple Glove Syndrome: a case report. *Journal of Medical Case Reports* 2010; 4 (48): 1-4.

⁴⁴ Yoshikawa H, Abe T, Oda Y. Purple glove syndrome caused by oral administration of phenytoin. *J Child Neurol.* 2000 Nov;15(11):762.

3.3.2 Published Studies of Purple Glove Syndrome

The original OSE Review identified epidemiological and clinical studies (case-control, retrospective and prospective observational studies and prospective randomized studies) describing PGS associated with IV phenytoin. No such studies were identified in the literature for fosphenytoin. Appendix J includes abstracts for each study found in the published literature and included in the prior OSE Review. The updated literature analysis (studies published between 2008 and 2010) failed to identify additional published studies for IV phenytoin and PGS, or any studies related to fosphenytoin and PGS.

Using data included in the original review (and Appendix J), several incidence estimates of phenytoin-associated PGS were identified based on the literature studies. When defined as a “progressive development of edema, discoloration, and pain in the limb” after intravenous administration, incidence ranged from zero to 5.9%.^{45,46,47} Different study designs were used to capture this incidence range. These are detailed below in Table 4 (with complete abstracts in Appendix J).

⁴⁵ O'Brien TJ, Cascino GD, So EL, Hanna DR. Incidence and clinical consequence of the purple glove syndrome in patients receiving intravenous phenytoin. *Neurology*. 1998 Oct;51(4):1034-9. Comment in: *Neurology*. 1998 Oct;51(4):942-3. *Neurology*. 1999 Oct 22;53(7):1611-2.

⁴⁶ Burneo JG, Anandan JV, Barkley GL. A prospective study of the incidence of the purple glove syndrome. *Epilepsia*. 2001 Sep;42(9):1156-9.

⁴⁷ Coplin WM, Rhoney DH, Rebuck JA, Clements EA, Cochran MS, O'Neil BJ. Randomized evaluation of adverse events and length-of-stay with routine emergency department use of phenytoin or fosphenytoin. *Neurol Res*. 2002 Dec;24(8):842-8.

Table 4: Characteristics of Studies Evaluating Purple Glove Syndrome Associated with IV Phenytoin.

	O'Brien, et al	Burneo, et al	Coplin, et al
<i>Study Design</i>	Retrospective Observational	Prospective Observational	Prospective Randomized
<i>Study Population</i>	IV Phenytoin, n=152	IV Phenytoin, n=157	IV Phenytoin, n=77 Fosphenytoin, n=202
<i>PGS Incidence</i>	5.9%	1.7%	0%
<i>Clinical Phenotype</i>	N=9 <ul style="list-style-type: none"> Resolved within 2 weeks without intervention (8). Required skin grafts (1) 	N=2 <ul style="list-style-type: none"> Resolved within 2 weeks (1). Resolved within 4 weeks (1). Warm heat or compresses applied (2) 	N/A
<i>Risk Factors</i>	<ul style="list-style-type: none"> Advanced Age Large doses Catheter size larger than 20G 	<ul style="list-style-type: none"> Female Large doses Catheter size 22-G 	N/A
<i>Comments</i>	<ul style="list-style-type: none"> Only 5 cases affected hand. Not recognized by treating MD in ~50% of cases. Information abstracted from hospital, nursing, and medical records Contradicts earlier finding that catheter size smaller than 20G is a risk factor.⁴⁸ 	<ul style="list-style-type: none"> Upper extremities were photographed and evaluated by blinded investigator. Mean age of participants was 57 years, 2 cases of PGS in 65 year-old and 33 year-old. 	<ul style="list-style-type: none"> Compared adverse events and ED LOS⁴⁹ Records were reviewed prospectively to identify patients that returned to ED. IV phenytoin was administered under specific guidelines.⁵⁰ Phenytoin patients more likely to have vein burning. Fosphenytoin patients more likely to have pruritus.

In contrast to the available data with IV Phenytoin, without identified studies in the literature, incidence estimates of PGS with fosphenytoin are unattainable.

3.4 DRUG UTILIZATION

This section describes drug utilization and average cost data for fosphenytoin and phenytoin. A companion review of utilization of these agents from the Division of Epidemiology (DEpi) provides additional information.⁵¹ Utilization data is based on projected number of U.S. hospital discharges for phenytoin or fosphenytoin between 2000-2009.^{51,52} The number of patients prescribed (based on the hospital discharge data)

⁴⁸ Spengler RF, Arrowsmith JB, Kilarski DJ, Buchanan C, Von Behren L, Graham DR. Severe soft-tissue injury following intravenous infusion of phenytoin. Patient and drug administration risk factors. Arch Intern Med. 1988 Jun; 148(6):1329-33. Comment in: Arch Intern Med. 1989 Aug; 149(8):1905.

⁴⁹ Length-of-stay

⁵⁰ Mixed in 50 ml normal saline, IV site was tested with saline flush, infused using an in-line filter and at a rate of 20 mg/min, and flushed with saline following administration.

⁵¹ Chai G. IV Phenytoin and Fosphenytoin Utilization Review. OSE RCM 2010-571. 4 October 2010.

⁵² Phelan K, Pamer CA. Purple Glove Syndrome. OSE RCM# 2007-1332. 9 July 2008.

fosphenytoin or IV phenytoin, and the corresponding annual market share, is described in Table 5 below.

Table 5. Phenytoin and Fosphenytoin Parenteral Projected U.S Hospital Discharges and Market Share Percentages 2000-2009

<u>Phenytoin</u>		Year	<u>Fosphenytoin</u>	
<i>Share %</i>	<i>Proj Discharges*</i>		<i>Proj Discharges*</i>	<i>Share %</i>
65.7%	283,902	2000	147,941	34.3%
65.1%	282,883	2001	151,769	34.9%
61.3%	274,590	2002	172,674	38.7%
60.9%	280,505	2003	179,731	39.1%
58.2%	274,797	2004	197,754	41.8%
56.1%	263,207	2005	206,154	43.9%
54.4%	241,151	2006	202,017	45.6%
52.5%	213,086	2007	192,514	47.5%
47.3%	181,541	2008	202,285	52.7%
41.4%	148,688	2009	210,150	58.6%

**Projected number of discharges with a hospital billing for fosphenytoin or phenytoin.*

Over the past decade usage for fosphenytoin has increased gradually (while IV phenytoin decreased gradually), with the largest increase (or decrease for IV phenytoin) since 2007. As a result, between 2000-2009 market share has reversed. The average cost of IV phenytoin and fosphenytoin over the past 5 years is displayed in Table 6 below.

Table 6. Average Price of Vials (Eaches) by year for IV Phenytoin and Fosphenytoin.

<u>IV Phenytoin (Dollars)</u>	<u>Year</u>	<u>Fosphenytoin (Dollars)</u>
\$1.92	2004	\$29.49
\$1.88	2005	\$31.45
\$1.74	2006	\$33.45
\$1.58	2007	\$25.07
\$1.56	2008	\$4.05
\$1.31	2009	\$2.61

Based on Table 6 above, over the past 5 years (2004-2009), the average cost of fosphenytoin has declined, with the most dramatic reduction between 2007 and 2008. Market share percentages and corresponding average prices (combining data from Table 5 and Table 6) are displayed in Appendix L.

4 DISCUSSION

4.1 PHENYTOIN

Clinical features⁵³ of Purple Glove Syndrome (PGS) were first described with IV phenytoin therapy in the 1980s.⁵⁴ Since then, several published case reports and studies complemented spontaneous post-marketing reports and product labeling. In conjunction with these early publications, PGS with phenytoin continues to be reported in AERS and the literature, with continued and unresolved issues surrounding this phenomenon. Although the exact mechanism is debatable, the published literature describes several risk factors: advanced age, female gender, pre-existing cardiovascular disease, administration through a small or fragile vein, acute administration of large doses, repeat dosing, and high infusion rates.^{54,55,56,57,58}

The 43 cases of PGS with IV phenytoin (33 from the initial OSE review and 10 cases from the current update) identified in AERS, and which met the pre-specified case definition, confirm many of the risk factors discussed in the literature. For example, 15 had pre-existing cardiovascular disease and 9 had received more than one dose. With many of the cases lacking important details, such as infusion rate, needle gauge, and performance of saline flush, it is difficult to determine if these factors contributed to the development of PGS.

The PGS risk factors identified in the literature and reinforced in the 43 AERS cases currently are not discussed in phenytoin's product labeling. The most recent product labeling (Section 1.3) only describes the signs and symptoms of PGS (edema, discoloration, pain of distal limb) following IV phenytoin administration and reported severe outcomes (skin necrosis and limb ischemia).

Various treatments and outcomes have been discussed in the literature involving PGS following IV phenytoin, ranging from benign to severe. Two observational studies evaluating PGS in phenytoin-treated patients concluded that although PGS is common (1.7%-5.9%) in a routine hospital setting, most cases are generally mild and benign, not

⁵³ Progressive pain, edema, and discoloration distal to IV site.

⁵⁴ Spengler RF, Arrowsmith JB, Kilarski DJ, Buchanan C, Von Behren L, Graham DR. Severe soft-tissue injury following intravenous infusion of phenytoin. Patient and drug administration risk factors. *Arch Intern Med.* 1988 Jun; 148(6):1329-33. Comment in: *Arch Intern Med.* 1989 Aug; 149(8):1905.

⁵⁵ Sonohata M, Asami A, Tsunoda K, Hotokebuchi T. Purple glove syndrome associated with intravenous phenytoin administration in a patient with severe mental and motor retardation. *J Orthop Sci.* 2006 Jul; 11(4):409-11.

⁵⁶ Chokshi R, Openshaw J, Mehta NN, Mohler E 3rd. Purple glove syndrome following intravenous phenytoin administration. *Vasc Med.* 2007 Feb; 12(1):29-31.

⁵⁷ Burneo JG, Anandan JV, Barkley GL. A prospective study of the incidence of the purple glove syndrome. *Epilepsia.* 2001 Sep; 42(9):1156-9.

⁵⁸ O'Brien TJ, Cascino GD, So EL, Hanna DR. Incidence and clinical consequence of the purple glove syndrome in patients receiving intravenous phenytoin. *Neurology.* 1998 Oct; 51(4):1034-9. Comment in: *Neurology.* 1998 Oct; 51(4):942-3. *Neurology.* 1999 Oct 22; 53(7):1611-2.

requiring hospitalization or specialized treatment.^{59,60} However, per labeling, more serious outcomes, like skin necrosis and limb ischemia, have occurred, resulting in fasciotomy, skin grafting, or amputation. The AERS data to date also depict various outcomes with varying severity. In the AERS cases series, though only specified in 9 cases, recovery time ranged from 12 hours to 3 months. Additionally, significant outcomes (1 each for amputation and compartment syndrome) were reported in a small percentage of cases. Although death was reported in two cases, both of these fatalities were attributed to other causes (not PGS). When interpreted as a whole, the AERS data to date reflects a variety of outcomes, with *rare* instances of severe complications.

The pathogenesis of PGS is unknown. Its relationship to the vehicle, its pH, the active ingredient, or venous irritation is unclear. The predominance of PGS related to IV phenytoin in the literature postulates it is related to a unique feature of IV phenytoin (basic pH, propylene glycol, ethanol component). However, a literature report of PGS after oral administration of a large phenytoin overdose in a child brings this uncertainty into question; nevertheless, there is only one such report with oral phenytoin after nearly 60 years of marketing.

The precise incidence of Purple Glove Syndrome is difficult to quantify. Three different studies, with varying methodology, concluded incidence rates of 0%, 1.7%, and 5.9% respectively (see Section 3.3 and Appendix J). With PGS's delayed presentation (post IV infusion), it may be difficult to recognize and diagnose, possibly contributing to a larger incidence in the retrospective analysis. Notably, the only prospective and randomized study found zero instances of PGS.⁶¹ Additionally, many factors, like mode of administration (infusion rate, dose, etc.) and patient age, can contribute to increased or decreased risk. In selected settings, the number of reported cases in AERS and corresponding drug utilization data are used to compute reporting rates. To be potentially valid, reporting rate analyses require the drugs in question (i.e., a test drug and one or more comparator drugs) to be very similar, including approximate year of initial marketing. Since IV phenytoin was approved more than 50 years ago a reporting rate analysis would not be valid, and is not included in this review.

4.2 FOSPHENYTOIN

To date, fosphenytoin-related PGS has not been identified in the medical literature. As a result, spontaneous post-marketing reports are necessary to determine if PGS has been reported and can occur with fosphenytoin. Four (4) possible cases (originally identified in a previous OSE review) of PGS associated with fosphenytoin have been identified. Additionally, a review of sponsor submitted post-marketing data identified one unique

⁵⁹ Burneo JG, Anandan JV, Barkley GL. A prospective study of the incidence of the purple glove syndrome. *Epilepsia*. 2001 Sep;42(9):1156-9.

⁶⁰ O'Brien TJ, Cascino GD, So EL, Hanna DR. Incidence and clinical consequence of the purple glove syndrome in patients receiving intravenous phenytoin. *Neurology*. 1998 Oct;51(4):1034-9. Comment in: *Neurology*. 1998 Oct;51(4):942-3. *Neurology*. 1999 Oct 22;53(7):1611-2.

⁶¹ Coplin WM, Rhoney DH, Rebuck JA, Clements EA, Cochran MS, O'Neil BJ. Randomized evaluation of adverse events and length-of-stay with routine emergency department use of phenytoin or fosphenytoin. *Neurol Res*. 2002 Dec;24(8):842-8.

cases of PGS not found in the AERS database, Combining all cases that fit the pre-defined case definition, 5 cases (4 AERS, 1 from sponsor) of possible PGS have been identified to date for fosphenytoin.

The literature describes that the elderly possess greater risk for developing PGS (with IV phenytoin), and accordingly two of the fosphenytoin cases occurred in the elderly (72 and 83 years of age). It is unknown whether PGS involves extravasation, and notably one (1) fosphenytoin case involving PGS noted extravasation. In the case of IV phenytoin, large, repeated doses put patients at risk for PGS; similarly, among the fosphenytoin cases a dose-related link is present (1 report describes a single dose of 1000mg PE⁶² administered, and another describes 500 mg, 100 mg, and 500 mg PE, over two days). As the literature and spontaneous reports indicate, clinical effects of PGS are usually self-limiting and do not tend to be life-threatening. The outcomes of possible PGS in the fosphenytoin case series were also predominantly minor in nature, with spontaneous improvement at 5 days to 2 weeks; however, one patient did require debridement and hyperbaric treatment, and was healing 30 days after onset.

In July 2008, Pfizer submitted their own post-marketing case evaluation and categorized cases, based on PGS clinical phenotype, as probable, possible, and unlikely. Of the eight categorized cases, one unique case (not previously identified in AERS) is included in this review. Additionally, one “unlikely” case was misclassified by the sponsor, and more appropriately should be categorized as “possible,” according to the sponsor's PGS classification criteria (see Appendix M for details). Although misclassified, this case does not meet the case definition outlined in Section 2.2 and is not included in this case series.

A main regulatory focus of PGS and fosphenytoin has been on future reporting, resulting in special enhanced reporting requirements for this drug-event combination (see Section 1.2.3 and Appendix B). Although the Office of Compliance recently sent an enforcement letter citing delayed implementation of these proposed practices (see Appendix E), the details of the actual specialty reporting proposal are concerning. Despite Pfizer adopting a thorough approach (initial screen, diligent follow-up, and hands-on case review), only diagnostically possible and probable PGS cases are intended to have expedited reporting to FDA. Under this protocol, if Pfizer deems a potential PGS case “unlikely,” (e.g. the poorly categorized case mentioned above and in Appendix M) it would not be reported to FDA, which could result in underreporting of potential PGS cases. Submitting cases targeted by their initial filter (“any adverse event in an extremity where fosphenytoin has been administered”) would be more comprehensive.

Additionally, part of Pfizer’s specialty reporting requirements for PGS with fosphenytoin included appropriate training of all of its global offices; this too was cited in the enforcement letter as not being properly implemented. All PGS cases for fosphenytoin (AERS and sponsor-submitted data) have been reported domestically, compared to phenytoin cases that include both domestic and foreign cases. Pfizer recently stated, in their letter response to Office of Compliance, that they have been 100% compliant with specialty reporting requirements (initiated in October 2009) between February and May

⁶² Phenytoin Equivalents

2010. This puts confidence in the AERS results during this recent small time frame. However the majority of the AERS analysis (1996-June 2010) was well outside this compliant time frame.

Based on potential adverse drug event reporting discrepancies, it is unclear if there has been underreporting by Pfizer. As noted above, reporting rates are not included in this review because the two products were approved roughly 40 years apart. As a result, well designed clinical studies would be necessary to compare incidence of PGS with phenytoin and fosphenytoin.

4.3 DRUG UTILIZATION

Drug utilization of IV phenytoin and fosphenytoin has changed dramatically over the past five years. The first generic approval of fosphenytoin in 2007 spurred a dramatic decrease in fosphenytoin price, while fosphenytoin gradually gained the overall market share over IV phenytoin (Table 5, Section 3.4). In the early 2000s, fosphenytoin cost approximately \$30/vial (compared to the steady price of < \$2/vial for phenytoin). This high price is reflected by a 34% market share in 2000 (Table 6, Section 3.4). In contrast, with generic competition, in 2009 fosphenytoin has already gained a 58.6% market share, with a cost per vial double that of phenytoin (\$2.61 versus \$1.31). Additionally, with generic sponsors competing, Pfizer's (Cerebyx) market share has dropped substantially from 2.1 million vials (Eaches) in 2005 to 58,000 vials (Eaches) in 2009.⁶³ Resultantly, Cerebyx currently represents a small fraction (2.5%) of the fosphenytoin market.

5 CONCLUSION

Based on AERS cases and sponsor data reviewed in this document, Purple Glove Syndrome (PGS), with clinically overlapping features, can occur with IV phenytoin and fosphenytoin. This conclusion is consistent with the original AERS review, and Pfizer's analysis of their data.^{64,65} From this data, and considering discrepancies (lack of compliance with specialty reporting requirements and potential of misclassification of cases) in PGS reporting of fosphenytoin and comparable market share (fosphenytoin currently has slight edge), one cannot definitively conclude that the drugs differ in the rate of or severity of such events. *However, only cases and studies of PGS involving IV phenytoin, but NOT fosphenytoin, have been reported in the medical literature. This lack of fosphenytoin-specific information lends to a conclusion that PGS occurs more frequently with IV phenytoin than fosphenytoin.* The data reviewed for both agents concur that certain risk factors exist for PGS. Typical outcomes are usually not serious in nature, though serious sequelae (e.g. amputation) have only been reported for IV

⁶³ IMS Health, IMS National Sales Perspectives™, Years 2004-2009, Extracted 05-10. File: 1005phen.xls.

⁶⁴ Phelan K, Pamer CA. Purple Glove Syndrome. OSE RCM# 2007-1332. 9 July 2008.

⁶⁵ Response to FDA Query Regarding Purple Glove Syndrome and Cerebyx® (Fosphenytoin sodium). Systematic Analysis of Association between Purple Glove Syndrome and Fosphenytoin. Pfizer Global Pharmaceuticals. 22 July 2008.

phenytoin. The evidence in this review also highlights inadequacies in current product labeling; specifically, a lack of critical PGS details (risk factors) in the phenytoin label and an absence of PGS information for fosphenytoin. Finally, based on inspections by the Office of Compliance, and the case characteristics of possible PGS with fosphenytoin, Pfizer's specialty reporting standards appear subpar and need improvement. Despite this uncertainty, with generic competition Pfizer's market share represents only a small fraction of the fosphenytoin market.

6 RECOMMENDATIONS

Based on the data included in this review, DPV-1 recommends the following actions:

- Revisions to the IV phenytoin label to include risk factors for Purple Glove Syndrome.
- Elevating PGS to a specific Warning/Precaution under the Structured Product Labeling (SPL) format or to a specific Precaution with its own section under the current labeling format for IV phenytoin.
- Label revision to the Post-marketing section of the fosphenytoin label to state, "Reports of Purple Glove Syndrome (PGS) with fosphenytoin therapy have been identified."
- Pharmacology/Toxicology reviews to shed light on a possible mechanism of Purple Glove Syndrome.
- All fosphenytoin sponsors, including Pfizer, should report all cases that include an adverse event in an extremity where fosphenytoin has been administered; these should be submitted as 15-day expedited reports, regardless of outcome and include follow-up information.
- Office of Compliance inspections of Pfizer's foreign Adverse Drug Event (ADE) practices to ensure compliance with fosphenytoin special enhanced reporting requirements.

7 APPENDICES

7.1 APPENDIX A: REVIEW OF CLINICAL DATA

NDA # 20-450

Brand name (generic name) Cerebryx (fosphenytoin)

Sponsor Pfizer

Materials reviewed OSE Review 2007-1332, Pfizer Submission
7/22/2008

Reviewer Marc Stone, MD

Date Completed 10/29/2008

Background

Fosphenytoin is a parenterally administered pro-drug of phenytoin. Injectable phenytoin is a highly alkaline preparation that must be administered slowly and intravenously in order to minimize irritation at the injection site as well as cardiac effects. Fosphenytoin is delivered in a less alkaline solution and, as a pro-drug, does not affect cardiac conduction until it has been metabolized. Because of these differences fosphenytoin can be administered more rapidly than phenytoin with a supposedly lower risk of adverse reactions at the vein and injection site.

Phenytoin injection has also been associated with “purple glove syndrome” (PGS): pain, edema and purplish discoloration in a hand or foot, usually distal to the site on injection. Although the cause of PGS is unknown, it has been plausibly considered to be a result of the highly alkaline solution in which phenytoin is administered, high local concentrations of phenytoin in the affected extremity, or both. If true, this belief would suggest that PGS would not occur with fosphenytoin administration; PGS was not seen in clinical trials of fosphenytoin. The Division, however, received reports of possible PGS with fosphenytoin and requested:

1. A review by OSE of the AERS database for reports of PGS
2. An analysis by Pfizer of the association between PGS and fosphenytoin. Pfizer based its analysis on a review of cases in their safety database, usage data, data available from clinical trials, data from animal studies, and a review of the literature.

Findings

Both the OSE review and the Pfizer submission take thorough and well-organized approaches to their tasks and produce sensible conclusions based on their findings. Their findings are largely in agreement:

1. OSE found four possible PGS and four serious local adverse event cases temporally associated with fosphenytoin, and 33 possible PGS cases temporally associated with phenytoin in AERS reports from 1996 and April 2008. The two best described fosphenytoin cases occurred in elderly patients who had already been treated with therapeutic dosages of fosphenytoin or oral phenytoin. Pfizer identified four “probable” and one “possible” case of PGS associated with fosphenytoin.
2. OSE declined to compare PGS reporting rates for phenytoin and fosphenytoin

because of the lack of comparability of two drugs that entered the market 40 years apart. Pfizer attempted this analysis and found that the rate of reporting of events with fosphenytoin either as PGS or events that could be interpreted as PGS was very low, as was the reporting rate for phenytoin-associated PGS. They concluded that reporting rates were not inconsistent with the low end of the range for phenytoin-associated PGS in published studies.

3. In Pfizer's clinical trial database, a few cases of skin necrosis were reported with fosphenytoin but were no more frequent than what was seen with placebo.

4. A case of PGS associated with high doses of oral phenytoin has been reported in the literature. If true, this would suggest that PGS may not be a reaction to the irritating properties of the solution containing phenytoin but a reaction of the extremities to any high concentration of phenytoin. Conceivably, this could occur after conversion of fosphenytoin to phenytoin. Cases of PGS related to fosphenytoin have not been reported in the literature.

5. PGS with fosphenytoin has not been demonstrated in animal studies but injection site reactions have been noted with intravenous injection.

Conclusions and Recommendations

There are credible cases of purple glove syndrome reported after administration of fosphenytoin. These cases appear to be uncommon. There is no good way to compare the incidence of PGS for fosphenytoin relative to phenytoin but there is no reason to believe that it is higher.

The labeling for fosphenytoin should be amended to inform physicians about the potential for purple glove syndrome in order that it be recognized should it occur. To be analogous to the labeling for phenytoin, it should be listed in the Precautions section:

Edema, discoloration, and pain of the distal limb (described as "purple glove syndrome") have been reported following peripheral ~~intravenous phenytoin sodium~~ IV Cerebryx injection. This may or may not be associated with extravasation. The syndrome may not develop for several days after injection. Although resolution of symptoms may be spontaneous, skin necrosis and limb ischemia ~~have may occurred~~ and required such interventions as fasciotomies, skin grafting and amputation. ~~Therefore, Phenytoin Sodium Injection should be administered as described above.~~

This language differs from the labeling for phenytoin by including an additional sentence informing the prescriber that PGS may not develop until several days after injection and omitting the final sentence, which implies the method of administration is responsible for the development of PGS.

7.2 APPENDIX B: PFIZER RESPONSE RELATED TO PURPLE GLOVE SYNDROME

Responses to Requests about Purple Glove Syndrome in FDA Letter Dated December 30, 2008 **NDA 20-450**

1. FDA REQUEST: Please develop and implement an effective plan to obtain complete and clinically meaningful information, such as hospital discharge summaries or copies of consultant's reports, for any new cases consistent with Purple Glove Syndrome or other severe local cutaneous reactions associated with fosphenytoin that are suggestive of this syndrome. Please submit your plan to us by February 15, 2009. Amongst other issues, the plan should include criteria used to identify cases that are not labeled as Purple Glove Syndrome, but are suggestive of the syndrome.

RESPONSE: Pfizer has developed and is implementing a plan to enhance our ability to obtain complete and clinically meaningful information, including hospital discharge summaries and copies of consultant's reports, for new cases that are consistent with or suggestive of Purple Glove Syndrome (PGS) associated with fosphenytoin. The plan outlined below includes a description of the criteria we will use to identify cases that may not be specifically reported as PGS but suggest severe local cutaneous reactions consistent with it. The plan also includes a method to clearly and quickly identify fosphenytoin cases across Pfizer worldwide affiliates and to rapidly enter these cases into the global safety database for access by our central Drug Safety Surveillance (DSS) group for medical assessment, to enhance follow up information gathering, and to meet expedited timelines for cases of interest to the FDA.

- Plan overview
 - Any report associated with the administration of fosphenytoin will be forwarded to the Pfizer central case processing group, Drug Safety Surveillance (DSS), within 2 business or 4 calendar days of initial receipt. This will apply to US and non-US reports.
 - All reports including an adverse event in an extremity where fosphenytoin has been administered will have extensive follow up performed to obtain further clarifying information that may be needed to accurately assess the case.
 - All reports including an adverse event in an extremity where fosphenytoin has been administered will have a timely review by a DSS physician. The review will include an assessment of whether or not the report meets the criteria for PGS or a severe local cutaneous reaction suggestive of it. Cases categorized as "probable" or "possible" will be considered consistent with or suggestive of PGS.
 - DSS will ensure that cases consistent with or suggestive of PGS are expedited to FDA regardless of the country of origin.

- Follow up information received by Pfizer will prompt reevaluation of the case for inclusion as a “probable” or “possible” case of PGS.
- Training for Pfizer worldwide affiliates and DSS will be completed by February 15, 2009. The training records will constitute documentation of the communication.
- The process will be implemented by February 15, 2009.
- Case inclusion criteria:
Pfizer will continue to define Purple Glove Syndrome as we did in our July 22, 2008 submission:

Purple glove syndrome (PGS) is an adverse reaction characterized by progressive development of discoloration, edema, and pain distal to the site of intravenously administered phenytoin. [1] Typically, the reaction occurs in three stages. In the first stage (2-12 hours post-infusion), there is a pale blue or purplish ecchymosis of the skin surrounding the intravenous (IV) insertion site. In the second stage (over the next 12-16 hours), the reaction progresses with discoloration spreading to the digits, hand, and forearm. The discoloration is accompanied by distal limb edema. In the last stage, the discoloration begins to fade, starting at the periphery and moving toward the original insertion site [1,2]

Our initial criteria to identify cases for inclusion will be very broad. This syndrome, and cases that are suggestive of it, has a wide range of potential local cutaneous signs and symptoms and relevant preferred terms that may be associated with it. The type of events reported and the preferred terms used to identify them depend on the stage of PGS at which they are reported and the interpretation of those events by the reporter. For this reason the trigger for identifying cases that may include PGS or are suggestive of it will be **all fosphenytoin** cases that contain **any** reference to **any adverse event** in the extremity where **fosphenytoin was administered**. This approach will be applied to all reports regardless of the country of origin.

Each of these reports will be carefully assessed by DSS physicians to determine if the report is truly a case of PGS or a severe local cutaneous reaction suggestive of PGS (see below for criteria to be used). These cases will also be followed up on, with targeted questions, to obtain additional meaningful information to help clarify whether or not they truly reflect PGS or a severe local cutaneous reaction suggestive of PGS.

- Obtaining additional clinically important information

Pfizer has in place a globally implemented process in which the extent of case follow up is based on CIOMS V criteria:

- Non-serious, listed: minimal
- Serious, listed and non-serious, unlisted: standard
- Serious, unlisted and special cases: extensive

Reports meeting the selection criteria will be considered special cases and will result in extensive targeted follow up. The intent of the targeted follow up efforts will be to help determine whether or not the report is truly consistent with or suggestive of PGS (see categories below), to collect additional meaningful clinical information required for an accurate assessment and to request medically relevant records including hospital discharge summaries and copies of consultant's reports.

Follow up requests may be made by regular mail, fax or phone depending on the country of origin and the contact information available in the report. Colleagues will be instructed that telephone calls will be the preferred method of contact. A cover letter describing PGS and the importance of gathering additional clinical information and a follow up data-collection tool to target specific clinical information have been created. They will be provided to the physician or other healthcare professional indicated as contactable on the report whenever available (when an initial report is provided by a consumer we will ask for their primary healthcare professional's contact information as per current practice) for each case meeting the initial selection criteria. This information will be communicated verbally when a phone call is made, and by letter when a written communication is deemed the appropriate method of contact or as follow up to a phone call. US cases will be followed-up by DSS; foreign reports will be followed up by the Pfizer worldwide country affiliates located in the country where the report originated. All follow-up activities will be performed with respect to local privacy laws.

- Determination of cases to expedite to FDA

All fosphenytoin cases meeting the selection criteria sent to DSS by Pfizer worldwide country affiliate offices or originating in the US will be reviewed by a Drug Safety Surveillance (DSS) physician upon receipt. The DSS physician will use the information available at the time of the initial report to determine whether or not the case is consistent with the definition of PGS or a severe local cutaneous reaction suggesting PGS consistent with Pfizer's previous methodology in Section 2.2.3.5 submitted to FDA on July 22, 2008.

All initial cases, regardless of the country of origin, seriousness or expectedness assessment, that are consistent with or suggestive of PGS, (Categories Probable and Possible) will be submitted to FDA in an expedited manner. When follow up information and/or the completed follow up data-collection tool is received by Pfizer the updated report will be processed and reassessed according to the timelines outlined for initial cases. Cases that are reassessed as PGS or are suggestive of it will be expedited to the FDA. Consistent with current practices any significant medical information received on a previously expedited case will be expedited to FDA.

2. FDA REQUEST: We request that you submit expedited 15-day reporting for all US and foreign reports of Purple Glove Syndrome or other severe reactions suggestive of this syndrome with fosphenytoin.

RESPONSE: Pfizer will ensure that these special cases of interest are submitted

to the FDA as per request. The current practice is to expedite all cases that are serious and unexpected to FDA within 15 days, regardless of the country of origin. However, it is possible that some of the reports that meet the inclusion criteria for this specific topic may be non-serious and/or expected according to the USPI. To ensure compliance with this special FDA request for expedited 15-day reporting, Pfizer worldwide country affiliates will be instructed to forward **any** report involving fosphenytoin use to the central DSS offices according to Pfizer internal “serious case” timelines (2 business or 4 calendar days whichever is shorter) irrespective of individual case seriousness assessment. All US and foreign cases will be processed according to Pfizer internal timelines for expedited cases.

3. FDA REQUEST: We ask that you communicate pro-actively with responsible Pharmacovigilance staff in the worldwide affiliate company offices located in countries where fosphenytoin is sold to assure that reports of serious unexpected adverse drug reactions are promptly reported to Health Authorities, including FDA. Please submit documentation of this effort to the NDA by February 15, 2009.

RESPONSE: Practices are in place to ensure that adverse event reporting regulatory requirements for all global health authorities for reports received by Pfizer are met.

All Pfizer worldwide affiliate pharmacovigilance staff will be trained by February 15, 2009 by Net Meeting by the Drug Safety Surveillance team responsible for fosphenytoin. This training will include an overview of Purple Glove Syndrome and specific directions regarding the new process for expediting any adverse event reports involving fosphenytoin use to DSS for further evaluation and follow up. Activities related to this training will be tracked.

In addition, central DSS personnel will be trained before February 15, 2009. Training will include an overview of Purple Glove Syndrome and careful instructions on how to identify the cases of interest, how to pursue follow up, and how the case should be processed within DSS. Activities related to this training will be tracked.

All training will include a review of timelines to ensure that any report that meets the selection criteria outlined above is expedited consistent with the FDA request. Pfizer has a licensing agreement and a specific pharmacovigilance agreement for fosphenytoin with Nobelpharma in Japan. We will communicate this plan and the reasons for it to Nobelpharma.

References

1. Spengler, R.F., et al., *Severe soft-tissue injury following intravenous infusion of phenytoin. Patient and drug administration risk factors.* Arch Intern Med, 1988. **148**(6) p. 1329-33.
2. O'Brien, T.J., et al., *Incidence and clinical consequence of the purple glove syndrome in patients receiving intravenous phenytoin.* Neurology, 1998. **51**(4): p. 1034-9.

7.3 APPENDIX C: PREFERRED TERMS UTILIZED IN PFIZER'S JULY 22, 2008 SUBMISSION

Complete list of preferred terms utilized in Pfizer's initial search.⁶⁶

The initial search included the following (MedDRA Version 11.0)
Preferred Terms (PTs):

Administration site reaction, Amputation, Amputation revision, Application site bruising, Application site discolouration, Application site induration, Application site irritation, Application site reaction, Application site swelling, Arm amputation, Arthralgia, Catheter site necrosis, Catheter site oedema, Catheter site pain, Catheter site phlebitis, Catheter site related reaction, Compartment syndrome, Erythema, Extravasation, Fasciectomy, Fasciitis, Fasciotomy, Finger amputation, Foot amputation, Induration, Infusion site bruising, Infusion site discolouration, Infusion site extravasation, Infusion site induration, Infusion site necrosis, Infusion site oedema, Infusion site pain, Infusion site phlebitis, Infusion site reaction, Infusion site swelling, Injected limb mobility decreased, Injection site bruising, Injection site discolouration, Injection site haematoma, Injection site injury, Injection site joint swelling, Injection site necrosis, Injection site oedema, Injection site pain, Injection site reaction, Injection site swelling, Ischaemic limb pain, Leg amputation, Limb discomfort, Local reaction, Local swelling, Localised oedema, Metatarsal excision, Necrotising fasciitis, Oedema, Oedema peripheral, Pain, Pain in extremity, Peripheral ischaemia, Phlebitis, Phlebitis deep, Phlebitis superficial, Pigmentation disorder, Post procedural complication, Procedural site reaction, Pruritus, Purple glove syndrome, Skin atrophy, Skin discolouration, Skin discomfort, Skin disorder, Skin exfoliation, Skin graft, Skin graft failure, Skin graft infection, Skin graft rejection, Skin necrosis, Skin oedema, Skin reaction, Skin swelling, Thrombophlebitis, Thrombophlebitis superficial, Toe amputation, Vascular graft, Vascular graft complication, and Vein discolouration.

⁶⁶ General Correspondence-Analysis of Association between Purple Glove Syndrome with Fosphenytoin. Pfizer, Inc. 22 July 2008.

7.4 APPENDIX D: PFIZER DIAGNOSTIC CATEGORIZATION CRITERIA FOR SYMPTOMS OF PURPLE GLOVE SYNDROME

Category	Definition
Probable	Case narrative mentions PGS*, case coded as PGS, patient developed significant sequelae (e.g., fasciotomy, necrosis in the absence of any other causative explanation), or the clinical course was consistent with the definition of PGS.
Possible	The majority of signs and symptoms and clinical course appear consistent with PGS but there is not enough specific information to categorize as probable or there are minor inconsistencies. Includes cases where the reaction moved away from the site of administration.
Unlikely	The majority of signs and symptoms and clinical course were inconsistent with PGS, but it could not be ruled out definitively.
Excluded**	Reports of clearly localized reactions, thrombosis only, extravasation only, cellulitis/infection and cases reporting use intra-arterial use (medication error)

*PGS= purple glove syndrome

**Reasons for exclusion included:

- Cases describing events other than purple glove syndrome (e.g., Stevens-Johnson syndrome, toxic epidermal necrosis, rash, vasculitis, cellulitis, deep vein or other thrombosis).
- Cases describing events in the medical history (e.g., osteomyelitis resulting in amputation of right arm, sarcoma resulting in amputation of left leg) other than purple glove syndrome that explained the signs, symptoms and clinical course.
- Cases describing extravasation with clearly localized reactions.
- Cases describing intra-arterial use.
- Patient was not receiving fosphenytoin or phenytoin when the event started.

**7.5 APPENDIX E: EXCERPT FROM OFFICE OF COMPLIANCE ENFORCEMENT LETTER
(MAY 2010)**

“For fosphenytoin, in your firm's letter to FDA dated February 13, 2009, your firm agreed to develop and implement an effective plan which would include criteria to correctly identify, assess, and report cases that are not labeled as Purple Glove Syndrome (PGS), but that are suggestive of this syndrome in association with fosphenytoin sodium use. However, your firm failed to do so.

Your firm also agreed to train all pharmacovigilance staff in the worldwide affiliates by February 15, 2009. Training was to include an overview of PGS and specific directions regarding the process for expediting any adverse event reports involving fosphenytoin use to Drug Safety Surveillance (DSS).

Despite your agreement, only six out of the required sixty-three country offices worldwide were trained and some of the offices that were trained were not trained on time, including the core DSS offices.

Your firm's response dated September 9, 2009 remains inadequate because it fails to include an effective plan to identify cases suggestive of PGS and fails to require medical evaluation of reports suggestive of PGS. Additionally, provisions for adequate training and documentation of training were not provided.”

7.6 APPENDIX F: PFIZER’S PURPLE GLOVE SYNDROME SEARCH STRATEGY

Pfizer’s Search Strategy to Identify Cases of Purple Glove Syndrome⁶⁷

1. Initial Search: Conservative search using a wide range of PTs in an effort to identify signs and symptoms that might be associated with PGS (see APPENDIX C for complete list of PTs).
2. Initial Keyword search: Text string searches performed on set retrieved from initial search. Text strings included: “glove”, “red”, “blu” (to capture blue and/or bluish), “purpl” (to capture purple or purplish), and/or “color” (to capture discoloration).
3. Comprehensive review: Comprehensive Review and assessment of cases not returned from keyword search on initial search to ascertain whether the reported signs and symptoms or clinical course could be consistent with PGS.
4. Outcomes search: Text string search of entire safety database (irrespective of reported PT) for outcomes consistent with PGS. Text strings included: “amput” (to capture amputated limbs/amputations resulting from purple glove syndrome), “graft” (to capture skin grafts resulting from purple glove syndrome) and/or “fasc” (to capture any cases of fasciotomy resulting from purple glove syndrome).
5. Full case set review and assessment. Cases retrieved from all searches outlined were merged and reviewed in detail to determine whether or not the events reported were consistent with a diagnosis of purple glove syndrome and if consistent, determine the degree of consistency (probable, possible, or unlikely). Diagnostic categorization criteria is detailed in Appendix D.

⁶⁷ Response to FDA Query Regarding Purple Glove Syndrome and Cerebyx® (Fosphenytoin sodium). Systematic Analysis of Association between Purple Glove Syndrome and Fosphenytoin. Pfizer Global Pharmaceuticals. 22 July 2008.

7.7 APPENDIX G: NARRATIVE SUMMARIES OF PURPLE GLOVE SYNDROME FROM THE AERS DATABASE

Narrative Summaries of Eight (8) Spontaneous Reports of PGS (n=4) or Severe Local Cutaneous Reactions (n=4) with Fosphenytoin Identified in Searches of the FDA AERS Safety Database:

Possible PGS

1. ISR 3566977-1: A pharmacy student (b) (6) reported that a patient who was hospitalized for depression and psychosis developed purple glove syndrome, considered medically significant, after receiving intravenous fosphenytoin 600 mg on 20SEPT1999 after unspecified testing. Fosphenytoin was discontinued the same day. On 22SEPT1999 the patient developed purple glove syndrome. The patient recovered. Concomitant medications included lorazepam, phenytoin, potassium, fluvastatin, levothyroxine, citalopram, terbinafine, dexamethasone, carbamazepine, pentoxifylline, tocopherol, selenium, quetiapine, rofecoxib, sertraline, Myadec, and warfarin. No other information was provided. (*Note: this is the same case as #2 in Appendix I, Mfr Report #001-0982-990045*).
2. ISR 5484058-7 (dup 5406600-4): A pharmacist (b) (6) reported that a 72 year-old-male with a history of liver disease developed “blisters on the right hand and dorsal forearm” and “purplish discoloration which darkened” after receiving 500 mg Cerebyx on July 11, 2007, followed by 100 mg eight hours later, for the treatment of subdural hematoma, subarachnoid hemorrhage and convulsions. The fingers were not affected. A wound consultant examined the patient on July 18. Treatment included debridement and hyperbaric treatment. Subsequent medication included IV Keppra which may have been administered through the same line. This was a Direct report and was classified as serious (required hospitalization). The patient’s chart included a notation of “PGS?” but no other information. The wound was reported to be “healing.” (*Note: this is the same case as #8 in Appendix I, Mfr Report #2007062067*).
3. ISR 5113338-X: A pharmacist (b) (6) reported that a 34-year-old male developed a “red, hard, swollen and painful” arm extending from the “elbow to the fingertips” within 30 minutes after receiving Cerebyx 1 gm intravenous infusion in normal saline on Sept 6, 2006. The line had been started by EMS in the field. Cerebyx was administered at the hospital. While administering the IV infusion, “the drug infiltrated into the arms and extravasation occurred.” Medical history, concomitant medications, treatment and outcome of the events were not reported. This was considered an important medical event. (*Note: this is the same case as #7 in Appendix I, Mfr Report#2006111007*).
4. ISR 4121846-3: A pharmacist (b) (6) reported that an unknown patient was given fosphenytoin via intravenous infusion and developed discoloration of the skin which he referred to as “black glove syndrome”

when the IV infiltrated. No other information was provided. (*Note: this is the same case as #6 in Appendix I, Mfr Report #2002052928*).

Local Cutaneous Reactions (LCR)

5. ISR 3942116-X: A pharmacist [REDACTED] (b) (6) reported that a one-day-old male developed extravasation after fosphenytoin 100mg/2mL (single dose) was administered on June 25, 2002 through a “peripheral vein.” The IV was stopped and Silvadene cream was applied to the lesion on the foot. No other information was provided.
6. ISR 4223551-1: A pharmacist [REDACTED] (b) (6) reported that a physician notified her of a patient (age and gender not stated) who developed extravasation after receiving Cerebyx sometime prior to Oct 17, 2003. No other information was provided. This was considered an important medical event.
7. ISR 4618759-7: A pharmacist [REDACTED] (b) (6) reported that a patient (age and gender not stated) experienced extravasation with redness and swelling at the site while receiving Cerebyx sometime prior to March 12, 2005. Cerebyx was stopped due to the events. This was considered an important medical event.
8. ISR 3311714-9: A pharmacist [REDACTED] (b) (6) reported that a 73-year-old male with a diagnosis of stroke and hypertension developed “a swollen arm from his wrist to elbow, with seven to eight blisters containing fluid” after receiving fosphenytoin 1.5 gm on 06AUG1998 for prophylactic treatment of seizures, followed by 100 mg fosphenytoin in D5NS with 20 mEq KCl every 8 hours, and “other unspecified medications”. Fosphenytoin was discontinued on 10AUG1998 when the arm swelling was noted. It was “unclear if infiltration occurred.” The pharmacist later reported that “the patient also experienced second degree burns to his right arm.” Treatment included Silvadene to the affected area. Concomitant medications included midazolam, furosemide, and mannitol. CT scan showed large intraparenchymal hematoma. Subsequent therapy included intravenous phenytoin. The patient was discharged to a nursing facility on 18AUG1998. His right arm was reported to be “healing slowly at that time.” No additional information was provided. (*Note: this is the same as Case #1 in Appendix I, Mfr Report #001-0982-980025*).

7.8 APPENDIX H: NARRATIVES SUMMARIES FOR SELECT REPORTS OF PURPLE GLOVE SYNDROME ASSOCIATED WITH IV PHENYTOIN.

Best case summaries from Recent Series (2008-2010)

ISR 6416548, literature report, foreign: A 55-year-old male received IV phenytoin (dose and date unknown) after presenting to Emergency room following prolonged tonic-clonic seizure. The patient had a history of tonic-clonic seizures. Within 2 hours of phenytoin infusion, his right hand became purple, edematous, and painful distal to cannula site. At 48 hours, bullous lesions developed, and Purple Glove Syndrome was diagnosed. Symptoms completely resolved within 4 weeks.

ISR 6526102, literature report, foreign: A 40-year-old female patient with previously diagnosed dissociative psychomotor seizures underwent laparoscopic surgery for endometriosis and an ovarian cyst. During the recovery phase, the patient exhibited psychomotor seizures that imitated a grand mal seizure. The patient was treated with intravenous (IV) phenytoin through a line in the radiodorsal aspect of the right forearm. A 500mg bolus was followed by continuous administration of 500mg over 12 hours. In the evening of the day of surgery, the patient complained of pain and reddening of the arm with the IV line. Phenytoin administration was continued through the existing line. Four days after phenytoin administration, the patient exhibited persistent pain, livid color around the injection site, swelling of the forearm and reduced range of motion of the fingers and wrist. Patient also exhibited massive edema and pain of the hand and forearm, including the fingers. There was no evidence of compartment syndrome. Surgical revision was performed and no macroscopic evidence of extravasation was found. Intraoperatively, perivascular necroses were identified around the vein used for the infusion, and the necrotic tissue was completely excised. The patient was discharged to outpatient care 5 days after surgery, and the patient received outpatient physical therapy. Three months after surgery, complete recovery had been achieved.

ISR 6186190, MFR# 2009199892, foreign, 2009. 82-year-old Asian female patient, was admitted to the hospital due to status epilepticus and was given a loading dose (750 mg) of phenytoin intravenous (IV). Relevant medical history included pneumonia. The patient was not taking any other concomitant medications. On an unknown date, the patient experienced "Phenytoin hand" described as swelling and the hand cannot be moved. The onset of the event was a day after administration (after 24 to 48 hours). In a follow-up the physician reported that the symptoms of the event showed the patient's hand to be blistering, cold, and purplish. Patient manifested progressive discoloration away from the administration site, progressive distal limb edema, mild limb ischemia, and mild vascular compression. There was no limb necrosis or compartment syndrome. There were no procedural complications which occurred in the conjunction with the event. Pain could not be determined as the patient was comatose. The event did not prolong patient's hospitalization. As per family's decision, patient went home although not fully recovered, however, recovering. The physician considered that there was no other alternative

explanation for the observed event other than "phenytoin hand." Phenytoin was discontinued and the patient was switched to another unknown seizure medication.

Amputation Case (n=1) from previous OSE Review⁶⁸

ISR# 3487892-8, MFR# 001-0073-980591, U.S., 2000. After 2 years hospitalization in a neurological care unit following a motor vehicle accident, a 30-year-old male received one 600 mg dose of phenytoin intravenously to treat a seizure. He immediately developed purple glove syndrome. Details were not provided, but the patient subsequently underwent left arm amputation.

Best Case Summaries (n=2) from previous OSE Review⁶⁷

ISR# 5153192-3, MFR# GXKR2006JP07063, Foreign, 2006, literature (Sonohata et. al. 2006) A 14-year-old male with microcephaly who weighed 20 kg received 200 mg phenytoin in saline through a catheter in the left hand to treat a seizure. The patient immediately developed flushing along the vein and petechiae around the injection site. The injection site was treated with hydrocortisone injection. Edema and discoloration appeared all over the hand, which developed blisters, petechiae, and cold fingers. Within 3 days, half of the left forearm was affected. C-reactive protein was 24.7 mg/dL (normal < 0.3). The limb was elevated and treated with a warm pack. The patient was considered too weak for fasciotomy. The discoloration receded from the edges back toward the original injury site and purple glove syndrome was resolved 5 weeks after phenytoin administration. Possible risk factors, per the authors, were immobility, small and fragile veins, and administration of diazepam through the same catheter before phenytoin.

ISR# 4456191-1, MFR# 04H-062-0274527-00, Foreign, 2004 literature (Cadenbach et. al. 1998)

A 37-year-old woman was treated with benzodiazepines in the intensive care unit for seizures. Seizures were not controlled, so the patient was administered 250 mg phenytoin through a vein on the dorsum of the left hand over 10 minutes followed by 750 mg phenytoin in 500 ml 0.9% NaCl through the same vein over 24 hours (< 0.6 mg/min). Within 24 hours after phenytoin administration was completed, "livid swelling" developed over the injection site. The intravenous catheter showed correct placement with free drainage of a test injection of saline solution. The catheter was removed and the arm was raised and cooled. Swelling and discoloration of the lower arm increased over 3 days and the patient could not move her hand because of pain. Radiographs ruled out broken bones and sonography showed unimpaired blood flow in all arteries and in axillary and brachial veins. However, a thrombus was assumed because of the absence of detectable blood flow in the lower arm veins. The patient was treated with limb elevation and cooling, physical therapy, lymph drainage, anti-inflammatory drugs, and antibiotics. The adverse event was improved when the patient was discharged 3 weeks after admission. However, 3 weeks after discharge, she was readmitted with clinical manifestations of Sudeck's dystrophy⁶⁹ including pain during motion, doughy induration,

⁶⁸ Phelan K, Pamer CA. Purple Glove Syndrome. OSE RCM# 2007-1332. 9 July 2008.

⁶⁹ Also known as reflex sympathetic dystrophy syndrome (RSDS).

pale-livid skin discoloration, painful contractures of fingers and wrist, and leioderma. Sudeck's dystrophy resolved over 2 weeks with sympathectomy, calcitonin, and physical therapy.

7.9 APPENDIX I: DETAILS OF FIVE (5) PROBABLE/POSSIBLE CASES OF PGS WITH FOSPHENYTOIN FROM PFIZER

Note: These cases were identified and categorized⁷⁰ by the sponsor in Pfizer's Proprietary Post-marketing Safety Database.

Line-Listing of Possible/Probable Cases (NOTE: Cases 1-4 are also included in Appendix G and identified in the AERS database.)

Case #	ISR #	Manufacturer #	Age/ Gender	Dose (PE)	Comments/Details	Pfizer Categorization ¹
1	3566977-1	001-0982-990045	83/M	600mg	A pharmacy student (b) (6) reported that a patient who was hospitalized for depression and psychosis developed purple glove syndrome, considered medically significant, after receiving intravenous fosphenytoin 600 mg	Probable
2	5484058-7	2007062067	72/M	500mg + 100mg	Patient developed "blisters on the right hand and dorsal forearm" and "purplish discoloration which darkened." Treatment included debridement and hyperbaric treatment. The patient's chart included a notation of "PGS?" but no other information. The wound was reported to be "healing."	Probable
3	5113338-X	2006111007	34/M	1000mg	Developed a "red, hard, swollen and painful" arm extending from the "elbow to the fingertips" within 30 minutes after receiving Cerebyx. While administering the IV infusion, "the drug infiltrated into the arms and extravasation occurred." Medical history, concomitant medications, treatment and outcome of the events were not reported. This was considered an important medical event.	Possible
4	4121846	2002052928	U	U	Patient was given fosphenytoin via intravenous infusion and developed discoloration of the skin which he referred to as "black glove syndrome" when the IV infiltrated.	Probable
5	N/A	001-0982-M0100021	U	U	Patient (age and gender not stated) developed "purple glove syndrome which was characterized by bruising up the hand similar to what occurs with intravenous Dilantin (phenytoin)" after receiving a dose of fosphenytoin. On follow up the pharmacist stated that "upon further investigation there was no adverse event to report" and the "nurse manager states the patient had other non-Cerebyx related clinical problems."	Probable

⁷⁰ See Appendix D for categorization definitions

Narrative Summaries of Three (3) **Unlikely** PGS Cases as Categorized by the Sponsor

1. Mfr Report #001-0982-980025: A pharmacist [REDACTED] (b) (6) reported that a 73 year-old male with a diagnosis of stroke and hypertension developed “a swollen arm from his wrist to elbow, with seven to eight blisters containing fluid” after receiving fosphenytoin 1.5 gm on 06AUG1998 for prophylactic treatment of seizures, followed by 100 mg fosphenytoin in D5NS with 20 mEq KCl every 8 hours, and “other unspecified medications”. Fosphenytoin was discontinued on 10AUG1998 when the arm swelling was noted. It was “unclear if infiltration occurred.” The pharmacist later reported that “the patient also experienced second degree burns to his right arm.” Treatment included Silvadene to the affected area. Concomitant medications included midazolam, furosemide, and mannitol. CT scan showed large intraparenchymal hematoma. Subsequent therapy included intravenous phenytoin. The patient was discharged to a nursing facility on 18AUG1998. His right arm was reported to be “healing slowly at that time.” No additional information was provided. *(Note: this is the same case as #8 in Appendix G, ISR 3311714-9 from FDA AERS database.)*

2. Mfr Report #001-0982-M0000027: A pharmacist [REDACTED] (b) (6) reported that an adult patient (gender not reported) developed extravasation after a single dose of fosphenytoin 100 mg via intravenous piggyback on 20SEPT2000. The extravasation was characterized by “erythema, flushed, irritation, and pain.” Indication for treatment, medical history, and concomitant medications were not reported. The patient left the hospital against medical advice, and the outcome is not known. No additional information was provided.

3. Mfr Report #001-0982-M0000038: A pharmacist [REDACTED] (b) (6) reported that a patient (age and gender not known) developed a “possible phlebitis” while receiving fosphenytoin in the Intensive Care Unit. The indication for therapy and dose were not reported. On 7DEC2000 the patient’s “IV infiltrated” during fosphenytoin administration. The next day the patient’s “skin was red and warm and looked like phlebitis”. Concomitant medications included nitroprusside. No additional information was provided.

7.10 APPENDIX J: PURPLE GLOVE SYNDROME LITERATURE RESULTS

Literature Results from Previous OSE Review⁷¹ (Purple Glove Syndrome)

Published Case Reports of PGS with Phenytoin

- Mahajan RP, Batra YK, Rajeev S. Intravenous phenytoin and percutaneous arterial cannulation: the purple-glove syndrome. *Eur J Anaesthesiol*. 2007 Oct; 24(10):900-1.
- Kirsch S, Bayard M, Darraj K. Distal upper extremity edema and discoloration. *Am Fam Physician*. 2007 Mar 15; 75(6):889-91.
- Chokshi R, Openshaw J, Mehta NN, Mohler E 3rd. Purple glove syndrome following intravenous phenytoin administration. *Vasc Med*. 2007 Feb; 12(1):29-31.
- Sonohata M, Asami A, Tsunoda K, Hotokebuchi T. Purple glove syndrome associated with intravenous phenytoin administration in a patient with severe mental and motor retardation. *J Orthop Sci*. 2006 Jul; 11(4):409-11.
- Bhattacharjee P, Glusac EJ. Early histopathologic changes in purple glove syndrome. *J Cutan Pathol*. 2004 Aug; 31(7):513-5.
- Endoh T, Miyake S. [A case of purple glove syndrome following an intravenous infusion of phenytoin] *No To Hattatsu*. 2001 Sep; 33(5):442-4.
- Yoshikawa H, Abe T, Oda Y. Purple glove syndrome caused by oral administration of phenytoin. *J Child Neurol*. 2000 Nov; 15(11):762.
- Cadenbach A, Röttger K, Müller MK. Purple glove syndrome. Severe soft tissue reaction following phenytoin infusion. *Dtsch Med Wochenschr*. 1998 Mar 13; 123(11):318-22.
- Helfaer MA, Ware C. Purple glove syndrome. *J Neurosurg Anesthesiol*. 1994 Jan; 6(1):48-9.
- Hayes AG, Chesney TM. Necrosis of the hand after extravasation of intravenously administered phenytoin. *J Am Acad Dermatol*. 1993 Feb; 28(2 Pt 2):360-3.
- Hanna DR. Purple glove syndrome: a complication of intravenous phenytoin. *J Neurosci Nurs*. 1992 Dec; 24(6):340-5.
- Spengler RF, Arrowsmith JB, Kilarski DJ, Buchanan C, Von Behren L, Graham DR. Severe soft-tissue injury following intravenous infusion of phenytoin. Patient and drug administration risk factors. *Arch Intern Med*. 1988 Jun; 148(6):1329-33. Comment in: *Arch Intern Med*. 1989 Aug; 149(8):1905.
- Earnest MP, Marx JA, Drury LR. Complications of intravenous phenytoin for acute treatment of seizures. Recommendations for usage. *JAMA*. 1983 Feb 11; 249(6):762-5.

Published Observational Studies

Several observational studies relevant to PGS have been published. Results have varied, probably depending on prospective versus retrospective study design, the patient population studied and the clinical definition of PGS used by the study investigators.

Case-Control Study

In 1988, Centers for Disease Control epidemiologists reported that between April 1982 through June 1984, 11 patients in a single hospital experienced 17 episodes of limb edema and discoloration after the intravenous (IV) administration of phenytoin sodium

⁷¹ Gelperin K. Purple Glove Syndrome. OSE RCM#2007-1332. 26 November 2008.

(Dilantin).⁷² One patient required a below-the-elbow amputation; all other patients recovered. No single drug lot was implicated. A case-control study was performed using three controls for each case; controls received IV infusions of phenytoin and were hospitalized close in time to the case patients. Compared with controls, patients with reactions were more often female and elderly and had underlying cardiovascular disease. Affected patients also received phenytoin through an IV catheter smaller than 20 gauge (50% vs. 6%), at a rate greater than 25 mg/min (63% vs. 19%), and in two or more IV infusions of phenytoin given "IV push" at the same site (81% vs. 24%). The authors concluded that "high-risk patients require careful monitoring and stricter guidelines for the IV administration of phenytoin."

Retrospective Observational Study

In 1998, O'Brien et al conducted a study at the Mayo Clinic in Minnesota to determine the incidence, risk factors, and long-term sequelae of purple glove syndrome (PGS) in hospital patients receiving IV phenytoin.⁷³ The pharmacologic records of the Mayo Foundation hospitals were reviewed to identify 179 consecutive patients who had IV phenytoin ordered during a 3-month period. Their hospital records were then reviewed to confirm IV phenytoin treatment, the frequency of PGS (defined as the progressive development of edema, discoloration, and pain in the limb after administration of IV phenytoin), and the outcome of PGS. A total of 152 patients received IV phenytoin, and nine (5.9%) developed PGS. PGS patients received a greater median initial dose of phenytoin, total 24-hour dose, and total number of doses (all $p < 0.05$). In addition, the median age of the PGS patients was older, their infusion was more often given for acute seizures, it was less likely to be administered in the operating room, and the length of their hospital stay was longer (all $p < 0.05$). One patient required surgical therapy, and all other patients resolved within 3 weeks with conservative management. The authors concluded that PGS is not rare, and that elderly patients and individuals receiving large, multiple doses are particularly at risk. They recommended that this iatrogenic complication may be preventable by substituting fosphenytoin for IV phenytoin.

Prospective Observational Studies

In 2001, Burneo et al published the results of a prospective study of 179 consecutive administrations of intravenous phenytoin at a single institution (Henry Ford Hospital in Detroit, MI) which found that the incidence of PGS was 1.7%.⁷⁴ This complication involved two patients who recovered without prolonged hospitalization or surgical intervention. Most patients received an initial loading dose (intravenous) followed by oral doses. The administration of phenytoin at that institution was standardized and managed by the Pharmacy Department, where parenteral phenytoin was packaged in normal saline

⁷² Spengler RF, Arrowsmith JB, Kilarski DJ, Buchanan C, Von Behren L, Graham DR. Severe soft-tissue injury following intravenous infusion of phenytoin. Patient and drug administration risk factors. Arch Intern Med. 1988 Jun;148(6):1329-33. Comment in: Arch Intern Med. 1989 Aug;149(8):1905.

⁷³ O'Brien TJ, Cascino GD, So EL, Hanna DR. Incidence and clinical consequence of the purple glove syndrome in patients receiving intravenous phenytoin. Neurology. 1998 Oct;51(4):1034-9. Comment in: Neurology. 1998 Oct;51(4):942-3. Neurology. 1999 Oct 22;53(7):1611-2.

⁷⁴ Burneo JG, Anandan JV, Barkley GL. A prospective study of the incidence of the purple glove syndrome. Epilepsia. 2001 Sep;42(9):1156-9.

and administered via IVPB at a rate not to exceed 20 mg/min, using an electronic infusion control device and a 0.22µm in-line filter, based on the manufacturer's recommendations.

Also in 2001, O'Brien et al (Australian Centre for Clinical Neuropharmacology) published the results of a prospective evaluation of the occurrence of subacute local cutaneous reactions (LCR) in patients receiving IV phenytoin over a 12-month period at a general hospital in Australia.⁷⁵ LCR were detected in 29 of 115 patients (25.2%; 22 mild and seven moderate). All resolved within 3 weeks. Patients with LCR were older (median 68 versus 54.5 years, $p = 0.004$), were more likely to be in a general ward (86% versus 66%, $p = 0.04$), and had larger catheters (median 16 G versus 18 G, $p = 0.05$). The authors conclude that LCR are common in routine hospital practice, but are generally mild and benign.

Prospective Randomized Studies

In 2004, Swadron et al published the results of a randomized study designed to compare three phenytoin-loading techniques⁷⁶ which was conducted at the Department of Emergency Medicine, Keck School of Medicine, in California. Patients with subtherapeutic phenytoin concentrations who presented within 48 hours of a seizure were randomized to receive either 20 mg/kg of oral phenytoin, divided in maximum doses of 400 mg every two hours, 18 mg/kg of intravenous phenytoin at an initial infusion rate of 50 mg/min, or 18 mg/kg (phenytoin equivalents) of intravenous fosphenytoin at an initial infusion rate of 150 mg/min. A total of 45 patients were enrolled: 16 in the oral group, 14 in the intravenous phenytoin group, and 15 in the intravenous fosphenytoin group. The times required to reach therapeutic drug concentrations were 5.62 hours, 0.24 hours, and 0.21 hours, respectively. A total of 17, 27, and 32 adverse drug events were observed in the oral, intravenous phenytoin, and intravenous fosphenytoin groups, respectively, with significantly fewer events in the oral group ($p = 0.02$, $p = 0.01$). No significant difference was found between the numbers of necessary adjustments to the infusions in the two IV groups. The average time to safe emergency department discharge was significantly shorter for the IV groups compared with the oral group ($p < 0.001$). The authors concluded that oral loading has fewer adverse drug events than either IV loading method, but its use may be limited when therapeutic concentrations are required quickly. Although intravenous fosphenytoin loading is faster, from an adverse-drug event perspective, no advantage of intravenous fosphenytoin over intravenous phenytoin was apparent.

Coplin et al⁷⁷ evaluated adverse events and length-of-stay during routine emergency department use in an open-label randomized study of phenytoin or fosphenytoin in 256

⁷⁵ O'Brien TJ, Meara FM, Matthews H, Vajda FJ. Prospective study of local cutaneous reactions in patients receiving IV phenytoin. *Neurology*. 2001 Oct 23;57(8):1508-10. Comment in: *Neurology*. 2002 Apr 9;58(7):1134; author reply 1134.

⁷⁶ Swadron SP, Rudis MI, Azimian K, Beringer P, Fort D, Orlinsky M. A comparison of phenytoin-loading techniques in the emergency department. *Acad Emerg Med*. 2004 Mar;11(3):244-52.

⁷⁷ Coplin WM, Rhoney DH, Rebuck JA, Clements EA, Cochran MS, O'Neil BJ. Randomized evaluation of adverse events and length-of-stay with routine emergency department use of phenytoin or fosphenytoin. *Neurol Res*. 2002 Dec;24(8):842-8.

Emergency Department patients prescribed 279 parenteral doses of a phenytoin-equivalent. All phenytoin was administered intravenously, and fosphenytoin was given intravenously or intramuscularly (physician preference). Adverse events and Emergency Department length-of-stay were recorded; re-presentation to the Emergency Department within three months was reviewed for evidence of the purple glove syndrome. Seventy-seven patients received phenytoin and 202 fosphenytoin; 28 (10.0%) received intramuscular fosphenytoin. The mean phenytoin-equivalent dose was similar between the groups. Eighteen patients required reduction in infusion rates because of an adverse event (phenytoin = 6.5%, fosphenytoin = 6.4%; OR 0.9, 95% CI 0.4 2.6; $p = 1.0$). Adverse events occurred with similar frequency (phenytoin 9.1%, fosphenytoin 15.8%; OR 0.7, 95% CI 0.3 1.4; $p = 0.3$). The most common events were: pruritus, pain on infusion, and paresthesias. One patient developed hypotension (fosphenytoin); there were no other serious adverse events, including phlebitis. Median Emergency Department length-of-stay was 6.7 h for phenytoin and 5.7 h for fosphenytoin ($p = 0.6$). The authors concluded that these results do not support formulary conversion from phenytoin to fosphenytoin in routine Emergency Department use, based on the incidence of adverse events or Emergency Department length-of-stay.

7.11 APPENDIX K: DETAILS OF PUBLISHED CASE REPORTS OF PURPLE GLOVE SYNDROME (PGS) ASSOCIATED WITH PHENYTOIN.

	Age/Gender	Dose	Infusion Rate/Details	Treatment	Outcome	Comment
Case Report ⁷⁸ #1	40/F	Unknown	Unknown	Surgical Revision	Unknown	
Case Report ⁷⁹ #2	55/M	Unknown	Unknown	IV heparin	Resolved at 4 weeks	
Case Report ^{80,81} #3	26/F	600 mg IV	<ul style="list-style-type: none"> Diluted in 500cc Normal Saline Administered via 20G needle in dorsal vein of right hand. 	Bupivacaine (0.1%) with fentanyl (2 µg/ml) x 7 days.	Recovered at 1 month.	
Case Report ⁸² #4	38/M	1230 mg IV + 100 mg IV	Administered through 18G cannula on ventral aspect of left forearm.	Limb elevation, anti-inflammatory drugs, antibiotics, heparin, bupivacaine 0.5%.	Recovered	History of thrombophlebitis in right arm.
Case Report ⁸³ #5	79/F	Unknown	Unknown	Unknown	Improved steadily.	History of cerebral artery infarct and recent cerebrovascular accident (CVA).
Case Report ⁸⁴ #6	14/M	200 mg IV	<ul style="list-style-type: none"> Diluted in 30cc of saline. Used 23G catheter. 	200mg hydrocortisone injected locally Limb elevation, warm packs	Symptoms resolved after 3 weeks.	Fasciotomy was considered, but too sick (aspiration pneumonia) to undergo surgery

⁷⁸ Warnecke I, et. al. Purple Glove Syndrome: a case report. Handchir Mikrochir Plast chir. 2010 Aug; 42(4): 260-2. (abstract only currently available, undergoing copyright clearance).

⁷⁹ Keane M.G., Shirazi H., Marsh P. and Khushal A. Purple Glove Syndrome following intravenous phenytoin infusion. British Journal of Surgery 2009 96:1065.

⁸⁰ Santoshi J, et al. Purple Glove Syndrome: a case report. Hand surgeons and physicians be aware. Journal of Plastic, Reconstructive and Aesthetic Surgery. 2009; XX: 1-3.

⁸¹ Singh G, Cherian V, Thomas B. Low-concentration ,continuous brachial plexus block in the management of Purple Glove Syndrome: a case report. Journal of Medical Case Reports 2010; 4 (48): 1-4.

⁸² Mahajan RP, Batra YK, Rajeev S. Intravenous phenytoin and percutaneous arterial cannulation: the purple-glove syndrome. Eur J Anaesthesiol. 2007 Oct; 24(10):900-1.

⁸³ Kirsch S, Bayard M, Darraj K. Distal upper extremity edema and discoloration. Am Fam Physician. 2007 Mar 15; 75(6):889-91.

⁸⁴ Sonohata M, Asami A, Tsunoda K, Hotokebuchi T. Purple glove syndrome associated with intravenous phenytoin administration in a patient with severe mental and motor retardation. J Orthop Sci. 2006 Jul; 11(4):409-11.

	Age/Gender	Dose	Infusion Rate/Details	Treatment	Outcome	Comment
Case Report ⁸⁵ #7	86/M	400 mg IV	Administered undiluted.	Dry heat and limb elevation	Complete resolution in 1 week.	Histopathology showed superficial ulceration, epidermal necrosis, and mild superficial and deep perivascular lymphoid infiltrate. There was also congestion of small vessels and numerous thrombi.
Case Report ⁸⁶ #8	10/M	1000 mg Oral	Administered through a nasogastric tube	Only drug discontinuation	Improved within 2 weeks.	Hands and feet swelled turned dark purple. 10-fold overdose given.
Case Report ⁸⁷ #9	37/F	250 mg IV and 750 mg IV	Administered at 25 mg/min (250 mg dose) and over 24 hours (750 mg dose)	Anti-inflammatory agents, antibiotics, and local measures.	Recovered, but re-admitted 3 weeks later with renewed pain and early Sudeck's atrophy	
Case Report ⁸⁸ #10	49/F	Unknown/ Seizure prophylaxis	Unknown	Wrist disarticulations		Severe tissue necrosis, sloughing in the epidermis; thrombotic occlusion of vessels; involved extravasation
Case Report ⁸⁹ #11	6 months/M	99 mg IV (12 mg/kg)	<ul style="list-style-type: none"> Diluted in 20cc normal saline Administered at 6.2 mg/min (0.75 mg/kg/min) via left saphenous vein. 	None	Resolved in 7 hours.	Purple discoloration (no swelling) occurred in foot.

⁸⁵ Bhattacharjee P, Glusac EJ. Early histopathologic changes in purple glove syndrome. J Cutan Pathol. 2004 Aug; 31(7):513-5.

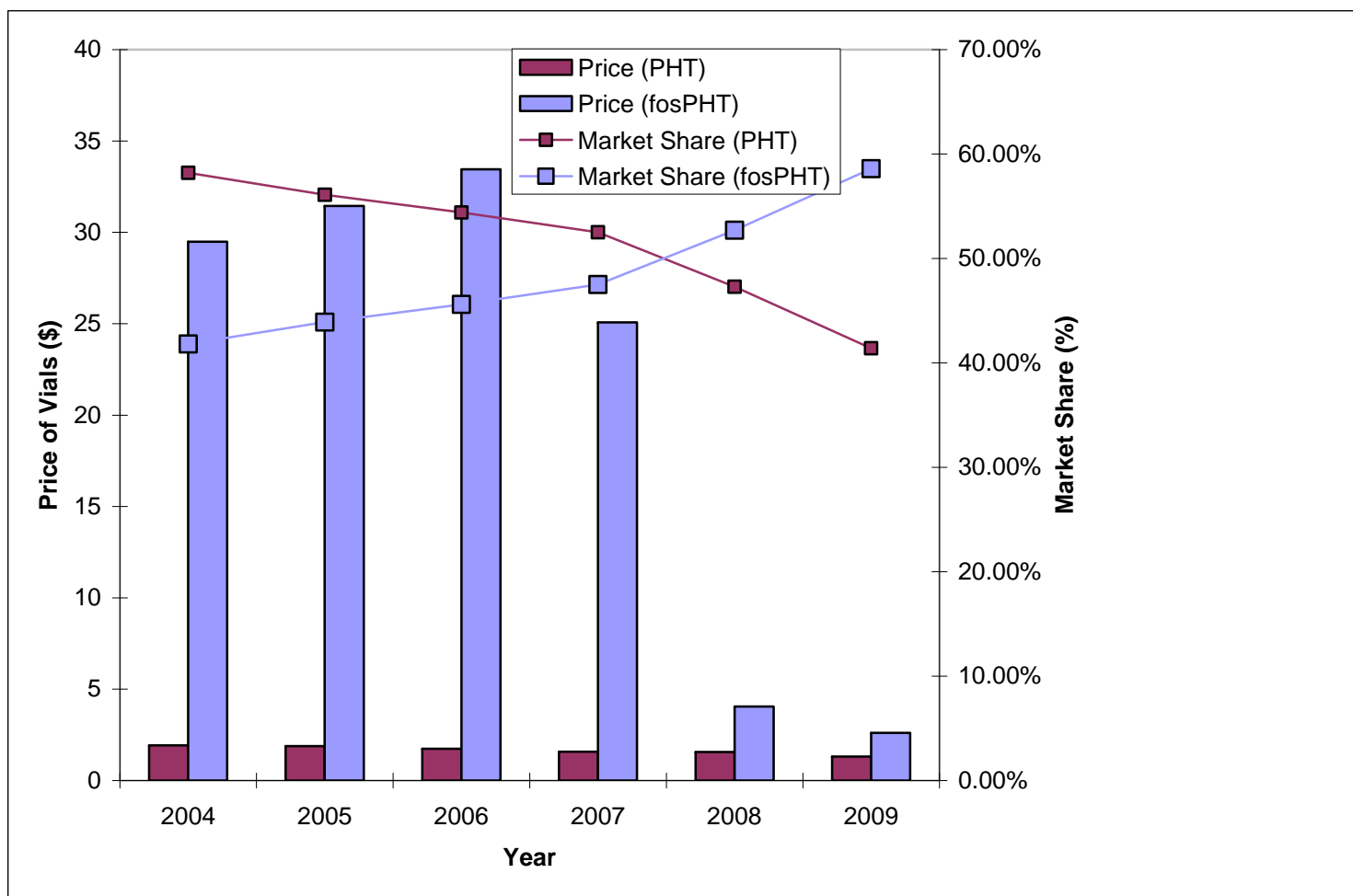
⁸⁶ Yoshikawa H, Abe T, Oda Y. Purple glove syndrome caused by oral administration of phenytoin. J Child Neurol. 2000 Nov; 15(11):762.

⁸⁷ Achenbach A, Röttger K, Müller MK. Purple glove syndrome. Severe soft tissue reaction following phenytoin infusion. Dtsch Med Wochenschr. 1998 Mar 13; 123(11):318-22.

⁸⁸ Hayes AG, Chesney TM. Necrosis of the hand after extravasation of intravenously administered phenytoin. J Am Acad Dermatol. 1993 Feb; 28(2 Pt 2):360-3.

⁸⁹ Helfaer MA, Ware C. Purple glove syndrome. J Neurosurg Anesthesiol. 1994 Jan; 6(1):48-9.

7.12 APPENDIX L: DRUG COST AND MARKET SHARE OF FOSPHENYTOIN AND IV PHENYTOIN: 2004-2009.



7.13 APPENDIX M: DETAILS OF MISCLASSIFIED CASE OF PGS (FROM PFIZER SUBMISSION JULY 2008)

One “unlikely” case (Mfr Report #001-0982-980025, ISR 3311714) was misclassified (see Appendix D) by the sponsor, and more appropriately should be categorized as “possible,” according to the sponsor. This case describes a 73 year-old with “blisters and a swollen arm after 1.5 g and 1 g doses of fosphenytoin; the patient also experienced second degree burns to his right arm. Fosphenytoin was discontinued, while IV phenytoin was initiated, and the patient’s arm was slowly healing at the time of the report.” This misclassified “unlikely” case is based on the sponsor’s categorization - Appendix C details Pfizer’s categorization criteria for PGS. The sponsor defines possible as, “the majority of signs and symptoms and clinical course appear consistent with PGS but there is not enough specific information to categorize as probable or there are minor inconsistencies. Includes cases where the reaction moved away from the site of administration.” Although minor PGS inconsistencies exist (reported event does not describe discoloration or hand involvement) in the clinical details above, given the age (elderly), repeated large doses, blisters, and swollen arm likely distal to the infusions site, a “possible” classification, based on the sponsor’s criteria, is more plausible. Furthermore, this case was also identified in the original OSE AERS review where it was classified as a serious cutaneous reaction. A disparity over this case exists between the current review and the sponsor’s submission. Based on the sponsor’s classification, the aforementioned case is deemed “possible” PGS, while based on the case in Section 2.3, this case is not PGS, rather a serious local reaction.

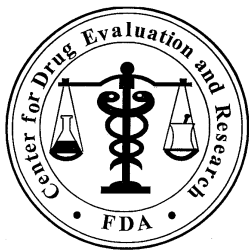
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10/05/2010

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

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Subject: Adverse Effects and Current Clinical
Considerations for Use of Phenytoin versus
Fosphenytoin, Excluding Purple Glove Syndrome

Drug Name: Cerebyx (Fosphenytoin Sodium) Injection, 100 Mg PE/2
mL, 500 Mg PE/10 mL
Phenytoin Sodium Injection, 100 mg/2 mL, 250 mg/5
mL

Application Type/Number:

NDA 020450	ANDA 089521
ANDA 077481	ANDA 089744
ANDA 078126	ANDA 040573
ANDA 078137	ANDA 084307
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ANDA 077989	
ANDA 078158	
ANDA 078417	
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Applicant/sponsor: Eisai Inc., Bedford, Apotex Inc., Wockhardt,
Pharmaforce, Teva Parenteral, Baxter Healthcare,
Hospira, Sun Pharma Global, Hikma Farmaceutica, App
Pharms, Akorn Strides, Strides Arcolab

OSE RCM #: 2010-571

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EXECUTIVE SUMMARY

To compare the safety of injectable fosphenytoin to intravenous phenytoin for adverse events outside of the Purple Glove Syndrome (PGS), this review evaluates reports from the Adverse Event Reporting System (AERS) database, sponsor submitted analyses, and published literature. Other than PGS for IV phenytoin and burning and paresthesias for fosphenytoin, the evaluation found no convincing evidence of a substantial difference between IV phenytoin and fosphenytoin in safety concerns especially for cardiotoxicity and hypotension adverse events, the category of AEs (Adverse Events) most emphasized in this review. Searches revealed no new and significant adverse events for either product.

- The review of the AERS data and the review of literature suggest that cardiac events and hypotension are comparable with fosphenytoin and IVphenytoin.
- Interest in other adverse events (other than those associated with local reactions) is notably sparse in the published literature. What can be inferred from labeling and confidential Pfizer data submitted to FDA is that there appear to be no substantial differences between the safety of the two drugs.
- A literature review suggests that both these agents are widely used in equivalent settings, age groups, and special populations.
 - One notable exception is use of IV phenytoin (a Class 1b antiarrhythmic) in patients with digitalis induced arrhythmias.
- Specific institutions, practitioners and referenced texts show preferences of one over the other based on local considerations and preferences.

Additionally, a broad overview of the state of current standard of practice and the context of use of each drug is compared and summarized.

This review was prepared for an upcoming joint Peripheral and Central Nervous System Drugs/Drug Safety and Risk Management Advisory Committees meeting.

Recommendations on Regulatory Actions and Labeling

- For IV phenytoin: Eliminate cardiac labeling from ADVERSE REACTIONS section and retain in the WARNINGS section ONLY.
- For fosphenytoin and IV phenytoin: Labeling will continue to include “Cardiovascular Depression” and “Serious Cardiovascular Events and Fatalities” (with CAUTION in patients with hypotension and severe myocardial insufficiency)
- For fosphenytoin and IV phenytoin: Broaden WARNINGS labeling to include specific diagnoses of cardiac arrest, asystole, ventricular tachycardia, ventricular fibrillation, prolonged QT interval, junctional rhythm, sudden death, and pulseless electrical asystole as identified in the AERS database.

- For fosphenytoin and IV phenytoin: Broaden WARNINGS labeling to include specific language that these events can occur in healthy adults and children without underlying cardiac disease or co-morbidities, and occurrence at or below recommended doses, at or below recommended infusion rates and during as well as after infusions. The current label for fosphenytoin and IV phenytoin will continue to have CONTRAINDICATIONS in patients with sinus bradycardia, sino-atrial block, second and third degree A-V block and Adams-Stokes syndrome.
- For fosphenytoin and IV phenytoin: Consider labeling under PRECAUTIONS for additional ECG and laboratory monitoring during and after infusion in special populations such as renal, cardiac, hepatic, elderly, CYP mutations & slow metabolizers, concurrent users of first line seizure treatment with benzodiazepine that interact with these drugs, and organ transplant patients.
- For fosphenytoin: Update the ADVERSE REACTION table in the Clinical section with more comprehensive data submitted from the integrated clinical trial adverse event profiles from Pfizer's 2008 systematic analysis. This data will more accurately reflect the rates of treatment-emergent adverse events for fatal, non-fatal, serious and non-serious Adverse Events.

Recommendations for Other Actions

- IV phenytoin: Consider issuance of a Dear professional letter to instruct in preferred dosing, use in special populations and recommendation for a proposed clinical algorithm for choosing fosphenytoin versus IV phenytoin. Include specific language that these events can occur in healthy adults and children without underlying cardiac disease or co-morbidities, and occurrence at or below recommended doses, at or below recommended infusion rates and during and after infusions.
- IV fosphenytoin: Consider issuance of a Dear professional letter stating that fosphenytoin does not have less hypotension or cardiac toxicity and include specific language that these events can occur in healthy adults and children without underlying cardiac disease or co-morbidities, and occurrence at or below recommended doses, at or below recommended infusion rates and during and after infusions. Inform practitioners that current updates in analysis show a possibility for PGS but require further analysis.
- Office of Compliance to follow through with reporting issues for fosphenytoin by Pfizer.

1 BACKGROUND

1.1 INTRODUCTION

The Division of Neurology Products (DNP) requested evaluation of the safety of injectable fosphenytoin (fosphenytoin) as compared to intravenous phenytoin (phenytoin) for adverse effects not designated as Purple Glove Syndrome (PGS). Therefore, the Division of Pharmacovigilance I (DPV I) searched and reviewed the Adverse Event Reporting System (AERS) database, sponsor submitted analyses, published literature including case reports and studies, and drug utilization for safety concerns. *For discussion on Purple Glove Syndrome with use of phenytoin and fosphenytoin see referenced reviews^{1,2, 3} notably the most recent 2010 and companion PGS reviews.* This document will discuss Non-PGS adverse events followed by discussion on the state of current standard of practice for using phenytoin or fosphenytoin. These include their use largely in the hospital and emergency room setting, in adult and pediatric groups, current clinical standards of practice and reviews of current published literature. The use of each drug in special populations such as elderly, renal and hepatic impaired, organ transplant and others is also discussed.

Cardiovascular and hypotensive adverse events are emphasized because they have been the basis of two prior OSE reviews^{4, 5} and they are among some of the most common and serious sequelae. In 1983, guidelines for proper administration of IV phenytoin were published in JAMA; the article focused on techniques to avoid burning at the administration site, hypotension, or arrhythmias associated with rapid infusion rate.⁶ Arrhythmias and hypotension have also been reported throughout the literature occurring at or above recommended doses or infusion rates. The active ingredient and the vehicle itself in IV phenytoin (propylene glycol) have been linked to these adverse effects. With IV phenytoin, Ziai⁷ states that hemodynamic complications can be as high as 27% for hypotension, 9.9% for respiratory depression, and 6.9% for cardiac arrhythmias.

¹ Phelan K, Pamer CA. Purple Glove Syndrome. OSE RCM# 2007-1332. 9 July 2008.

² Gelperin K. Purple Glove Syndrome. OSE RCM#2007-1332. 26 November 2008

³ Fine A, Gatti JG, Purple Glove Syndrome. OSE RCM#2010-571. 4 October 2010

⁴ Mease M. Monitored Adverse Reaction (MAR) for Cerebyx (fosphenytoin sodium), phenytoin sodium, diazepam, lorazepam, and phenobarbital. Reactions: Cardiovascular adverse events.

⁵ Thambi L. Drugs: Cerebyx (fosphenytoin sodium), intravenous phenytoin. Reactions: serious cardiovascular events, hypotension. PID# D010566.

⁶ Earnest MP, Marx JA, Drury LR. Complications of intravenous phenytoin for acute treatment of seizures. Recommendations for usage. JAMA. 1983 Feb 11; 249(6):762-5.

⁷ Ziai WC, Kaplan PW, Seizures and Status epilepticus in the Intensive Care Unit. Seminars in Neurology. 2008;28(50):668-679. Based on Treiman,DM, et al. Comparison of four treatments for generalized convulsive status epilepticus. NEJM 1998 Sept;339(12):792-798.

This review includes AERS data divided into two adverse event categories. The first category provides the most frequently reported preferred terms (PTs) for IV phenytoin and fosphenytoin covering all serious adverse events reported since market approval (1956 for IV phenytoin and 1996 for fosphenytoin). In the second category, only cardiovascular (CV) and hypotension events from AERS are described for both products.

This review was prepared for an upcoming joint Peripheral and Central Nervous System Drugs/Drug Safety and Risk Management Advisory Committees meeting which will inform on potential regulatory action. *References will be made to the companion documents which develop many of these concepts in more detail.*

1.2 DRUG PROPERTIES AND MECHANISM OF ACTION

Mechanisms of Action

- Both phenytoin and fosphenytoin block neuronal and cardiac voltage-sensitive Na⁺ channels and Ca²⁺ fluxes across neuronal membranes.
- It is highly likely that both drugs can rapidly induce bradycardia, hypotension, and sympathetic nerve blockade⁸ by their action as a sodium channel blocker. In addition, phenytoin contains propylene glycol which might also affect ionic currents.
- Phenytoin is a class I-b anti-arrhythmic agent (along with lidocaine and mexiletine).

⁸ DeToledo JC, Ramsay RE. Fosphenytoin and phenytoin in patients with status epilepticus: improved tolerability versus increased costs. *Drug Safety* 2000;22:459-66.

Table 1: Drug Properties: Injectable Fosphenytoin versus Intravenous Phenytoin

Characteristic	Fosphenytoin ⁹	IV Phenytoin
PH	pH 8.6 to 9	weak organic acid, alkaline pH 12
Chemical properties	phosphate ester pro-drug of phenytoin ¹⁰	vehicle of ethanol and propylene glycol added to its carrier sodium hydroxide to enhance its solubility
Solubility, compatibility with parenteral fluids	water soluble and compatible with most standard IV fluids, including dextrose.	cannot be mixed with IV fluids
Local Skin Effects	designed to diminish the complications of IV phenytoin; less local irritation	irritating to the skin; tissue necrosis with extravasation
Mode of Administration	IV/IM	PO/IV
Doses (for SE=status epilepticus in adults only)	load IV: 15-20 mg/kg PE (phenytoin equivalents: 1.5 mg fosphenytoin=1 mg phenytoin) over 5-7 mins. at max rate 50-150 mg/min. Maintain 4-6 mg PE/kg/day. IM dose: single day dose at 1-2 sites	load IV: 10-15 mg/kg (or 250 mg) over 10 mins. at max rate 50 mg/min. Maintain 100mg q 6-8 hr.

⁹ Eriksson K, Keranen T, Kalviainen R, Fosphenytoin. Expert Opinion Drug Metab Toxicol.2009; 5 (6); 695-701

¹⁰ Pro-drug=disodium phosphate ester of 3-hydroxymethyl- 5,5-diphenylhydantoin

Table 2: Pharmacokinetics and metabolism of IV/IM Fosphenytoin and IV Phenytoin

Characteristic	IV/IM <u>Fosphenytoin</u>	IV <u>Phenytoin (data from label approved 1956)</u>
C max*	at end of infusion (IV); 20 – 39 min (IM)	plasma half-life in man after IV administration 10 to 15 hours
Metabolized	<ul style="list-style-type: none">• completely to phenytoin by phosphatase in liver, RBCs and many other tissues• conversion half-life is 8 – 15 min (IV) (No drugs are known to affect the conversion of fosphenytoin to phenytoin)• independent of fosphenytoin or phenytoin concentration	not specifically stated
Plasma protein binding	<ul style="list-style-type: none">• bound 95 – 99%• competitively displaces phenytoin*• IM: displacement of phenytoin is minor because the slower absorption limits the concentrations of fosphenytoin achieved	not specifically stated
Peak plasma levels of phenytoin	<ul style="list-style-type: none">• determination of plasma fosphenytoin is not relevant to pharmacological activity• fosphenytoin therapy monitored by plasma phenytoin• 90 – 190 min (IM)	plasma levels may fall changing from oral to intramuscular due to slower absorption, and the poor water solubility of phenytoin**.
Bioavailability	complete for both IV/IM	not specifically stated
Elimination	similar to phenytoin for both IV/IM	not specifically stated Comment: intramuscular depot of poorly soluble material is eventually absorbed, as determined by urinary excretion of 5-(p-hydroxyphenyl)-5-phenylhydantoin (HPPH), the principal metabolite, as well as the total amount of drug eventually appearing in the blood.

*Increases in the unbound fraction of phenytoin are observed during the initial 30 – 60 min with IV administration of fosphenytoin, after which the phenytoin binding returns to normal. Displacement is most pronounced after doses > 15 mg PE/kg and high infusion rates (50 – 150 mg PE/min. The clinical relevance of this interaction is that the free phenytoin plasma

concentration–time profile will vary with the rate of delivery of fosphenytoin into the body.

The displacement of phenytoin from plasma protein binding sites at faster infusion rates of fosphenytoin (100 – 150 mg PE/min) compensates for the conversion-related delay in the appearance of phenytoin in the plasma. Thus, therapeutic plasma concentrations of unbound phenytoin are achieved in the same time frame as in the case when IV phenytoin is administered at its maximum recommended infusion rate (50 mg/min).

** Patients stabilized on a daily oral regimen of phenytoin experience a drop in peak blood levels to 50-60 percent of stable levels if crossed over to an equal dose administered intramuscularly. Patients do not experience the expected drop if phenytoin IM dose is increased by 50 percent over the previously established oral dose. To avoid drug accumulation due to absorption from the muscle depots, it is recommended that for the first week after transition to oral phenytoin, the dose be reduced to half of the original oral dose (one third of the IM dose).

Table 3: Pharmacokinetics of Fosphenytoin in Special Populations

5 – 18 years of age, elderly	similar to adults except clearance of phenytoin is 20% less in >70 years compared with younger adults
hepatic and renal diseases	one study of 4 renal and 4 hepatic patients: there is increased fosphenytoin clearance and earlier peak plasma concentrations of phenytoin in both populations due to decreased binding of fosphenytoin to plasma proteins and an increased unbound fraction of fosphenytoin, which in turn are associated with disease related decreases in plasma protein concentrations

1.3 REGULATORY HISTORY OF NON-PGS ADVERSE EVENTS

Intravenous phenytoin (Dilantin) was approved in 1956 and intravenous fosphenytoin (Cerebyx) in 1996. In 1997, subsequent to fosphenytoin's approval, Parke-Davis removed intravenous Dilantin from the market. Current IV phenytoin ANDA's¹¹ reference Baxter's product in the Approved Drug Products with Therapeutic Equivalence Evaluations book (also known as the Orange Book). *See Appendix 2 & 3.*

The regulatory history includes two 2008 PGS reviews, the current 2010 review update on PGS^{1,2,3}, and two cardiovascular/hypotension reviews.^{4,5} This section only describes the relevant regulatory history of cardiovascular and hypotension safety concerning IV phenytoin and fosphenytoin.

- The first review⁴, which analyzed AERS data through 1999, identified 28 IV fosphenytoin cases and 55 IV phenytoin cases associated with serious cardiac arrhythmias. Also included were 25 cases of hypotension associated with fosphenytoin use, and 13 cases linked to IV phenytoin administration. The review concluded that the events occurred in patients of all ages and in some patients without compromising medical conditions. Additionally, the majority of cases (for both products) occurred at or below the recommended doses and infusion rates, and the events occurred during and after the infusion. Finally, there was no identified pattern with regard to seizure type and CV event.

¹¹ ANDA=Abbreviated New Drug Application, Office of Generic Drugs

- The second AERS review⁵ served as an updated analysis of the original CV safety analysis. From the original cutoff date (August 1999) through December 2001, 24 IV fosphenytoin cases and 21 IV phenytoin cases associated with serious CV events were identified. Five (5) additional cases of hypotension attributed to fosphenytoin, and 10 cases associated with IV phenytoin were included in this follow-up analysis. Similar to the original AERS review, the events occurred in patients of all ages, and where known, the majority of cases occurred below the recommended doses and infusion rates for both agents.

Due to the presence of serious CV events and hypotension occurring at normal doses and normal infusion rates, and affecting a variable (all ages, with/without pre-existing conditions) patient population, both reviews recommended revisions to the prescribing information in the fosphenytoin and IV phenytoin label.

Current Draft Labeling proposed by Pfizer 5/09 is under the *section 1.5 LABELING*.

On 5/27/10, Pfizer's annual report on Cerebyx also referred to a pediatric PK and safety postmarketing commitment of 5/02 that was ongoing.

Table 4: Summary of the current labeling and other sections of labeling for approved age groups for use, indications for use, warnings for IV/IM fosphenytoin and IV phenytoin

Approved label listing	IV/IM Fosphenytoin	IV Phenytoin
Approved ages	No mention of exact ages	No mention of exact ages
Indications for use and Type of patients	<ul style="list-style-type: none"> • Short-term parenteral use when other means of IV phenytoin administration are not available, inappropriate or deemed less advantageous • Substitute short-term oral phenytoin in status epilepticus (SE) • prevent and treat generalized SZ during neurosurgery 	<ul style="list-style-type: none"> • Status epilepticus (grand mal) • prevent and treat seizures (SZ) during neurosurgery
Dose for age	<ul style="list-style-type: none"> • Do not administer rate greater than 150 mg PE/min. For SE give at IV dose of 15-20 mg PE/kg at 100-150 mg PE/min. If non-emergent loading dose of 10-20 mg PE/kg IV or IM not to exceed 150 mg PE/min. Daily maintenance dose of 4-6 mg PE/kg/day. 	<p>Intravenous administration should not exceed 50 mg per minute in adults.</p> <p>In neonates, the drug should be administered at a rate not exceeding 1-3 mg/kg/min</p>
Contraindications	<ul style="list-style-type: none"> • Hypersensitivity to Cerebyx or ingredients, phenytoin or other hydantoin • Effects on Ventricular automaticity: sinus bradycardia, sino-atrial block, second and third degree A-V block, Adams-Stokes syndrome 	<ul style="list-style-type: none"> • Hypersensitivity to hydantoin • Effects on Ventricular automaticity: sinus bradycardia, sino-atrial block, second and third degree A-V block, Adams-Stokes syndrome

Warnings in label	<ul style="list-style-type: none"> • Phenytoin sodium equivalents-do not adjust recommended doses • SE dosing regimen • Withdrawal precipitated SZ, SE • Cardiovascular depression • Rash • Hepatic injury • Hemopoietic system • Alcohol use • Use in pregnancy 	<p>Intravenous administration should not exceed 50 mg per minute in adults.</p> <p>In neonates, the drug should be administered at a rate not exceeding 1-3 mg/kg/min</p>
Drug Interactions	No known drugs interfere with conversion of fosphenytoin to phenytoin.; drug interactions with same drugs as phenytoin	Drugs that increase phenytoin serum levels include: Chloramphenicol, dicumarol, disulfiram, tolbutamide, isoniazid, phenylbutazone, acute alcohol intake, salicylates, chlordiazepoxide, phenothiazines, diazepam, estrogens, ethosuximide, halothane, methylphenidate, sulfonamides, cimetidine, trazodone.*
Hepatic and/or Renal impairment	Caution especially with hypoalbuminemia (see table 3)	May show early toxicity
Geriatric Use	No geriatric studies. Phenytoin clearance may be decreased and dose may need to be adjusted downward.	May show early toxicity or severe complications.
Pediatric Use	Safety not established. Limited Number studied in age 5-10 yr. olds. No major differences from adults	See statement on neonate dose

*Drugs that increase or decrease phenytoin serum levels include: phenobarbital, valproic acid and sodium valproate. Similarly, the effect of phenytoin on phenobarbital, valproic acid and sodium valproate serum levels are unpredictable. Drugs that decrease phenytoin levels include: carbamazepine, chronic alcohol abuse, reserpine. Moban® brand of Molindone Hydrochloride contains calcium ions which interfere with the absorption of phenytoin. Ingestion times of phenytoin and antacid preparations containing calcium should be staggered in patients with low serum phenytoin levels to prevent absorption problems. Tricyclic antidepressants may precipitate seizures. Drugs that are impaired by phenytoin include: Corticosteroids, coumarin anticoagulants, oral contraceptives, quinidine, vitamin D, digitoxin, rifampin, doxycycline, estrogens, furosemide.

1.4 CLINICAL CONSIDERATIONS

Since its approval in 1956, IV phenytoin has been used widely for treatment of status epilepticus (SE), acute seizures and prophylaxis in head trauma¹². Because it lacks the propylene glycol vehicle and an alkaline pH,¹³ fosphenytoin was initially marketed in 1996 as a safer alternative to IV phenytoin. It was designed to diminish the complications of IV phenytoin: less local irritation, fewer cardiac arrhythmias, and less hypotension. Early optimism of this improved pro-drug of phenytoin may have been premature¹⁴. According to the sponsor (Parke-Davis/Warner Lambert), postmarketing experience indicates that hypotension and arrhythmias may occur more frequently with administration of large doses and fast infusion rates especially in the elderly, and in patients with existing cardiac disease¹³.

Current anti-epileptic drug (AED) treatment guidelines must consider multiple factors in choosing an appropriate AED. It is generally well accepted in the majority of patients that the first-line drugs for treatment of SE are the IV benzodiazepines followed by one of the longer acting second-line agents, IV phenytoin or fosphenytoin.⁵⁸

Listed below are some of the factors that affect the decision to choose fosphenytoin or IV phenytoin for seizure⁶⁰:

- The onset, duration, type, and range of antiepileptic activity.
- The possible effects on consciousness, cardiovascular status, or respiratory compromise.
- The ease of administration (filter, compatibility with IV fluids, route and rapidity of administration, and size of the patient's veins).
- The alternative drugs available to the patient and the prior use of other AEDs¹⁵.
- Other factors¹⁶ including ease and availability in some facilities of cardiac and drug monitoring and refrigeration.
- Patient factors including predisposing medical illnesses, age of patients, reproductive considerations, and patient preference and compliance.
- Concomitant medications, drug-drug interactions, and inhibition of CYP2 effects.

¹² According to the Washington Manual of Therapeutics: Treatment of repetitive seizures (prolonged) or Status epilepticus (SE) is defined as greater than 30 minutes of seizure activity or recurrent seizures without full recovery between episodes (SZ lasting > 5 minutes); Treatment of acute symptomatic seizures as defined by two or more unprovoked seizures; Prophylaxis after head trauma- Short-term 7 day treatment.

¹³ Knapp LE, Kugler AR. Clinical experience with fosphenytoin in adults: pharmacokinetics, safety, and efficacy. *J Child Neurol* 1998 Oct; 13 Suppl. 1:S15-8.

¹⁴ Appleton RE, Gill A. Adverse events associated with intravenous phenytoin in children: a prospective study. *Seizure* 2003; 12:369-372.

¹⁵ Eriksson K, et.al. Fosphenytoin. *Expert Opin Drug Metab Toxicol*. 2009 Jun; 5(6):695-701.

¹⁶ Jobst BC, Holmes GL. Prescribing Antiepileptic Drugs Should Patients be switched on the basis of cost?, *CNS Drugs* 2004;18(10): 617-628.

- Clinician's familiarity with the drug and inherent standards/biases of clinical use
- Practical considerations including cost (individual patient's financial and insurance situation) and availability in formulary and cost to institution.

Major adverse events being evaluated for the Peripheral and Central Nervous System Drugs and the Drug Safety and Risk Management Advisory Committees meeting include PGS, selected cardiovascular and Adverse Events, drug error and overdosing issues¹⁷, and equivalence of safety clinical considerations between fosphenytoin and IV phenytoin. See companion DEPI and DMEPA¹⁸ reviews.

1.5 PRODUCT LABELING

This section outlines safety concerns as described in current product labeling for IV phenytoin and fosphenytoin. *Complete product labeling for both agents is located in Appendix 8.11.*

IV Phenytoin¹⁹

The IV phenytoin label (WARNINGS and PRECAUTIONS) advises the following:

- Administration must be administered slowly, not exceeding 50 mg/min in adults, and 1-3 mg/kg/min in neonates.
- Severe cardiotoxic reactions and fatalities have been reported, and are most commonly encountered in the elderly.
- Hypotension usually occurs when drug is administered rapidly.
- Intramuscular route is not recommended.
- Reports suggest a relationship between phenytoin and the development of lymphadenopathy.
- Acute alcohol intake may increase phenytoin serum levels while chronic alcohol use may decrease serum levels.
- A number of reports suggest an association between the use of antiepileptic drugs by pregnant women and a higher incidence of birth defects.
- Phenytoin Sodium Injection often precipitates when added to intravenous infusions.
- Phenytoin should be injected slowly (not exceeding 50 mg per minute in adults), directly into a large vein, through a large-gauge needle or intravenous catheter.
- Each injection of IV Phenytoin should be followed by an injection of sterile saline through the same needle or intravenous catheter to avoid local venous irritation due to the alkalinity of the solution.
- Continuous infusion should be avoided.

¹⁷ Taylor K, Paparella S. Fatal Errors with Cerebyx. Journal of Emergency Nursing. 2008;34: 360-361.

¹⁸ Pfizer June 28, 2010 Response to FDA's May 26, 2010 Warning letter concerning Pfizer's compliance with postmarketing adverse drug experience and prescription drug marketing act reporting requirement

¹⁹ Phenytoin Sodium injection, solution. Baxter Healthcare Corporation.

- Soft tissue irritation and inflammation has occurred at the site of injection with and without extravasation of IV phenytoin.
- Edema, discoloration and pain of the distal limb (described as “purple glove syndrome”) have been reported following peripheral IV phenytoin sodium injection.
- Some individuals have been shown to be slow metabolizers.
- IV Phenytoin should be discontinued if a skin rash appears.
- Hyperglycemia, resulting from the drug’s inhibitory effects on insulin release, has been reported.
- IV Phenytoin is not indicated for seizures due to hypoglycemic or other metabolic causes.
- IV Phenytoin is not effective for absence (petit mal) seizures.
- Serum levels of phenytoin sustained above the optimal range may produce confusional states.

IV Phenytoin is contraindicated in the following patients:

- Patients with a history of hypersensitivity to hydantoin products.
- Patients with sinus bradycardia, sino-atrial block, second and third-degree A-V block, and patients with Adams-Stokes syndrome.

Fosphenytoin²⁰

****Note** this section includes fosphenytoin-specific information. The current label for fosphenytoin (because it is converted to phenytoin) also mentions phenytoin-related information (i.e. pregnancy, not indicated for absence seizures, etc).

See Appendix 8.11.

The fosphenytoin label (WARNINGS and PRECAUTIONS) advises the following:

- DOSES OF CEREBYX ARE EXPRESSED AS THEIR PHENYTOIN SODIUM EQUIVALENTS (PE)
- Do not administer Cerebyx at a rate greater than 150 mg PE/min.
- The typical Status Epilepticus dose is administered over less time (typically between 5 and 7 minutes) than the identical molar dose of phenytoin (typically 15-20 minutes).
- If rapid phenytoin loading is a primary goal, IV administration of Cerebyx is preferred over IM administration.
- Cardiovascular Depression (severe reactions and fatalities) and hypotension especially after high doses and high rates of administration. Severe complications are most commonly encountered in elderly or gravely ill.
- Careful cardiac monitoring is needed when administering IV loading doses of Cerebyx.
- Cerebyx should be used with caution in patients with hypotension and severe myocardial insufficiency.
- Fosphenytoin should be discontinued if a skin rash appears.
- Sensory disturbances, severe burning, itching, and/or paresthesia were reported.

²⁰ Cerebyx-fosphenytoin sodium injection, solution. Parke-Davis Div of Warner Lambert LLC. Rev August 2001.

- Patients administered Cerebyx at doses of 20 mg PE/kg at 150 mg PE/min are expected to experience discomfort of some degree. The occurrence and intensity of the discomfort can be lessened by slowing or temporarily stopping the infusion.
- Phosphate load of 0.0037 mmol phosphate/mg PE should be considered.
- IV administration to patients with renal and/or hepatic disease, or in those with hypoalbuminemia, fosphenytoin clearance to phenytoin may be increased without a similar increase in phenytoin clearance.

Fosphenytoin is contraindicated in the following patients:

- Patients with a history of hypersensitivity to fosphenytoin or its ingredients, or to phenytoin or other hydantoin products.
- Patients with sinus bradycardia, sino-atrial block, second- and third-degree A-V block, and patients with Adams-Stokes syndrome.

Clinical Considerations for Labeling

For fosphenytoin, the last substantial label revision was in 2001. This revision clarified dosing with the intent to reduce drug errors. Several generic approvals, such as in 2007, have labels that closely resemble the original 2001 label for Cerebyx. These should be updated to include new data on adverse events that were submitted by the Sponsor in 2008. *See Appendix 8.4.* Although these tables were derived from data collected in 1994, and submitted in Pfizer's systematic analysis in 2008, they include more extensive data that analyzes approximately 800 patients as opposed to the two clinical trials included in the 2001 label that analyzed approximately 300 patients. *See Appendix 8.4, for Adverse event tables from Pfizer and the Cerebyx label clinical trials. Refer to the DMEPA review for highlights, especially for drug errors in children.*

Of note is a proposed draft labeling from April 2010 that will clarify dosing amounts and units and may include a pediatric statement:

- “Pediatrics: Cerebyx is not indicated for use in pediatric patients. Since pediatric pharmacokinetics data are limited, the kinetics of fosphenytoin in children are not well understood.”
- Appendix 8.6 is a table, in Draft Labeling form, that proposes the volume of Cerebyx to administer to a patient for the emergency treatment of Status Epilepticus using a 15 mg PE/kg loading dose to assist in reducing administration errors which continue to be reported. *See Appendix 8.6*

2 METHODS AND MATERIALS

2.1 INTRODUCTION

To compare the safety of IV phenytoin to fosphenytoin for non-PGS adverse events, the following strategies were used:

ADVERSE EVENTS

- AERS data was analyzed for cardiac adverse events and for other non-PGS adverse events. Prior reviews (1999, 2001)^{4,5} of AERS data of Cardiovascular and Hypotension Events were also analyzed.
- Searches for findings of non-PGS AEs in published literature was performed.
- Pfizer's compiled safety data collected in 1994 from 849 patients of which 736 received fosphenytoin was analyzed. Although Pfizer's analysis was focused on PGS and not on alternative adverse events,^{21,22} these were compared to Premarketing Clinical Trials (Cerebyx label Tables). *See Appendix 8.4.*

CLINICAL SECTION

- Extensive published literature search for findings of comparisons of IV phenytoin and fosphenytoin

2.2 AERS SELECTION OF CASES

2.2.1 Frequently Reported Adverse Events in AERS

AERS was searched for frequently reported adverse events for IV phenytoin and fosphenytoin during their entire postmarketing period. The following search strategy was applied to IV phenytoin AND fosphenytoin:

- Search terms: All
- Date search was conducted: August 27, 2010
- Dates (Product approval through July 31, 2010)
 - IV Phenytoin: March 1, 1956 to July 31, 2010
 - Fosphenytoin: August 5, 1996 to July 31, 2010
- Countries: All
- Ages: All
- Outcome: Serious²³

²¹ Pfizer, Inc, Response to FDA Query Regarding purple glove syndrome and Cerebyx (fosphenytoin sodium) Systematic Analysis of Association between Purple Glove Syndrome and Fosphenytoin. 22 July 2008.

²² Fosphenytoin anticonvulsant program consisted of 19 clinical studies, 13 clinical pharmacology studies (11 in healthy subjects, 2 in patients with seizures), 6 clinical studies in SE, seizure or neurosurgical patients. Some patients received IM mode of administration.

²³ Death, life-threatening, hospitalization, disability, congenital anomaly, required intervention

- Only the resulting cases were ranked in descending order according to preferred term (PT) counts.

2.2.2 Cardiovascular and Hypotension events

SEARCH STRATEGY

The AERS database was searched for possible cases of cardiovascular events or hypotension resulting from IV phenytoin or fosphenytoin. In an effort to capture all possible cases, the following broad search strategy was applied:

- Cardiac Arrhythmias (HLGT²⁴)
- Decreased and nonspecific blood pressure disorders and shock (HLGT)
- Cardiac and vascular investigations (HLGT)

CASE DEFINITION

Relevant cases were then analyzed and included in the cases series if they met ALL of the following criteria:

- 1) Temporal relationship (during infusion or soon after infusion) between cardiovascular event or hypotension and drug administration.
- 2) Objective evidence (blood pressure, ECG, etc.) or diagnosis of CV event and/or hypotension.
- 3) No alternate explanation for adverse event.

On August 10, 2010, AERS was searched for cases of CV events and hypotension with IV phenytoin and fosphenytoin. The previous analysis of these events with both agents searched AERS through December 3, 2001. As a result only cases received between December 4, 2001 and July 31, 2010 were included in this analysis.

2.3 SPONSOR SUBMISSION

The 2008 Pfizer submission which focused on PGS included compiled safety data from 1994 which included 849 patients of which 736 received fosphenytoin. The methodology for this systematic analysis (described in their section 4.2) used a working definition of PGS and did not actively search for alternative adverse events. Therefore, the overview of treatment emergent adverse events (which may have counted an event more than once) may provide a very broad adverse event update from the initial two approval clinical trials data presented in the Cerebyx labeling²⁵.

²⁴ High level group term.

²⁵ The current Cerebyx label: One trial compares IV Cerebyx (N=90) to IV Phenytoin (N=22) and the other trial compares IM Cerebyx to Oral Dilantin. It does not include the compiled systematic analysis data submitted in 2008 for studies done by September 1, 1994. For instance, the label states the incidence (at maximum dose and rate to epileptic or neurosurgical patients) of headache is 4.4% (IV Cerebyx) versus 0% (IV phenytoin) whereas the Pfizer submission of 2008 states headache incidence of all adverse events as 7.7% (IV fosphenytoin) versus 5.9% (IV Dilantin).

In another instance for hypotension, incidence is cited as 7.7% (IV fosphenytoin) versus 9.1% (IV Dilantin)—slightly better for IV fosphenytoin, whereas the 2008 submission shows 2.4% versus 2.9% with a nominal difference. Nystagmus was better for IV phenytoin at 13.7% compared with IV Cerebyx at

2.4 LITERATURE SEARCH

Cardiac Adverse Event Literature

Since the publication of the above article, a search for “cardiac, cardiac arrest, bradycardia, arrhythmias AND fosphenytoin, “hypotension AND fosphenytoin” in Pub Med, Web of Science, and EMBASE for all years was performed on 8/12/10.

Other Non-PGS Labeled and UnLabeled Adverse Events in literature

A search for “Adverse effects or events AND fosphenytoin”, in Pub Med, Web of Science, and EMBASE for all years was performed on August 12, 2010. This included findings for any respiratory, renal, CNS, dermatologic, gastrointestinal system citations.

Pub Med was searched on 9/10/10 for all years for “fosphenytoin AND Stevens Johnson Syndrome”, “fosphenytoin AND nausea or vomiting”, fosphenytoin AND hepatotoxicity”, fosphenytoin AND agranulocytosis”, fosphenytoin AND lupus-like reactions”.

3 RESULTS

3.1 ADVERSE EVENTS CASES

This section provides AERS data for IV phenytoin and fosphenytoin related to ALL frequently reported adverse events and cardiovascular and hypotension events.

3.1.1 Frequently Reported Adverse Events

This section provides details regarding the most frequently reported adverse events in the AERS database for IV phenytoin and fosphenytoin. Using the search strategy described in Section 2.2.1, AERS was searched on August 27, 2010, yielding 1285 serious reports (257 deaths) for IV phenytoin and 466 serious reports (109 deaths) for fosphenytoin. Table 5 below contains the top 25 adverse events (by Preferred Term) reported for IV phenytoin and fosphenytoin respectively.

18.5%. This is unlike the label that indicates the following : IV phenytoin at 59.1% compared with IV fosphenytoin at 44.4%.

In Table 8, Serious Adverse Events are informative. In 736 patients 0.42% (N=3) had apnea, cardiac arrest , hypotension, intracranial hypertension, bradycardia, or cerebral hemorrhage. There was 0.28% (N=2) bradycardia, cerebral hemorrhage, cerebrovascular accident, sepsis, shock, stupor, and 0.14% (N=1) arrhythmia, aspiration pneumonia, ataxia, brain edema, cerebral infarct, CNS depression, dizziness, encephalitis, encephalopathy, meningitis, myasthenia, myopathy, neuropathy, nystagmus, overdose, subdural hematoma, surgeries/procedures, tachycardia and abnormal thinking.

Table 5: Top 25 Adverse Events Reported with Fosphenytoin (N=466) and IV Phenytoin (N=1285).

Source: AERS, U.S. and Foreign Serious*cases, marketing through July 31, 2010

<u>Fosphenytoin</u>	<u>IV Phenytoin</u>
Hypotension	Convulsion
Convulsion	Stevens-Johnson Syndrome
Medication Error	Pyrexia
Cardiac Arrest	Drug Interaction
Bradycardia	Cardiac Arrest
Pruritus	Hypotension
Pyrexia	Toxic Epidermal Necrolysis
Stevens-Johnson Syndrome	Injection Site Reaction
Overdose	Dermatitis
Coma	Drug Level Above Therapeutic
Drug Level Above Therapeutic	Coma
Toxic Epidermal Necrolysis	Skin Discolouration
Dizziness	Drug Level Below Therapeutic
Thrombocytopenia	Bradycardia
Arrhythmia	Cyanosis
Blood Pressure Decreased	Pneumonia
Status Epilepticus	Oedema Peripheral
Rash	Medication Error
Condition Aggravated	Grand Mal Convulsion
Drug Interaction	Injection Site Necrosis
Loss Of Consciousness	Injection Site Oedema
Renal Failure Acute	Sepsis
Cardio-Respiratory Arrest	Rash Maculo-Papular
Multi-Organ Failure	Blister
Acute Generalised Exanthematous	Alanine Aminotransferase Increased
Pustulosis	

*Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.

The events organized in the table above are unanalyzed reports (“crude counts”). These may contain duplicate reports, other suspect medications or confounding factors, and do not always reflect a true causal relationship between drug and event.

Based on the data in Table 5 above, medication errors, cardiovascular (CV) events, and serious skin reactions (e.g. Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome) have been reported both for IV phenytoin and fosphenytoin. Local injection site reactions (e.g. injection site necrosis, injection site oedema, injection site reaction) are in this top listing only under IV phenytoin.

Additionally, the frequently reported adverse events (PTs) described in death cases (phenytoin, n=257; fosphenytoin, n=109) were identified. Table 6 below contains the top 25 PTs described in this subset of cases.

Table 6: Top 25 Adverse Events Reported with Fosphenytoin (N=109) and IV Phenytoin (N=257).	
Source: AERS, U.S. and Foreign DEATH cases, marketing through July 31, 2010	
<u>Fosphenytoin</u>	<u>IV Phenytoin</u>
Cardiac Arrest	Cardiac Arrest
Convulsion	Toxic Epidermal Necrolysis
Hypotension	Hypotension
Medication Error	Multi-Organ Failure
Bradycardia	Sepsis
Coma	Stevens-Johnson Syndrome
Cardio-Respiratory Arrest	Drug Interaction
Septic Shock	Pneumonia
Arrhythmia	Convulsion
Condition Aggravated	Pyrexia
Loss Of Consciousness	Respiratory Failure
Multi-Organ Failure	Coma
Overdose	Bradycardia
Stevens-Johnson Syndrome	Death
Agranulocytosis	Injection Site Reaction
Blood Pressure Decreased	Medication Error
Death	Cardio-Respiratory Arrest
Myocardial Infarction	Cyanosis
Pyrexia	General Physical Health Deterioration
Renal Failure Acute	Skin Discolouration
Toxic Epidermal Necrolysis	Apnoea
Drug Interaction	Coagulopathy
Incorrect Dose Administered	Hepatic Failure
Metabolic Acidosis	Shock
Respiratory Failure	Vomiting

As stated previously, these terms are based on crude report counts: therefore they may contain duplicates, other suspect medications or confounding factors, and do not imply a causal relationship. Based on some of these terms (i.e. multi-organ failure, sepsis, pneumonia), the suspect drug was likely given to a hospitalized, critically-ill patient, who died of causes unrelated to IV phenytoin or fosphenytoin administration. Many of these terms (e.g. CV events and medication errors) are likely causally related to IV phenytoin and fosphenytoin. Fatal Medication Errors are listed for both agents, and a companion review²⁶ discusses these errors in detail. Several cardiovascular terms exist in both

²⁶ Crandall A. Fosphenytoin and Phenytoin Medication Error Review. RCM# 2010-571.

columns, and for both drugs; these events are discussed in more detail below, and as prespecified in Section 2.2.2.

3.1.2 Cardiovascular and Hypotension events

This section provides the results from AERS data for cardiovascular events and/or hypotension resulting from fosphenytoin or IV phenytoin administration between the end of 2001 and July 31, 2010.

On August 10, 2010, the AERS database was searched for cases of CV events and hypotension with IV phenytoin and fosphenytoin. During the identified time frame, 301 total reports were retrieved from AERS for fosphenytoin, and 90 (30%) fit the initial search strategy of the three HLGs listed in Section 2.2.2. Additionally, 616 total reports were retrieved from AERS for IV phenytoin, and 124 (20%) fit the initial search strategy of the three HLGs. The 90 fosphenytoin and 124 IV phenytoin cases were further analyzed to meet the predefined case definition.

After removing duplicates (n=11) and cases not meeting the predefined case definition (n=30), 49 relevant fosphenytoin cases were included in this case series. Additionally, of the 124 potential cases for IV phenytoin, 44 cases were included in this cases series after removing duplicates (n=23) and cases not meeting the predefined cases definition (n=57). The most common reason for exclusion in either group was the lack of a temporal and causal relationship between administration of the drug and development of a CV event and/or hypotension.

The characteristics of fosphenytoin and IV phenytoin cases are summarized in Appendix 8.7, and complement the specific CV and hypotension events listed below in Table 7 described in the case series. The events below are divided into two groups (hypotension and cardiac arrhythmias) based on the search strategy described in Section 2.2.2 and stratification used in prior AERS reviews. Cases describing both hypotension AND a cardiac arrhythmia are grouped under **Hypotension** (if the arrhythmia was bradycardia alone), or under **Cardiac Arrhythmias** if the arrhythmia was severe/significant (e.g. asystole).

Table 7: Cardiovascular and hypotension events associated with Fosphenytoin and IV Phenytoin from December 4, 2001 to July 31, 2010		
Fosphenytoin (N=49)	Adverse Event	IV Phenytoin (N=44)
<u>n=23</u>	<u>Hypotension</u>	<u>n=21</u>
20	Hypotension alone	13
3	Hypotension + Bradycardia	8
<u>n=26</u>	<u>Cardiac Arrhythmias</u>	<u>n=23</u>
8	Asystole	7
4	Bradycardia	5
3	Cardiac arrest	5
3	Ventricular tachycardia	1
0	Cardiac fibrillation	1
0	Junctional rhythm	1
0	Tachycardia	1
1	Ventricular fibrillation	1
0	Premature ventricular contractions	1
1	2 nd and 3 rd Degree Heart block	0
1	Arrhythmia NOS	0
1	3 rd Degree heart block	0
1	PEA	0
1	Prolonged QT interval	0
1	Sudden Death	0
1	Total AV block	0

There are several important observations with regards to these case series:

- Of the 49 cases involving fosphenytoin and 44 cases with IV phenytoin, there were 13 and 9 deaths respectively. The details of these fatal cases are located in Appendix 8.8 and Appendix 8.9.
- One case (ISR 68444923) describes events resulting from IV phenytoin AND fosphenytoin administration. This case is included in both case series.
- Five (5) fosphenytoin cases involved medication errors. Three (3) of these cases²⁷ (2 pediatric, 1 adult) involved fatal overdoses, and two cases²⁸ involved incorrectly administering undiluted fosphenytoin.
- Four (4) phenytoin cases (1 adult, 3 unknown) involved inappropriate administration of phenytoin. Three of these reports²⁹ (1 death) involve rapid (or excessive) rates of IV administration, and one case³⁰ describes IV administration of phenytoin oral suspension, resulting in death.

²⁷ ISR#'s 4860889, 4780432, 4110495.

²⁸ ISR#'s 4013284, 4144158

²⁹ ISR#'s 3850961, 3853216, 5692872.

³⁰ ISR#4020948

- Two positive rechallenges³¹ (one of bradycardia for phenytoin and one of hypotension for fosphenytoin) were included in this case series.

Essential details of the cases outlined above are found in Appendix 8.10. Details involving death cases are included Appendix 8.8 & 8.9.

Combining the results from this analysis with the data from the prior reviews, cumulative AERS data for CV events and hypotension can be compiled. This information is displayed in Table 8 below.

Table 8: Cumulative AERS Cases of Cardiovascular and Hypotension Events for Fosphenytoin and IV Phenytoin^{4,5}		
<u>Fosphenytoin</u>		<u>IV Phenytoin</u>
78	CV Events*	99
53	Hypotension	44
131	Total	143
35	Deaths	36
110	Adults	120
14	Pediatric	7
7	Unknown Age	16

* “CV events” used as broad category in Thambi review⁵, “Cardiac arrhythmias” used as broad category in Mease review⁴ and current review.

The postmarketing experience for IV phenytoin and fosphenytoin both describe more CV events than isolated hypotension. These events are reported more often in adults and result in serious outcomes, many times death.

3.2 LITERATURE SEARCH

Cardiac

In July 2006, K. Phelan and A. Brinker³² reviewed the Adam’s article titled “*Fosphenytoin May Cause Hemodynamically Unstable Bradydysrhythmias*” for its adequacy in evaluating the AERS database for CV events and hypotension associated with *fosphenytoin* infusion from 1997-2002:

- The authors concurred that the 29 cases that included 10 cardiac deaths³³, four cases of high-grade atrioventricular block, 5 cases of transient sinus arrest were

³¹ ISR#’s 5680733, 4494263

³² PID #D060597 July 2006 DDRE assessment of the publication Adams BD, Buckley NH, Kim JY and Tipps LB. Fosphenytoin May Cause Hemodynamically Unstable Bradydysrhythmias. J of Emerg Med 2006; 30 (1): 75-79

³³ 10 fatalities--8 asystole or bradyasystole, 1 cardiac arrest, 1 hypotension-- all with confounders except 6 yr. old who had excess dose, and status epilepticus (SE); Adams BD, Buckley NH, Kim JY and Tipps LB.

consistent with the dysrhythmic properties of *fosphenytoin* and the labeling adequately addressed these events. “Cardiac adverse events” which included dysrhythmia or cardiac arrest and consisted of N=67 (32.5%) eventually were narrowed to 29 cases.

- Adams article included cardiac analyses of findings from premarket studies showing 1 case of 1st degree AVB (atrioventricular block), 1 case of recurrent 2nd degree AVB, 1 case of 24 seconds of bradysystole that resolved;
- Two published articles of one pediatric OD causing cardiac arrest and one case of hypocalcemic ECG changes were included.
- Additionally, there were 11 cases of isolated hypotension (7.8%) that were included as “Non-cardiac adverse events”.

The Committee on Safety of Medicines of the Medicines Control Agency³⁴ published “*Fosphenytoin Sodium (Pro-Epanutin): Serious Arrhythmias and Hypotension in May 2000*. “Worldwide, 21 cases of asystole, ventricular fibrillation or cardiac arrest in association with IV *fosphenytoin* have been reported. Five cases had rates or doses above recommendations. There were 35 reports of hypotension, 15 reports of bradycardia, and 10 reports of a variety of heart blocks.” Most of these reactions occurred within 30 minutes of infusion. Recommendations included monitoring of vital signs and observation for at least 30 minutes post-infusion, potential discontinuation of infusion if hypotension occurred, and lowering by 10-25% of loading dose and/or infusion rate in elderly, and renal and hepatic impaired.

Kassab MY³⁵, described more than 10 mmHg decrease in systolic, diastolic and mean blood pressure post-infusion of *fosphenytoin* in a study comparing 50 patients who received *fosphenytoin* compared with 50 patients who received levetiracetam.

Keegan³⁶ reported ECG changes due to hypocalcemia from phosphate binding of calcium or a direct effect on cardiac conduction after IV *fosphenytoin* use. Since hypocalcemia itself can cause bradycardia and heart block, the author hypothesized that the inorganic phosphate load (iatrogenic hyperphosphatemia) of *fosphenytoin* created the transient hypocalcemia that resulted in a prolonged QT interval.

Fosphenytoin May Cause Hemodynamically Unstable Bradydysrhythmias. J of Emerg Med 2006; 30 (1): 75-79

19 non-fatalities-- 3 had no confounders, 2 had ODs, 2 had SE, rest had other illnesses; Adams BD, Buckley NH, Kim JY and Tipps LB. Fosphenytoin May Cause Hemodynamically Unstable Bradydysrhythmias. J of Emerg Med 2006; 30 (1): 75-79

³⁴ The Committee on Safety of Medicines of the Medicines Control Agency. Fosphenytoin sodium (Pro-Epanutin):serious arrhythmias and hypotension. May 2000. 26:1

³⁵ Kassab MY, et.al. Blood pressure changes after intravenous fosphenytoin and levetiracetam in patients with acute cerebral symptoms. Epilepsy Research 2009. 87, 268-271.

³⁶ Keegan MT et al. Hypocalcemia-like Electrocardiographic Changes After Administration of Intravenous Fosphenytoin. Mayo Clin proc. 2002;77:584-586.

Abend ^{37,63} states “*fosphenytoin* IV infusion causes fewer infusion-related adverse reactions than *phenytoin* “, with less hypotension, and that it is less likely to cause cardiac arrhythmias—but some cases have been reported. This being said, in Abend’s algorithm presented in the article, *fosphenytoin* and IV *phenytoin* are used interchangeably.

In 1996, Boucher³⁸ evaluated 118 patients receiving intramuscular *fosphenytoin* doses ranging from 480-1500 mg PE and daily maintenance doses ranging from 130-1250 mg PE for 3-14 days. The other cohort consisted of 88 patients who received IV *fosphenytoin* and 28 who received IV *phenytoin* for 3-4 days. Patients in both IV groups had systolic blood pressure decreases greater than 20mm Hg, *fosphenytoin* (66%) and *phenytoin* (61%). He noted that more IV *phenytoin* patients (11%) experienced dizziness with the drop in BP than with *fosphenytoin* (7%). He concluded that IM and IV *fosphenytoin* were effective in neurosurgical patients for up to 14 days and, in addition, that IV *fosphenytoin* appeared to have better tolerability than IV *phenytoin* in this patient population although the frequencies of adverse events associated with *fosphenytoin* (32%) and *phenytoin* (39%) were similar. There was one severe ataxia with IV *fosphenytoin*. With IM *fosphenytoin*, there were mostly CNS events of somnolence and nystagmus. There was a range of local reactions requiring more frequent IV changes with *phenytoin*. Other common adverse events for both were dizziness, incoordination, ataxia, nausea, constipation, phlebitis, hiccups, peripheral edema, pruritis, rash, diaphoresis, thrombocytopenia, dysgeusia, and apnea.

Fischer ³⁹ sites three double-blind, randomized trials involving neurosurgery and seizure patients that used infusion rates from 50 mg/min for IV *phenytoin* and 50 to 150 mg PE/min for *fosphenytoin*. CNS (nystagmus, dizziness, ataxia, somnolence) were the most common AEs for both drugs. Both drugs also have similar decreases in mean blood pressure and heart rate. He states that “although cardiovascular events with *fosphenytoin* were rare in these controlled trials, postmarketing experience indicates that hypotension and cardiac arrhythmias may occur at high *fosphenytoin* doses and infusion rates in the same types of patients (elderly, pre-existing heart disease).

Respiratory

Respiratory depression is rare but cases have been reported³⁰. For example, respiratory failure occurred in an 83 year old woman with renal failure after a tonic-clonic seizure and hypotension that eventually led to sinus arrest with a ventricular escape rate of 35 beats/min. Since respiratory arrest may often precede cardiac arrest especially in children, cases reported may not separate out respiratory versus cardiac arrest.

³⁷ Abend NS, et al. Anticonvulsant medications in the Pediatric emergency room and Intensive Care Unit, Pediatric Emergency Care, 2008 Oct; 24 (10):705-721.

³⁸ Boucher BA, et al. The safety, tolerability, and pharmacokinetics of Fosphenytoin after intramuscular and intravenous administration in neurosurgery patients. Pharmacotherapy. 1996; 16 (4):638-645.

³⁹ Fischer JH, Patel TV, Fischer PA. Fosphenytoin - Clinical pharmacokinetics and comparative advantages in the acute treatment of seizures. *Clinical Pharmacokinetics (New Zealand)* 2003;42:33-58.

Renal and Electrolyte

Oellerich⁴⁰ discusses the prodrug metabolite oxymethylglucuronide that was identified in the plasma of uremic patients who received *fosphenytoin*. It is apparently not pharmacologically active but, it did cross react to earlier immunoassays for *phenytoin* thus giving falsely high concentration readings. It may especially accumulate in renal failure patients as the glucuronide conjugate (HPPH –G).

Meek⁴¹ states that in renal failure patients the serum phosphate levels may increase but are not clinically significant. McBryde KD⁴², describes a case of hyperphosphatemia in a 17 year old male s/p renal transplant who presented to the ED (Emergency Department) with abnormal chemistries (K+=6.2 mmol/L; glucose=128 mg/dL; BUN=163 mg/dL and creatinine=36.1 mg/dL) with a renal allograft biopsy demonstrating marked fibrosis consistent with chronic allograft nephropathy and mild acute cellular rejection. He subsequently developed a partial seizure and was started on IV *fosphenytoin* 1000mg over one hour. Eventually he required hemodialysis. His initial serum phosphorus level was 6.7 mg/dL (normal 3.0-5.2 mg/dL with a serum calcium of 2.2 mmol/L) and it rose to 12.1 mg/dL. His total and ionized calcium stayed essentially normal.

Dermatologic

Systemic reactions such as hypersensitivity to IV *phenytoin* are known and labeled. Other AEs such as rashes, Stevens Johnson Syndrome (SJS) and pseudolymphoma are also labeled for IV *phenytoin*. PubMed search yielded no results for SJS, but retrieved Choi's⁴³ article with two cases of *phenytoin* associated pseudolymphoma syndrome.

Local reactions such as PGS are labeled and defined for IV *phenytoin* only. Although most articles addressed the advantage of *fosphenytoin* in preventing PGS or other local irritation, only about half pointed out the burning³⁸ and paresthesias often associated with *fosphenytoin*. *Fosphenytoin* (Cerebyx label-sensory disturbances section) was noted to cause pruritis in 48.9 % of patients using *fosphenytoin* as opposed to 4.5% in IV *phenytoin*. Paresthesias were noted for 4.4% of *fosphenytoin* patients as opposed to 0% of IV *phenytoin* patients. They occurred more with IV than IM *fosphenytoin*, were dose and rate related, and majority of alert patients (41/64 or 64%) experienced some degree of discomfort at doses ≥ 15 mg PE/kg at 150 mg PE/min. These tingling, burning, itching events were not usually at the infusion site but rather occurred frequently at the groin. They were transient usually lasting only up to 10 minutes but some had symptoms for

⁴⁰ Oellerich M, Armstrong VW. Prodrug Metabolites: Implications for Therapeutic Drug Monitoring. *Clin Chem* 2001;47:805-806.

⁴¹ Meek PD, et al. Guidelines for Nonemergency Use of Parenteral Phenytoin products: Proceedings of an expert Panel Consensus process. *Archives of Internal Medicine*. Dec 1999; 159 (22): 2639-2644.

⁴² McBryde KD, Wilcox J, Kher KK. Hyperphosphatemia due to fosphenytoin in a pediatric ESRD patient. *Pediatric Nephrology* 2005;20:1182-1185.

⁴³ Choi TS, et al.. Clinicopathological and genotypic aspects of anticonvulsant-induced pseudolymphoma syndrome. *British Journal of Dermatology* 2003;148: 730-736.

hours. Fischer ³⁸ states “drawbacks include occurrence of transient paraesthesias and pruritis”.

Immunologic/ Hematologic

Lupus-like reaction, aplastic anemia and agranulocytosis with IV *phenytoin* (See Appendix 8.11 for label) and no mention of increased cases with I were noted in the literature search. PubMed search yielded no reports for lupus like reaction or for agranulocytosis. Also, no search results revealed increased cases of porphyria exacerbation.

CNS

Dizziness, somnolence, ataxia, nystagmus^{8,9} and tinnitus are prevalent in both drugs. Nystagmus has been noted to be worse from the Cerebyx label. See Appendix 8.11.

GI

Nausea, vomiting⁹, hepatotoxicity is known with IV *phenytoin*. No increased hepatotoxicity was found in the literature search for *fosphenytoin*. Some abnormal LFTs (liver function tests) were noted in clinical trial data. Nausea and vomiting have been noted in cases of overdose. PubMed search yielded Craig’s ⁴⁴ article on *phenytoin* overdose.

Metabolic.

IV *phenytoin* is labeled for its effects on hyperglycemia due to its inhibition on insulin release. It is noted as “infrequent” on the *fosphenytoin* label. Slow metabolism due to limited enzyme availability is noted in the *fosphenytoin* label. Ikeda noted gynecomastia⁴⁵ (an unlabelled adverse event that may be treatment related) in an 18 year old male patient having a CYP2C9 and CYP2C19 subfamily mutation who developed gynecomastia after increasing his *phenytoin* dose. V max can be 40% lower in these patients with the mutation and therefore higher doses may be required.

3.3 OTHER DATABASES: DRUG UTILIZATION AND AVERAGE PRICE

This section describes drug utilization³ and average cost data for *fosphenytoin* and IV *phenytoin*. Utilization data is based on projected number of U.S. hospital discharges for IV *phenytoin* or *fosphenytoin* between 2000-2009.^{46,47} The number of patients prescribed (based on the hospital discharge data) *fosphenytoin* or IV *phenytoin*, and the corresponding annual market share, is described in Table 9 below.

⁴⁴ Craig S. Phenytoin poisoning. *Neurocritical Care* 2005;3:161-170.

⁴⁵ Ikeda, A. Letters to the Editor: Gynecomastia in association with phenytoin and zonisamide in a patient having a CYP2C subfamily mutation. *J Neurol Neurosurg Psychiatry*. 1998;65:803-804.

⁴⁶ Phelan K, Pamer CA. Purple Glove Syndrome. OSE RCM# 2007-1332. 9 July 2008.

⁴⁷ Chai G. IV Phenytoin and Fosphenytoin Utilization Review. OSE RCM# 2010-571.

Table 9: Fosphenytoin Parenteral and IV Phenytoin Projected U.S. Hospital Discharges and Market Share Percentage 2000-2009

Fosphenytoin		IV Phenytoin		
Share %	Proj Discharges*	Year	Proj Discharges*	Share %
34.3%	147,941	2000	283,902	65.7%
34.9%	151,769	2001	282,883	65.1%
38.7%	172,674	2002	274,590	61.3%
39.1%	179,731	2003	280,505	60.9%
41.8%	197,754	2004	274,797	58.2%
43.9%	206,154	2005	263,207	56.1%
45.6%	202,017	2006	241,151	54.4%
47.5%	192,514	2007	213,086	52.5%
52.7%	202,285	2008	181,541	47.3%
58.6%	210,150	2009	148,688	41.4%

**Projected number of discharges with a hospital billing for fosphenytoin or phenytoin.*

Over the past decade usage for *fosphenytoin* has increased gradually (while IV phenytoin decreased gradually), with the largest increase (or decrease for IV phenytoin) since 2007. The average cost of IV phenytoin and *fosphenytoin* over the past 5 years is displayed in Table 10 below.

Table 10: Average Price of Vials (Eaches) by year for Fosphenytoin and IV Phenytoin.

Year	Fosphenytoin (Dollars)	IV Phenytoin (Dollars)
2004	\$29.49	\$1.92
2005	\$31.45	\$1.88
2006	\$33.45	\$1.74
2007	\$25.07	\$1.58
2008	\$4.05	\$1.56
2009	\$2.61	\$1.31

Based on Table 10 above, over the past 5-6 years (2004-2009), the average cost of *fosphenytoin* has declined, with the most dramatic reduction between 2007 and 2008.

4 DISCUSSION

4.1 ADVERSE EVENTS (AE) DISCUSSION

AERS search

The pharmacologic effects of *fosphenytoin* include those of IV *phenytoin*. The main difference lies in the formulation and administration of each drug. Based on a comparison of frequently reported adverse events in the AERS database, in general, administration site conditions (*injection site reaction, injection site necrosis, and injection site edema*) and skin and soft tissue disorders (*dermatitis, skin discoloration, blisters*) appear to be reported more often for IV *phenytoin* versus *fosphenytoin* (Section 3.1.1, Tables 5 and 6). These events are expected based on the high pH and propylene glycol component of IV *phenytoin*, and can be a consequence of incorrect administration (e.g., fast infusion rate). Reports of cardiac disorders, hypotension, and medication errors appear to be consistently reported for each drug. Medication errors for both agents are analyzed in a separate review⁴⁸.

Consistent with prior AERS reviews^{49,50} and based on Appendix 8.7 and Tables 5 and 6 (from Section 3), CV and/or hypotension events are among the most frequent events to be reported with both IV *phenytoin* and *fosphenytoin*. This includes events that occur during and after the infusion and can have fatal outcomes.

Intravenous *phenytoin* was marketed several decades prior to *fosphenytoin*. It is clear that the propylene glycol component of *phenytoin* can rapidly induce bradycardia and hypotension, which was further supported by cases of bradycardia and asystole following the inadvertent, rapid infusion of *phenytoin*. Risk factors advanced for serious cardiovascular complications with IV *phenytoin* treatment include advanced age, rapid infusion rates, and known cardiac disease.⁵¹ However, the literature, the current case series, and prior AERS reviews emphasize that CV and hypotension events can also occur in younger patients, without significant cardiovascular risk factors, and at recommended doses and infusion rates.

Similar to IV *phenytoin*, previous literature articles and current product labeling emphasize that age, cardiac history, elevated dose and infusion rate are also predisposing risk factors for *fosphenytoin*-induced cardiovascular events.⁵² However, based on data from this case series, and reinforcing prior postmarketing reviews, these events also

⁴⁸ Crandall A. Fosphenytoin and Phenytoin Medication Error Review. RCM# 2010-571.

⁴⁹ Mease M. Monitored Adverse Reaction (MAR) for Cerebyx (fosphenytoin sodium), phenytoin sodium, diazepam, lorazepam, and phenobarbital. Reactions: Cardiovascular adverse events.

⁵⁰ Thamby L. Drugs: Cerebyx (fosphenytoin sodium), intravenous phenytoin. Reactions: serious cardiovascular events, hypotension. PID# D010566.

⁵¹ Earnest MP, Marx JA, Drury LR. Complications of intravenous phenytoin for acute treatment of seizures. Recommendations for usage. JAMA. 1983 Feb 11;249(6):762-5.

⁵² Knapp LE, Kugler AR. Clinical experience with fosphenytoin in adults: pharmacokinetics, safety, and efficacy. J Child Neurol 1998 Oct; 13 Suppl. 1:S15-8.

appear to occur in patients without significant cardiac histories, at recommended doses (1000 PE mg for both agents), and at labeled infusion rates. *See DMEPA companion reviews on further details concerning reporting.*

In a few instances, serious CV events were attributed to medication errors for both IV *phenytoin* and *fosphenytoin*. Medication errors have been commonly reported for both agents and reviewed by the Division of Medication Errors Prevention Analysis (DMEPA).⁵³ Additionally, DMEPA is currently investigating the potential for misleading packaging for IV *phenytoin* that may be contributing to inappropriate and dangerous administration of the drug.⁵⁴

Literature Search

Multiple authors^{33,34,35,36,38} cite instances of hypotension and cardiac arrhythmias with *fosphenytoin*. Early optimism was premature for the proposed improved cardiac profile. Based on AERS cases and literature, it does not demonstrate that *fosphenytoin* has a more favorable cardiac profile compared to *phenytoin*. Local cutaneous reactions with paresthesia, burning, tingling, and pruritis are more common than PGS for *phenytoin*. CNS reactions-- especially hypertonia and nystagmus-- may be higher for *fosphenytoin* than expected based on the 2008 Pfizer submission that included compiled clinical trial data. Other CNS symptoms such as ataxia, somnolence, and dizziness have been noted in the literature with *fosphenytoin*.

Reviewer's Comments: Though fosphenytoin was cited in earlier literature as appearing to be selectively advantageous, this may have been premature and practitioners may still adhere to this suggestion. From more recent literature, there appears to be no selective advantage of one drug over the other for cardiovascular, hypotensive, and CNS effect adverse reactions. There do not appear to be any other major differences in other adverse events outside of PGS.

4.2 CLINICAL CONSIDERATIONS

Mode of Administration, access to venous site and monitoring, ease of preparing and administering IV Fosphenytoin and IV Phenytoin

Fischer⁵⁵ states *fosphenytoin* advantages include: decrease in infusion site pain and irritation; fewer infusion rate reductions due to fewer AEs; greater water solubility thus being compatible with IV fluids, less precipitation of microcrystals, no need for a filter, and no need for a large bore needle or a large vein. Faster infusion rates allow for 3 times faster administration. With IV *phenytoin*, injection site reactions diminish with slower and lower infusion rates (20 mg/min to no more than 50 mg/min), and choosing a larger vein and using a larger gauge or catheter followed by saline. Irritation and inflammation may occur with or without extravasation; and a filter was needed. The intramuscular

⁵³ Crandall A. Fosphenytoin and Phenytoin Medication Error Review. RCM# 2010-571.

⁵⁴ Crandall A. Phenytoin Medication Error Review. RCM#2008-876 (DRAFT).

⁵⁵ Fischer JH, Patel TV, Fischer PA. Fosphenytoin - Clinical pharmacokinetics and comparative advantages in the acute treatment of seizures. *Clinical Pharmacokinetics (New Zealand)* 2003;42:33-58.

fosphenytoin form is a well tolerated alternative to IV and extends its use to clinical situations involving difficult access or limited cardiac monitoring in certain facilities.

Reviewer's Comments: There appears to be a selective advantage of fewer PGS designated adverse events with fosphenytoin. One factor that may influence this is its categorization under "burning and paresthesias" which is a frequent adverse event.

There appears to be a selective advantage of intramuscular route of fosphenytoin in those patients with poor access, but, absorption is less predictable.

There appears to be a selective advantage of oral phenytoin in allowing ease of continued use from inpatient to outpatient settings after emergent treatment. IV phenytoin also was noted to have a stratified pediatric dosing regimen listed in Merck manual.

There appears to be a selective advantage of fosphenytoin in ease of IV use: it can be mixed with intravenous fluids readily, can be given more rapidly infused and requires no filter or flush.

There appears to be a selective advantage of fosphenytoin in allowing smaller size venous access and the use of smaller gauge catheters for infusions.

There appears to be a selective advantage of IV phenytoin in not requiring refrigeration.

Cost of acquisition of Fosphenytoin and IV Phenytoin. Four economic studies compare the pricing of *fosphenytoin* to the cost of treating adverse effects. One favors *phenytoin*. Two studies showed lower overall costs, one showed that cost was off set by the decrease in cost of treatment of adverse events. Marchetti⁵⁶ Armstrong⁵⁷, Touchette⁵⁸ and Jobst⁵⁹ state that "an initial pharmacoeconomic analysis comparing IV *fosphenytoin* and IV *phenytoin* shows the costs of treating AEs outweighed the initial acquisition costs of *fosphenytoin*. "However, recent cost-minimization analysis found *phenytoin* to be the appropriate medication in 97.3% of patients as the cost of adverse events were mainly driven by the occurrence of the purple glove syndrome.⁵⁴ Therefore, *fosphenytoin* may be the IV medication of choice only in selected populations such as patients with poor venous access or those with cardiac abnormalities." *Fosphenytoin* did cost 10-15x more but now is only 2-3x³¹ more expensive than *phenytoin*.

Reviewer's Comments: There appears to be a selective advantage of IV phenytoin in cost but fosphenytoin use is still often driven by formulary restrictions and cost savings.

⁵⁶ Marchetti A, et al. A pharmacoeconomic evaluation of intravenous fosphenytoin (Cerebyx) versus intravenous phenytoin (Dilantin) in hospital emergency departments. *Journal of Clinical Therapeutics*. 2009; 18 (5): 953-966.

⁵⁷ Armstrong EP, Sauer KA, Downey MJ. Phenytoin and Fosphenytoin: A Model of Cost and Clinical Outcomes. *Pharmacotherapy*. 1999; 19 (7):844-853.

⁵⁸ Touchette DR, Rhoney DH. Cost-Minimization Analysis of Phenytoin and Fosphenytoin in the Emergency Department. *Pharmacotherapy* 2000;20(8):908-916.

⁵⁹ Jobst BC, Holmes GL. Prescribing Antiepileptic Drugs Should patients Be Switched on the Basis of Cost? *CNS Drugs* 2004;18(10):617-628.

Current settings for Clinical Use of IV Fosphenytoin and IV Phenytoin

- Adult ED- IV *phenytoin* is often used for SE or for those who are seizing and in those who may have been non-compliant⁷⁶ on *phenytoin*.
- *Phenytoin* is not generally used for arrhythmias but can be an alternative for digitalis induced arrhythmia especially with QT prolongation. The 33rd edition of The Washington Manual lists it in an algorithm to treat SE *Step 1*: 20 mg/kg PE IV max 150 mg/min, *Step 2*: (if continues) additional 10 mg/kg IV.

Reviewer's Comments: There appears to be a selective advantage of having an alternative treatment using IV phenytoin for patients with digitalis induced arrhythmia, though Digibind or Fab may still be preferred (see Rosen Textbook and Washington Manual of Therapeutics 33rd edition).

- *Fosphenytoin* may be Preferred in Peds ED due to improved access in smaller veins. (See *Institution Use Restrictions* bullet). In children, Kirmani⁶⁰ uses both drugs interchangeably and states “benzodiazepines (lorazepam or diazepam) should be initiated as the initial therapy followed by IV *phenytoin* or *fosphenytoin* and Phenobarbital. ...Randomized blind comparison trials between valproate, levetiracetam and *fosphenytoin* as second-line agents after lorazepam or diazepam would provide more information regarding modifying the established protocol for SE in the future”. In children, neonates, and infants, Appleton¹⁴ states “although the numbers in this prospective study are relatively small, it is unlikely that the results could be used to support or justify the replacement of IV *phenytoin* with IV *fosphenytoin* in routine pediatric practice.” Eriksson¹⁵ state that “intravenous *fosphenytoin* (in children and adults) has a similar adverse effect profile than *phenytoin* when it is administered as recommended. There is no evidence of clear benefit that would justify the higher price of the *fosphenytoin* compared to *phenytoin*”.

Reviewer's Comments: Other than the 33rd edition of Washington Manual, there appears to be no obvious preference of one drug over the other for acute seizures and status epilepticus in much of the literature or an equal preference of one drug as opposed to the other.

- In the Neonatal ICU, Rosen suggests that in neonatal seizures both IV *phenytoin* and *fosphenytoin* is erratically absorbed metabolically. Therefore, phenobarbital is recommended as first line treatment and *fosphenytoin* at 20 PE/kg should follow. In pediatric SE, if benzodiazepines do not control the initial seizures, then *fosphenytoin* loading dose of 18-20 PE/kg at 150 mg per minute and *phenytoin* loading dose of 18-20 mg/kg at 1 mg/kg/min should be initiated.

⁶⁰ Kaimani B, Acute seizure management in children. Pediatric health 2009. 3 (6), 543-549. (Futuremedicine.com)

- Abend suggests that in the PICU or pediatric emergency units, that *fosphenytoin* 30 mg/kg IV at 2-3 mg/kg/ min (max 150 mg/min) or *phenytoin* 30 mg/kg IV at 1 mg/kg/min (max 50 mg/min) be given.
- In the Adult ICU, a neurologist or neurointensivist is consulted. Ziai suggests using *fosphenytoin* or IV *phenytoin* with BP and ECG monitoring. *Phenytoin* is recommended at 18-20 mg/kg IV for first or second line treatment of SE and *fosphenytoin* is recommended at 15-20 mg/kg PE IV. Varelas states loading doses of *phenytoin* 20 mg/kg at 50 mg/ minute or *fosphenytoin* 20 mg/kg PE at 150 mg/ minute in recurrent or refractory seizures.
 - Neurologic ICU ⁶⁴ and neurologists seems to use both interchangeably.
IV *phenytoin* or *fosphenytoin* is used prophylactically in UK for 7 days post-trauma; and according to Varelas, its use remains controversial. Boucher states that *fosphenytoin* is better tolerated in this patient subset.
 - Institution use restrictions at the Cleveland Clinic Foundation (CCF) ⁶¹ suggested that in adult seizure patients, *fosphenytoin* is restricted to Depts. Of Neurology, Neurosurgery, and emergency medicine, but, it is available to all pediatric patients. In 2004, the American College of Emergency Physicians 2004 clinical policy for management of adults with seizures in the ED ⁶², suggested that the use of *phenytoin* with benzodiazepines was associated with longer duration compared with Phenobarbital and the use of *fosphenytoin* with benzodiazepines.
 - In instances of patients in the ED who had a seizure and found to have sub-therapeutic *phenytoin* levels, either IV or oral loading of IV *phenytoin* or IV or intramuscular *fosphenytoin* followed by restart of daily oral maintenance dosing is suggested ⁴².
 - Likewise, Varelas ⁶³ suggests a clinical algorithm that considers chronic therapy with IV *phenytoin* or *fosphenytoin* for brief single seizure <60 seconds, or if prolonged or > 1 seizure to use IV *phenytoin* or *fosphenytoin* for concurrent loading with benzodiazepine, or for recurrent or refractory seizures > 5 minutes or > 2 discrete seizure without interludes of consciousness to use either IV *phenytoin* or *fosphenytoin* at the maximal dose ranges.
 - Knake ⁶⁴ from Germany uses an algorithm for adults and children that suggests using IV *phenytoin* if seizures continues >20 minutes. *Fosphenytoin* is cited as an alternative drug for adults. The article then states that “we prefer *fosphenytoin*

⁶¹ Lin T. Fosphenytoin (Cerebyx) Cleveland Clinic Foundation:Pharmacotherapy Update, Nov/Dec 2005. 7;6: no pagination.

⁶² American College of Emergency Physician's. Clinical policy: Critical Issues in the evaluation and management of Adults patients presenting to the Emergency Department the with seizures. *Ann Emerg Med* 2004;43:605-625.

⁶³ Varelas P, Mirski M. Treatment of seizures in the neurologic intensive care unit. *Current Treatment Options in Neurology* 2007;9:136-145.

⁶⁴ Knake S, Hamer HM, Rosenow F. Status epilepticus: A critical review. *Epilepsy & Behavior* 2009;15:10-14.

rather than *phenytoin*, especially when peripheral venous administration is planned”.

- Mayo Clinic Proceedings⁶⁵ state that *fosphenytoin* has reduced cardiovascular adverse effects and no adverse tissue effects, though its expense may not justify its widespread use. Regardless, its algorithm uses IV *phenytoin* and *fosphenytoin* interchangeably.
- In the Washington Manual of Therapeutics⁶⁶, Step 1 of its current seizure algorithm recommends lorazepam and *fosphenytoin*.
- In the Merck Manual⁶⁷ most adult indications for use are interchangeable for both *fosphenytoin* and IV *phenytoin*.

Reviewer’s Comment: There appears to be almost equivalent drug utilization and physician traditional use or embedded practice with both drugs.

⁶⁵ Manno EM. New management strategies in the treatment of status epilepticus, *Mayo Clin Proc* 2003;78:508-518.

⁶⁶ Foster C, Mistry NF, Peddi PF, Sharma S. Washington Manual of Therapeutics. Wolters Kluwer/Lippincott Williams & Wilkins. 33rd Edition. Baltimore, MD. 2010

Use of IV Fosphenytoin and IV Phenytoin in Special Populations

- In the 32rd edition ⁶⁷ of the Washington Manual (2007), IV *phenytoin* was recommended as treatment for arrhythmias associated with overdoses of tricyclic antidepressants, ecstasy, and neuroleptic syndrome. But, in the recent April 2010 (33rd) edition this was removed. In treatment of digitalis-induced ventricular arrhythmias associated with congenital long QT syndrome, IV *phenytoin* use is acceptable in the current Washington Manual (2010). The following dosing is suggested: IV loading at 250 mg over 10 min (max 50 mg/min), 100 mg over 5 min as needed as BP tolerates up to 1000mg. Continuous infusion is not recommended whereas monitoring of ECG, BP, and neurologic status is recommended. Rosen ⁷³ also states that *phenytoin* can be used to treat this diagnosis.
- In organ transplant ⁶⁸ patients drug interactions with immunosuppressants alter the serum protein levels with subsequent increase in free drug levels. Monitoring of free drug level not just the total drug level is needed. *Fosphenytoin* and IV *phenytoin* are both used.
- Seizure prophylaxis in bacterial meningitis or encephalitis in malaria ⁶⁹ patients has a global impact on developing countries which may not have *fosphenytoin* available or be able to afford it. Ogutu ⁷⁰ found that neither *fosphenytoin* nor *phenytoin* controlled SE in his study of 38 children (approximate ages 1-14 years) and there were few cardiovascular effects.

Reviewer's Comments: There appear to be an almost equivalent and interchangeable recommendations for use of both drugs in children and in patients with comorbidities such as heart disease that require monitoring and dose reductions of 10%—25% in rate and volume (Committee on Safety of Medications). Both drugs are labeled for renal and cardiac use, mention some defined drug-drug interactions, and use in CYP 2C mutation populations. Some ECG and lab monitoring is recommended in both labels for these populations especially among those who receive high doses and fast rates of infusion.

⁶⁷ Cooper DH et al. Washington Manual. Therapeutics. 32rd edition. Wolters Kluwer/Lippincott Williams & Wilkins. Baltimore, MD. 2007.

⁶⁸ Chabolla DRm Wszolek ZK. Pharmacologic management of seizures in organ transplant. *Neurology* . Dec 2006. 67;(S4):S34-S38.

⁶⁹ Ogutu BR, et al. Phenytoin pharmacokinetics and clinical effects in African children following fosphenytoin and chloramphenicol coadministration. *British Journal of Clinical Pharmacology* 2002;54,635-642.

⁷⁰ Ogutu BR, Newton CR, Muchohi SN, Otieno GO, Kokwaro GO. Pharmacokinetics and clinical effects of phenytoin and fosphenytoin in children with severe malaria and status epilepticus *British Journal of Clinical Pharmacology* 2003;56:112-119.

Drug Error Confusion of IV Fosphenytoin

- In 1999, a label change, and Dear Professional letter was issued. A ISMP (Institute for Safe Medication Practices⁷¹) report states in 2008 that “root cause analyses of recent errors regarding *fosphenytoin* suggest that the per mL concentration of 50mg PE/mL product continues to be misinterpreted as the total amount of drug in the vial despite the prominent display of total drug content on the vial label and carton labeling”. Apparently, in many healthcare inventory listings using databases such as the automated dispensing cabinet (ADC), the screen still displays 50 mg PE/mL, 10 mL instead of total drug content of 500mg PE/10 mL. ISMP⁷² recommended stocking the lower 2 mL to lessen potential confusion since many overdoses involve the 10 mL vial so that it may be a red flag to the person preparing the vials if an excessive number of vials have to be drawn up. Presentations of *fosphenytoin* and *phenytoin* doses vary within texts and across articles, so practitioners find a variation in dosing range, but usually not in the upper limits or maximum amounts recommended in infusion rate and doses.⁷³ In the same text, one author presents the *fosphenytoin* dosing (Table 173-4) as 20 mg PE/kg IV initial dose (listed under the title “Initial dose mg/kg) at rate of 150 mg PE/min in the pediatric population (text states 18-20 PE/kg) and in another chapter Table 15-3 *fosphenytoin* for pediatrics is presented as 20-25 mg/kg up to 3 mg/kg/min IF up to 159 mg/min IV. Merck Manual⁷⁴ lists *fosphenytoin* for children at 10-20 PE/kg IV once with max rate of 150 mg/min. Appleton¹⁴ states “phenytoin equivalents may result in potential confusion and prescribing errors”.

Reviewer’s Comment: See Anne Crandall’s DMEPA review which classifies most fosphenytoin errors as “Wrong Dosing” resulting in 10 deaths of which seven were in ≤ 3 year olds. Specifically, this was associated with the lack of pediatric dosing in product Insert labeling, the lack of consistent dose strength labeling, and ambiguity from the phenytoin equivalency (mg PE) dosing units. For IV phenytoin, 6 deaths were associated with wrong route and wrong rate in patients 16 years and older. Even with changes in labeling in 2001 to reduce drug error, errors are still occurring with fosphenytoin especially with pediatric fatalities.

⁷¹ Cohen MR. ISMP Medication Error Report Analysis Flawed Dispensing Practice and Cerebyx Label Confusion Result in Child’s Death. *Hospital Pharmacy*. 33;(7) 828-832.

⁷² ISMP (Institute for Safe Medication Practices) Medication Safety Alert! April 10,2008 Volume 13 Issue 7, page 1-2.

⁷³ Marx J, et al. Rosen’s Emergency Medicine Concepts and Clinical Practice. Chapters 15 Seizures, Chapter 150 Cardiovascular drugs,Chapter 173 Neurologic Disorders, 7 th edition. Mosby Elsevier Publishers Philadelphia, PA 2010.

⁷⁴ Beer MH, et al. The Merck Manual Eighteenth edition Merck Research Laboratories Whitehouse, NJ 2006.1822-1834.

Fosphenytoin and IV Phenytoin Monitoring

- Knapp¹³ and CSM³³ suggested reduced loading doses and slower infusion rates with CV monitoring 10-20 minutes after dose, when C max is reached.
- Currently labeled subpopulations of elderly, cardiac, renal disease, hepatic disease still require close monitoring for blood work and ECG.
- Heterozygous CYP2C subfamily mutations⁴⁴ and poor metabolizers of CYP2C19 exacerbates AEs and may require monitoring. The current labeling in phenytoin states that poor metabolizers of CYP2C19 represent approximately 3-5% of Caucasians, a similar percentage of African-Americans and 12-100% of Asian groups. The polymorphism affects metabolism of the anticonvulsant agent mephenytoin, proton pump inhibitors such as omeprazole, the anxiolytic agent diazepam, certain antidepressants, and the antimalarial drug proguanil.⁷⁵
- Rosen's Text 2010⁷³ textbook on Emergency Medicine also suggests monitoring *fosphenytoin* and *phenytoin* for hypotension and arrhythmia.

Consider the feasibility of further epidemiologic studies or clinical trials for *fosphenytoin* versus IV *phenytoin* in attempt to fill in gaps in knowledge that currently exist for pediatric PK studies. The analyses would help to better define standard guidelines for dosing in neonates, infants, children, and adolescents.

5 CONCLUSIONS

IV Phenytoin has been marketed for over 5 decades and still appears to be in wide use based on projected drug utilization data. While IV *phenytoin* use has diminished, fosphenytoin has grown from 34% of the market share in 2000 to 59% in 2009. This change over the recent past may be due to real or perceived advantages over IV phenytoin, but, probably has been largely driven by the 10 fold drop in average cost of a vial of fosphenytoin in 2004 from about \$29.50 to \$2.60 in 2009.

Briefly, the advantages of *fosphenytoin* appear to be mostly drug administration based—faster infusion, no filter needed, intramuscular alternative, no flush, use with smaller gauge needle, and use with smaller veins. But, on the other hand, drug errors in prescribing, dispensing, administration of this drug and limitations in which settings it can be used based on its need for refrigeration continue despite its label change in 2001. This is frequently attributed to confusion of the designation of “PE” units per ml in each of the vial sizes with total content (mg) by healthcare providers or by users of an electronic database entry such as at the ADC level (medication errors are discussed in

⁷⁵ Goldstein JA. Clinical relevance of genetic polymorphisms in the human CYP2C subfamily. Br J Clin Pharmacol. 2001. 52; 349-355.

detail by DMEPA in a companion document). In addition, storage of this product requires refrigeration.

Cardiovascular events occur with both drugs. Though the initial marketing of *fosphenytoin* touted its potential for a lower incidence of cardiovascular adverse events, much of the literature seems to suggest there is no difference. Data presented herein suggest that some practitioners may still believe there is a better cardiac profile for *fosphenytoin* and may not employ cardiac monitoring.

The postmarketing experience represented by AERS data, isolates administration site/local reactions, cardiac disorders, and medication errors as the most prominent adverse events of IV *phenytoin* and *fosphenytoin*; where local administration site reactions are reported far more frequently with IV *phenytoin*. The current case series of CV and hypotension events related to IV *phenytoin* or *fosphenytoin* is the largest OSE analysis of postmarketing data to date. Combining this data with previous analyses, IV *phenytoin* and *fosphenytoin* can induce serious cardiovascular events and hypotension at various doses and infusion rates (predominately within recommended doses and rates), and in a variety of patient populations. It is extremely difficult to quantify or compare the rate of these serious events between the two agents largely because this analysis is based on spontaneously reported data for agents marketed decades apart. Only adequately controlled studies can make confident risk comparisons. Based on the similar abundance and continual postmarketing reports and potential for serious, even fatal, outcomes, cardiovascular and hypotension events are the most prominent adverse event for either agent.

Although there are considerably more reports of purple glove syndrome (PGS) for *phenytoin* in comparison to *fosphenytoin*, most of these reports have been received from consumers. See PGS review 2010³. A request for a manufacturer response to this discrepancy is pending.

Phenytoin is still a recommendation for digitalis induced dysrhythmias with congenital QT prolongation. Though the introduction of Digibind would supplant this treatment, in situations where cost or availability is still an issue IV *phenytoin* can be used. IV *phenytoin* also appears to be preferentially used in ESRD patients who may become hyperphosphatemic or hypocalcemic.

Both agents are used in children currently without specific age stratified labeling that include dosing recommendations. But, *fosphenytoin* may be preferred for smaller veins or poorer venous access in pediatrics. Elderly patients also with poor access may also benefit from this advantage. Use in clinical situations where cardiac monitoring is not readily available has been a mentioned use for *fosphenytoin*,⁷⁶ but this may not be prudent if comparable cardiovascular and hypotensive adverse events exist in both drugs.

⁷⁶ Ramsey RE, DeToledo J. Intravenous administration of fosphenytoin: Options for the management of seizures. *Neurology* 1996; 46 (Suppl 1): S17-S19.

6 RECOMMENDATIONS

Recommendations on Regulatory Actions and Labeling

- For IV phenytoin: Eliminate cardiac labeling from ADVERSE REACTIONS section and retain in the WARNINGS section ONLY.
- For fosphenytoin and IV phenytoin: Labeling will continue to include “Cardiovascular Depression” and “Serious Cardiovascular Events and Fatalities” (with CAUTION in patients with hypotension and severe myocardial insufficiency).
- For fosphenytoin and IV phenytoin: Broaden WARNINGS labeling to include specific diagnoses of cardiac arrest, asystole, ventricular tachycardia, ventricular fibrillation, prolonged QT interval, junctional rhythm, sudden death, and pulseless electrical asystole as identified in the AERS database.
- For fosphenytoin and IV phenytoin: Broaden WARNINGS labeling to include specific language that these events can occur in healthy adults and children without underlying cardiac disease or co-morbidities, and occurrence at or below recommended doses, at or below recommended infusion rates and during and after infusions. The current label for fosphenytoin and IV phenytoin will continue to have CONTRAINDICATIONS in patients with sinus bradycardia, sino-atrial block, second and third degree A-V block and Adams-Stokes syndrome.
- For fosphenytoin and IV phenytoin: Consider labeling under PRECAUTIONS for additional ECG and laboratory monitoring during and after infusion in special populations such as renal, cardiac, hepatic, elderly, CYP mutations & slow metabolizers, concurrent users of first line seizure treatment with benzodiazepines that interact with these drugs, and organ transplant patients.
- For fosphenytoin: Update the ADVERSE REACTION table in the Clinical section with more comprehensive data submitted from the integrated clinical trial adverse event profiles from Pfizer’s 2008 systematic analysis. This data will more accurately reflect the rates of treatment-emergent adverse events for fatal, non-fatal serious and non-serious AE’s.

Recommendations for Other Actions

- IV phenytoin: Consider issuance of a Dear professional letter to instruct in preferred dosing, use in special populations and recommendation for a proposed clinical algorithm for choosing fosphenytoin versus IV phenytoin. Include specific language that these events can occur in healthy adults and children without underlying cardiac disease or co-morbidities, and occurrence at or below recommended doses, at or below recommended infusion rates and during and after infusions.

- IV fosphenytoin: Consider issuance of a Dear professional letter stating that fosphenytoin does not have less hypotension or cardiac toxicity and include specific language that these events can occur in healthy adults and children without underlying cardiac disease or co-morbidities, and occurrence at or below recommended doses, at or below recommended infusion rates and during and after infusions. Inform practitioners that current updates in analysis show a possibly for PGS but requires further analysis.
- Office of Compliance to follow through with reporting issues for fosphenytoin by Pfizer.

7 REFERENCES

References are included as footnotes.

8 APPENDICES

8.1 APPENDIX 1: ADVERSE EVENTS TABLE FROM RANDOMIZED, DOUBLE-BLIND, CONTROLLED CLINICAL TRIAL FROM THE 2001 CEREBYX LABEL

Table appears on following page (page 44).

Table 2. Treatment-Emergent Adverse Event Incidence Following IV Administration at the Maximum Dose and Rate to Patients With Epilepsy or Neurosurgical Patients (Events in at Least 2% of Fosphenytoin Sodium Injection-Treated Patients)		
BODY SYSTEM	IV Fosphenytoin Sodium Injection	IV Phenytoin
Adverse Event	N=90	N=22
BODY AS A WHOLE		
Pelvic Pain	4.4	0.0
Asthenia	2.2	0.0
Back Pain	2.2	0.0
Headache	2.2	4.5
CARDIOVASCULAR		
Hypotension	7.7	9.1
Vasodilatation	5.6	4.5
Tachycardia	2.2	0.0
DIGESTIVE		
Nausea	8.9	13.6
Tongue Disorder	4.4	0.0
Dry Mouth	4.4	4.5
Vomiting	2.2	9.1
NERVOUS		
Nystagmus	44.4	59.1
Dizziness	31.1	27.3
Somnolence	20.0	27.3
Ataxia	11.1	18.2
Stupor	7.7	4.5
Incoordination	4.4	4.5
Paresthesia	4.4	0.0
Extrapyramidal Syndrome	4.4	0.0
Tremor	3.3	9.1
Agitation	3.3	0.0
Hypesthesia	2.2	9.1

Dysarthria	2.2	0.0
Vertigo	2.2	0.0
Brain Edema	2.2	4.5
SKIN AND APPENDAGES		
Pruritus	48.9	4.5
SPECIAL SENSES		
Tinnitus	8.9	9.1
Diplopia	3.3	0.0
Taste Perversion	3.3	0.0
Amblyopia	2.2	9.1
Deafness	2.2	0.0

8.2 APPENDIX 2: FOSPHENYTOIN SODIUM PRODUCTS AVAILABLE AS (EQ 50MG PHENYTOIN NA/ML) INJECTABLE/INJECTION BY PRESCRIPTION

<u>FOSPHENYTOIN SODIUM (NDA # 020450)</u>	PARKE DAVIS
<u>FOSPHENYTOIN SODIUM (ANDA # 076886)</u>	TEVA PARENTERAL
<u>FOSPHENYTOIN SODIUM (ANDA # 077481)</u>	BEDFORD
<u>FOSPHENYTOIN SODIUM (ANDA # 077989)</u>	BAXTER HLTHCARE
<u>FOSPHENYTOIN SODIUM (ANDA # 078052)</u>	APP PHARMS
<u>FOSPHENYTOIN SODIUM (ANDA # 078126)</u>	APOTEX INC
<u>FOSPHENYTOIN SODIUM (ANDA # 078137)</u>	WOCKHARDT
<u>FOSPHENYTOIN SODIUM (ANDA # 078158)</u>	HOSPIRA
<u>FOSPHENYTOIN SODIUM</u>	PHARMAFORCE

<u>(ANDA # 078277)</u>	
<u>FOSPHENYTOIN SODIUM</u> <u>(ANDA # 078417)</u>	SUN PHARMA GLOBAL
<u>FOSPHENYTOIN SODIUM</u> <u>(ANDA # 078476)</u>	AKORN STRIDES
<u>FOSPHENYTOIN SODIUM</u> <u>(ANDA # 078736)</u>	STRIDES ARCOLAB
<u>FOSPHENYTOIN SODIUM</u> <u>(ANDA # 078765)</u>	HIKMA FARMACEUTICA

**8.3 APPENDIX 3: PHENYTOIN SODIUM PRODUCTS AVAILABLE AS
(50MG/ML) INJECTABLE/INJECTION BY PRESCRIPTION**

<u>PHENYTOIN</u> <u>SODIUM</u> <u>(ANDA # 040573)</u>	HIKMA FARMACEUTICA
<u>PHENYTOIN</u> <u>SODIUM</u> <u>(ANDA # 040781)</u>	PHARMAFORCE
<u>PHENYTOIN</u> <u>SODIUM</u> <u>(ANDA # 084307)</u>	BAXTER HLTHCARE
<u>PHENYTOIN</u> <u>SODIUM</u> <u>(ANDA # 089521)</u>	HOSPIRA
<u>PHENYTOIN</u> <u>SODIUM</u> <u>(ANDA # 089744)</u>	HOSPIRA

8.4 APPENDIX 4 : PFIZER 2008 SUBMISSION OF 1994 COMPILED SAFETY DATA

Tables begin on following page.

Table 7. All and Associated Adverse Events Occurring in ≥1% of Patients by Body System and Treatment^a

[Number (%) of Patients]

(Page 1 of 2)

BODY SYSTEM/ Preferred Term	Cerebyx N = 534				Dilantin N = 102			
	All		Associated		All		Associated	
NERVOUS								
Nystagmus	99	(18.5)	71	(13.3)	14	(13.7)	7	(6.9)
Dizziness	48	(9.0)	43	(8.1)	10	(9.8)	9	(8.8)
Ataxia	48	(9.0)	20	(3.7)	9	(8.8)	2	(2.0)
Somnolence	45	(8.4)	25	(4.7)	10	(9.8)	8	(7.8)
Tremor	31	(5.8)	19	(3.6)	9	(8.8)	5	(4.9)
Incoordination	28	(5.2)	15	(2.8)	4	(3.9)	2	(2.0)
Paresthesia	26	(4.9)	19	(3.6)	3	(2.9)	2	(2.0)
Neuropathy	25	(4.7)	2	(0.4)	4	(3.9)	0	(0.0)
Reflexes Increased	16	(3.0)	1	(0.2)	3	(2.9)	0	(0.0)
Speech Disorder	15	(2.8)	4	(0.7)	3	(2.9)	2	(2.0)
Hypertonia	12	(2.2)	2	(0.4)	0	(0.0)	0	(0.0)
Reflexes Decreased	10	(1.9)	2	(0.4)	4	(3.9)	2	(2.0)
Intracranial Hypertension	9	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)
Stupor	8	(1.5)	3	(0.6)	1	(1.0)	0	(0.0)
Anxiety	7	(1.3)	2	(0.4)	0	(0.0)	0	(0.0)
Confusion	6	(1.1)	2	(0.4)	0	(0.0)	0	(0.0)
Agitation	6	(1.1)	0	(0.0)	1	(1.0)	0	(0.0)
BODY AS A WHOLE								
Headache	41	(7.7)	13	(2.4)	6	(5.9)	2	(2.0)
Fever	35	(6.6)	0	(0.0)	6	(5.9)	0	(0.0)
Pain	29	(5.4)	10	(1.9)	2	(2.0)	2	(2.0)
Accidental Injury	22	(4.1)	2	(0.4)	7	(6.9)	2	(2.0)
Infection	17	(3.2)	0	(0.0)	5	(4.9)	0	(0.0)
Injection-Site Reaction	15	(2.8)	10	(1.9)	5	(4.9)	2	(2.0)
Asthenia	9	(1.7)	7	(1.3)	2	(2.0)	1	(1.0)
Back Pain	9	(1.7)	1	(0.2)	0	(0.0)	0	(0.0)
Face Edema	9	(1.7)	0	(0.0)	4	(3.9)	0	(0.0)
Injection-Site Pain	8	(1.5)	7	(1.3)	7	(6.9)	7	(6.9)
Reaction Unevaluable	7	(1.3)	2	(0.4)	1	(1.0)	1	(1.0)
Sepsis	7	(1.3)	0	(0.0)	1	(1.0)	0	(0.0)
DIGESTIVE								
Nausea	30	(5.6)	12	(2.2)	6	(5.9)	1	(1.0)
Constipation	26	(4.9)	2	(0.4)	3	(2.9)	0	(0.0)
Vomiting	17	(3.2)	2	(0.4)	5	(4.9)	0	(0.0)

^a Associated adverse events are the events considered by the investigator to be related, probably related, possibly related, or of unknown relationship to treatment. Events occurring in ≥1% of patients were based upon all adverse events occurring in Cerebyx-treated patients.

TABLE 7 (cont'd). All and Associated Adverse Events Occurring in ≥1% of Patients by Body System and Treatment^a

[Number (%) of Patients]

(Page 2 of 2)

BODY SYSTEM/ Preferred Term	Cerebyx N = 534				Dilantin N = 102			
	All		Associated		All		Associated	
CARDIOVASCULAR								
Hypotension	13	(2.4)	4	(0.7)	3	(2.9)	2	(2.0)
Hypertension	10	(1.9)	1	(0.2)	2	(2.0)	0	(0.0)
Tachycardia	9	(1.7)	0	(0.0)	2	(2.0)	0	(0.0)
Bradycardia	7	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
SKIN AND APPENDAGES								
Pruritus	27	(5.1)	24	(4.5)	0	(0.0)	0	(0.0)
Rash	7	(1.3)	1	(0.2)	2	(2.0)	1	(1.0)
HEMIC AND LYMPHATIC								
Ecchymosis	30	(5.6)	13	(2.4)	4	(3.9)	2	(2.0)
SURGERIES/PROCEDURES								
Surgeries/Procedures	26	(4.9)	0	(0.0)	5	(4.9)	0	(0.0)
RESPIRATORY								
Pneumonia	10	(1.9)	0	(0.0)	6	(5.9)	0	(0.0)
Lung Disorder	7	(1.3)	0	(0.0)	1	(1.0)	0	(0.0)
UROGENITAL								
Urinary Retention	8	(1.5)	0	(0.0)	3	(2.9)	0	(0.0)
Urinary Tract Infection	6	(1.1)	0	(0.0)	2	(2.0)	0	(0.0)
MUSCULOSKELETAL								
Myasthenia	11	(2.1)	1	(0.2)	2	(2.0)	0	(0.0)
SPECIAL SENSES								
Amblyopia	9	(1.7)	4	(0.7)	3	(2.9)	3	(2.9)
METABOLIC AND NUTRITIONAL								
Hypokalemia	8	(1.5)	0	(0.0)	2	(2.0)	0	(0.0)

^a Associated adverse events are the events considered by the investigator to be related, probably related, possibly related, or of unknown relationship to treatment. Events occurring in ≥1% of patients were based upon all adverse events occurring in Cerebyx-treated patients.

Table 8. Serious Adverse Events

[Number (%) of Participants]

Adverse Event ^a	Cerebyx N = 736 ^b	
Apnea	3	(0.42)
Cardiac Arrest	3	(0.42)
Hypotension	3	(0.42)
Intracranial Hypertension	3	(0.42)
Bradycardia	2	(0.28)
Cerebral Hemorrhage	2	(0.28)
Cerebrovascular Accident	2	(0.28)
Sepsis	2	(0.28)
Shock	2	(0.28)
Stupor	2	(0.28)
Arrhythmia	1	(0.14)
Aspiration Pneumonia	1	(0.14)
Ataxia	1	(0.14)
Brain Edema	1	(0.14)
Cerebral Infarct	1	(0.14)
CNS Depression	1	(0.14)
Dizziness	1	(0.14)
Encephalitis	1	(0.14)
Encephalopathy	1	(0.14)
Meningitis	1	(0.14)
Myasthenia	1	(0.14)
Myopathy	1	(0.14)
Neuropathy	1	(0.14)
Nystagmus	1	(0.14)
Overdose ^c	1	(0.14)
Subdural Hematoma	1	(0.14)
Surgeries/Procedures	1	(0.14)
Tachycardia	1	(0.14)
Thinking Abnormal	1	(0.14)

^a COSTART preferred term^b N represents the number of participants who received Cerebyx in studies as of September 1, 1994.^c Considered an overdose by study investigator because patient took PO Dilantin from own supply for 2 days, in addition to IM Cerebyx. However, sponsor did not consider this sufficient exposure to provide guidance on handling an overdose situation.

8.5 APPENDIX 5: COMMON ADVERSE EVENTS ASSOCIATED WITH PHENYTOIN AND FOSPHENYTOIN BASED ON LABELING AND 2008 SUBMISSION FROM PFIZER, INC. (RESPONSE TO FDA QUERY REGARDING PURPLE GLOVE SYNDROME AND CEREBYX (FOSPHENYTOIN SODIUM) SYSTEMATIC ANALYSIS OF ASSOCIATION BETWEEN PURPLE GLOVE SYNDROME AND FOSPHENYTOIN. 22 JULY 2008).

<u>Adverse Event</u>	<u>IV Fosphenytoin (%)</u>		<u>IV ***Phenytoin (%)</u>	
	Clinical Trial * N=90	Clinical Trial ** N=534	Clinical Trial* N=22	Clinical Trial ** N=102
<u>Cardiac Arrhythmia: tachycardia</u>	2.2	1.7	0	2.0
<u>Cardiac Arrhythmia bradycardia</u> (CV events in AERS: fosphenytoin =78. phenytoin=99.)	Infrequent ****	1.3	Not stated	0
<u>Hypotension</u> (AERS: fosphenytoin =53,phenytoin =44;fosphenytoin 66%; phenytoin 61% ³⁸⁾)	7.7	2.4	9.1	2.9
<u>Fever</u>	Frequent ****	6.6	Not stated	5.9
<u>Hypersensitivity Reaction</u>	Not stated			
<u>Injection-Site Reaction</u>	Frequent	2.8	Not stated	4.9
<u>Injection-Site Pain</u>	Frequent	1.5	Not stated	6.9

Dizziness	31.1	9.0	27.3	9.8
Somnolence	20.0	8.4	27.3	9.8
Ataxia	11.1	9.0	18.2	8.8
<u>Agranulocytosis</u>	Not stated		<u>Not stated</u>	
<u>Eosinophilia</u>	Not stated			
<u>Lupus-like Reaction</u>	Not stated			
<u>Pseudo lymphoma</u>	Infrequent (lymph-adenopathy)	Not stated		
<u>Rash (Steven's Johnson Not stated)</u>	Frequent; Infrequent =maculopapular rash, skin discoloration, pustular rash	1.3	Not stated	2.0
Pruritus	48.9	5.1	4.5	0
<u>Hepatic Toxicity</u>	Not stated Infrequent =LFT abnl	Not stated	Not stated	Not stated
<u>Nausea</u>	8.9	5.6	13.6	5.9
<u>Vomiting</u>	2.2	3.2	9.1	4.9

No placebo controlled studies for fosphenytoin or phenytoin.

*from Appendix 1: Fosphenytoin 2001 Label's clinical trials (at least 2% of patients)

** from Appendix 4: Pfizer 2008 Submission of 1994 compiled Safety Data using Cerebyx and Dilantin (in ≥1% of patients) Limited data on details of studies were provided. Data is confidential to Pfizer.

*** study 982-013 had 61 Phenytoin po patients, study 982-014/-026 had N=180 for IV/po phenytoin. No further details.

**** from Fosphenytoin label that included 859 patients during all clinical trials, with all AE seen at least twice: **Frequent**= > 1/100 individuals; **infrequent** in 1/100 to 1/1000 individuals

8.6 APPENDIX 6: TABLE, IN DRAFT LABELING FORM, PROPOSES THE VOLUME OF CEREBYX TO ADMINISTER TO A PATIENT FOR THE EMERGENCY TREATMENT OF STATUS EPILEPTICUS USING A 15 MG PE/KG LOADING DOSE TO ASSIST IN REDUCING ADMINISTRATION ERRORS WHICH CONTINUE TO BE REPORTED.

Calculating a loading dose for emergency treatment of Status Epilepticus only

Patient body weight (kg)	Cerebyx Dose (mg PE)	Volume to be withdrawn from Cerebyx Vial (mL)
100	1500	30
90	1350	27
80	1200	24
70	1050	21
60	900	18
50	750	15
45	675	13.5

8.7 APPENDIX 7: CHARACTERISTICS OF CARDIOVASCULAR AND HYPOTENSION CASES ASSOCIATED WITH PHENYTOIN AND FOSPHENYTOIN

Characteristics of Cardiovascular and hypotension cases associated with Phenytoin and Fosphenytoin December 4, 2001 to July 31, 2010

Fosphenytoin (N=49)		Phenytoin (N=44)
	<u>Origin</u>	
39	US	23
10	Foreign	21
	<u>Gender</u>	
27	Male	23
18	Female	15
4	U	6
<u>n=42^A</u>	<u>Age</u>	<u>n=29^B</u>
55 yrs	Mean	54.2 yrs
64.5 yrs	Median	55 yrs
1 day to 91 years	Range	17 days to 87 years
	<u>Report type</u>	
20	Expedited	28
29	Direct	16
<u>n=41^C</u>	<u>Dose</u>	<u>n=36</u>

1130 mg PE	Mean	807 mg
1000 mg PE	Median	1000 mg
41.5 mg PE – 4500 mg PE	Range	15 mg – 1500 mg
<u>n=19</u>	<u>Infusion</u>	<u>n=13^D</u>
58.9 mg PE/min	<u>Rate</u>	30 mg/min
60 mg PE/min	Mean	27.7 mg/min
2.75 mg PE/min – 150 mg PE/min	Median	2.1 mg/min – 50 mg/min
	Range	
During infusion (21)	Time to	During infusion (11)
< 30 min after infusion (11)	onset	< 30 min after infusion (10)
> 30 min after infusion (4)		> 30 min after infusion (6)
Unknown (13)		Unknown (17)
Seizure NOS (22)		Seizure NOS (21)
Phenytoin Loading (11)	Indication	Phenytoin Loading (5)
Status Epilepticus (6)		Status Epilepticus (2)
Maintenance therapy (1)		Maintenance therapy (6)
New onset seizures (1) Pain (1)		Epilepsy (1) Post-stroke Seizure (1)
Unknown (7)		Grand-mal Seizure (1)
		Unknown (7)
ED (11) ICU (3) OR (1)	Setting	ED (2) ICU (3) OR (4)
Medicine Unit (3) Unknown (31)		Medicine Unit (1) Unknown (34)
CAD/MI ^E (5) HTN ^F (4)	Relevant	CAD/MI (4) HTN (5) Afib (4)
Type 2 DM (5) Renal insuff. (4)	Cardiac	Type 2 DM (2) Renal insuff. (1)
Cardiomyopathy (1) 3 rd Degree	History	Stroke (2) AVR ^G (2)
Hearth Block (1) Cocaine Use (1)	(not	Cardiac Surgery (1) Vfib (1)
Hyperlipidemia (1)	mutually	Hyperlipidemia (1) CHF (1)
None (13) Unknown (16)	exclusive)	Pulm. HTN (1) Cocaine Use (1)
		None (7) Unknown (15)

A: 5 Pediatric cases and 38 Adult cases

B: 2 pediatric and 27 adult cases

C: Includes three cases involving fosphenytoin overdose (2 pediatric cases, 1 adult case)

D: Does NOT include 4 cases of IV push

E: Coronary Artery Disease/Myocardial Infarction

F: Hypertension

G: Aortic Valve Replacement

8.8 APPENDIX 8: CASE DETAILS OF FOSPHENYTOIN DEATHS (N=12)

Characteristics of Cardiovascular and hypotension DEATH cases associated with Fosphenytoin from December 4, 2001 to July 31, 2010. (N=13)

<u>ISR</u>	<u>Age</u>	<u>Dose</u>	<u>Infusion Rate</u>	<u>Event</u>	<u>Outcome</u>	<u>Comment/ Confounders</u>
3996347	78	1800 mg PE	60 mg PE/min	Hypotension	Death 1 week later	Recovered, died after “new attack.”
4005857	74	1000 mg PE	Unknown	Bradycardia	Death	Limited information
4110495	U	4500 mg	Unknown	Hypotension	Death	Overdose
4349468	83	750 mg PE	Unknown	Hypotension	Death 6 months later	Death secondary to underlying brain damage
4502969	65	1000 mg PE	67 mg PE/min	Cardiac Arrest	Death 3 weeks later	ESRD, recent intracerebral bleed.
4502976	68	750 mg PE	8.3 mg PE/min	Hypotension	Death 1 week later	Intracerebral bleed, Acute MI
4615970	60	1000 mg PE	Unknown	Ventricular tachycardia	Death 2 weeks later	Ischemic heart disease, cerebral lesion
4717866	50	500 mg PE	Unknown	2 nd and 3 rd Degree heart block	Death 1 week later	History of cocaine abuse and Hepatitis C
4780432	18 months	2000 mg PE	Unknown	Asystole	Death 3 hours later	Overdose
4860889	2 days	225 mg PE	3.75 mg PE/min	Cardiac arrest	Death 3 hours later	Overdose
4970141	45	1500 mg PE	U	Sudden Death	Death	Limited information
5805070	78	Unknown	Unknown	Hypotension	Death 10 days later	Limited information
6333306	13 months	160 mg PE	16 mg PE/min	Asystole	Death 1 hour later	Probable viral myocarditis on autopsy

8.9 APPENDIX 9: CASE DETAILS OF PHENYTOIN DEATHS (N=9)

Characteristics of Cardiovascular and hypotension DEATH cases associated with Phenytoin from December 4, 2001 to July 31, 2010. (N=9)

<u>ISR</u>	<u>Age</u>	<u>Dose</u>	<u>Infusion Rate</u>	<u>Event</u>	<u>Outcome</u>	<u>Comment/ Confounders</u>
3853216	U	U	Unknown (IV push)	Asystole	Death	"Nurse may have pushed drug too fast."
3981771	44	1000 mg	Unknown	Cardiac Arrest	Death 1 hour later	History of CHF
4020948	U	250 mg	50 mg/min	Tachycardia	Death	Incorrectly injected phenytoin oral suspension
4173279	27 months	170 mg	Unknown	Ventricular fibrillation	Death	Recent acute respiratory distress
4706270	36	400 mg	50 mg/min	Asystole	Death	History of DM and HTN
5009729	63	1000 mg	16.7 mg/min	Hypotension	Death	Admitted for change in mental status and not responsive to stimuli.
5878108	29	1000 mg	Unknown	Ventricular tachycardia	Death Same day	Being treated for venlafaxine overdose
6133784	45	300mg	Unknown	Hypotension	Death Same day	Recovered from hypotension, died of sepsis
6393935	77	20 mg/kg	Unknown	Asystole	Death	History of Afib

8.10 APPENDIX 10: CHARACTERISTICS OF SELECTED CASES (EXCLUDING DEATHS)

ISR	Suspect Drug	Age	Dose	Infusion Rate	Event	Outcome	Comment/ Confounders
4013284	Fosphenytoin	U	1000mg PE	U	Bradycardia, 3rd Degree Heart block	Intubated, externally paced, readmitted to ICU	Undiluted administration. History of ESRD and DM.
4144158	Fosphenytoin	83	800 mg PE	U	Asystole	Returned to sinus rhythm after 18 hours Treated with IV fluids and pressors.	Undiluted administration. History of ESRD
5680733	Fosphenytoin	48	1600 mg PE	U	Hypotension	fosphenytoin eventually DC'd.	Positive Rechallenge with 100 mg.
6844923	Fosphenytoin and Phenytoin	55	1000 mg PE 100 mg	U	Hypotension	Both agents DC'd.	Similar reaction with both agents. History of Uncontrolled HTN
3850961	Phenytoin	U	1500 mg	Rapid IV push	Cardiac Arrest	Resuscitated	IV push in OR
4494263	Phenytoin	U	900 mg	U	Bradycardia	Recovered without intervention	Positive rechallenge; bradycardia on repeat administration Attributed to confusion over packaging, "No infusion."
5692872	Phenytoin	29	1000 mg	IV push	Asystole	CPR, recovery	

8.11 APPENDIX 11: RELEVANT SECTIONS OF LABELS OF FOSPHENYTOIN AND PHENYTOIN

8.11.1 FOSPHENYTOIN

Special Populations

Patients with Renal or Hepatic Disease

Due to an increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminemia, the interpretation of total phenytoin plasma concentrations should be made with caution (see [DOSAGE AND ADMINISTRATION](#)). Unbound phenytoin concentrations may be more useful in these patient populations.

After IV administration of fosphenytoin sodium injection to patients with renal and/or hepatic disease, or in those with hypoalbuminemia, fosphenytoin clearance to phenytoin may be increased without a similar increase in phenytoin clearance. This has the potential to increase the frequency and severity of adverse events (see [PRECAUTIONS](#)).

Age

The effect of age was evaluated in patients 5 to 98 years of age. Patient age had no significant impact on fosphenytoin pharmacokinetics. Phenytoin clearance tends to decrease with increasing age (20% less in patients over 70 years of age relative to that in patients 20-30 years of age). Phenytoin dosing requirements are highly variable and must be individualized (see [DOSAGE AND ADMINISTRATION](#)).

Gender and Race

Gender and race have no significant impact on fosphenytoin or phenytoin pharmacokinetics.

Pediatrics

Only limited pharmacokinetic data are available in children (N=8; age 5 to 10 years). In these patients with status epilepticus who received loading doses of fosphenytoin sodium injection, the plasma fosphenytoin, total phenytoin, and unbound phenytoin concentration-time profiles did not signal any major differences from those in adult patients with status epilepticus receiving comparable doses.

Clinical Studies

Infusion tolerance was evaluated in clinical studies. One double-blind study assessed infusion site tolerance of equivalent loading doses (15-20 mg PE/kg) of fosphenytoin sodium injection infused at 150 mg PE/min or phenytoin infused at 50 mg/min. The study demonstrated better local tolerance (pain and burning at the infusion site), fewer disruptions of the infusion, and a shorter infusion period for fosphenytoin sodium injection-treated patients ([Table 1](#)).

TABLE 1. Infusion Tolerance of Equivalent Loading Doses of IV Fosphenytoin Sodium Injection and IV Phenytoin

	IV Fosphenytoin Sodium Injection	IV Phenytoin
	N=90	N=22
Local Intolerance	9%*	90%

Infusion Disrupted	21%	67%
Average Infusion Time	13 min	44 min

Fosphenytoin sodium injection-treated patients, however, experienced more systemic sensory disturbances (see [PRECAUTIONS, Sensory Disturbances](#)).

Infusion disruptions in fosphenytoin sodium injection-treated patients were primarily due to systemic burning, pruritus, and/or paresthesia while those in phenytoin-treated patients were primarily due to pain and burning at the infusion site (see [Table 1](#)).

In a double-blind study investigating temporary substitution of fosphenytoin sodium injection for oral phenytoin, IM fosphenytoin sodium injection was as well-tolerated as IM placebo. IM fosphenytoin sodium injection resulted in a slight increase in transient, mild to moderate local itching (23% of patients vs. 11% of IM placebo-treated patients at any time during the study). This study also demonstrated that equimolar doses of IM fosphenytoin sodium injection may be substituted for oral phenytoin sodium with no dosage adjustments needed when initiating IM or returning to oral therapy. In contrast, switching between IM and oral phenytoin requires dosage adjustments because of slow and erratic phenytoin absorption from muscle.

INDICATIONS AND USAGE

Fosphenytoin sodium injection is indicated for short-term parenteral administration when other means of phenytoin administration are unavailable, inappropriate or deemed less advantageous. The safety and effectiveness of fosphenytoin sodium injection in this use has not been systematically evaluated for more than 5 days.

Fosphenytoin sodium injection can be used for the control of generalized convulsive status epilepticus and prevention and treatment of seizures occurring during neurosurgery. It can also be substituted, short-term, for oral phenytoin.

CONTRAINDICATIONS

Fosphenytoin sodium injection is contraindicated in patients who have demonstrated hypersensitivity to fosphenytoin sodium injection or its ingredients, or to phenytoin or other hydantoins.

Because of the effect of parenteral phenytoin on ventricular automaticity, fosphenytoin sodium injection is contraindicated in patients with sinus bradycardia, sino-atrial block, second and third degree A-V block, and Adams-Stokes syndrome.

WARNINGS

DOSES OF fosphenytoin SODIUM INJECTION ARE EXPRESSED AS THEIR PHENYTOIN SODIUM EQUIVALENTS IN THIS LABELING (PE=phenytoin sodium equivalent).

DO NOT, THEREFORE, MAKE ANY ADJUSTMENT IN THE RECOMMENDED DOSES WHEN SUBSTITUTING fosphenytoin PHENYTOIN SODIUM INJECTION FOR PHENYTOIN SODIUM OR VICE VERSA.

The following warnings are based on experience with fosphenytoin sodium injection or phenytoin.

STATUS EPILEPTICUS DOSING REGIMEN

- **Do not administer fosphenytoin sodium injection at a rate greater than 150 mg PE/min.**

The dose of IV fosphenytoin sodium injection (15 to 20 mg PE/kg) that is used to treat status epilepticus is administered at a maximum rate of 150 mg PE/min. The typical fosphenytoin sodium injection infusion administered to a 50 kg patient would take between 5 and 7 minutes. Note that the delivery of an identical molar dose of phenytoin using parenteral Dilantin or generic phenytoin sodium injection cannot be accomplished in less than 15 to 20 minutes because of the untoward cardiovascular effects that accompany the direct intravenous administration of phenytoin at rates greater than 50 mg/min.

If rapid phenytoin loading is a primary goal, IV administration of fosphenytoin sodium injection is preferred because the time to achieve therapeutic plasma phenytoin concentrations is greater following IM than that following IV administration (see [DOSAGE AND ADMINISTRATION](#)).

WITHDRAWAL PRECIPITATED SEIZURE, STATUS EPILEPTICUS

Antiepileptic drugs should not be abruptly discontinued because of the possibility of increased seizure frequency, including status epilepticus. When, in the judgement of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

CARDIOVASCULAR DEPRESSION

Hypotension may occur, especially after IV administration at high doses and high rates of administration. Following administration of phenytoin, severe cardiovascular reactions and fatalities have been reported with atrial and ventricular conduction depression and

ventricular fibrillation. Severe complications are most commonly encountered in elderly or gravely ill patients. Therefore, careful cardiac monitoring is needed when administering IV loading doses of fosphenytoin sodium injection. Reduction in rate of administration or discontinuation of dosing may be needed.

Fosphenytoin sodium injection should be used with caution in patients with hypotension and severe myocardial insufficiency.

RASH

Fosphenytoin sodium injection should be discontinued if a skin rash appears. If the rash is exfoliative, purpuric, or bullous, or if lupus erythematosus, Stevens-Johnson syndrome, or toxic epidermal necrolysis is suspected, use of this drug should not be resumed and alternative therapy should be considered. If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further fosphenytoin sodium injection or phenytoin administration is contraindicated.

HEPATIC INJURY

Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with phenytoin. These incidents have been associated with a hypersensitivity syndrome characterized by fever, skin eruptions, and lymphadenopathy, and usually occur within the first 2 months of treatment. Other common manifestations include jaundice, hepatomegaly, elevated serum transaminase levels, leukocytosis, and eosinophilia. The clinical course of acute phenytoin hepatotoxicity ranges from prompt recovery to fatal outcomes. In these patients with acute hepatotoxicity, fosphenytoin sodium injection should be immediately discontinued and not readministered.

HEMOPOIETIC SYSTEM

Hemopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression.

There have been a number of reports that have suggested a relationship between phenytoin and the development of lymphadenopathy (local or generalized), including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness, e.g., fever, rash, and liver involvement. In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs.

PRECLINICAL

Increased frequencies of malformations (brain, cardiovascular, digit, and skeletal anomalies), death, growth retardation, and functional impairment (chromodacryorrhea, hyperactivity, circling) were observed among the offspring of rats receiving fosphenytoin during pregnancy. Most of the adverse effects on embryo-fetal development occurred at doses of 33 mg PE/kg or higher (approximately 30% of the maximum human loading dose or higher on a mg/m² basis), which produced peak maternal plasma phenytoin concentrations of approximately 20 µg/mL or greater. Maternal toxicity was often associated with these doses and plasma concentrations, however, there is no evidence to suggest that the developmental effects were secondary to the maternal effects. The single occurrence of a rare brain malformation at a nonmaternotoxic dose of 17 mg PE/kg (approximately 10% of the maximum human loading dose on a mg/m² basis) was also considered drug-induced. The developmental effects of fosphenytoin in rats were similar to those which have been reported following administration of phenytoin to pregnant rats.

No effects on embryo-fetal development were observed when rabbits were given up to 33 mg PE/kg of fosphenytoin (approximately 50% of the maximum human loading dose on a mg/m² basis) during pregnancy. Increased resorption and malformation rates have been reported following administration of phenytoin doses of 75 mg/kg or higher (approximately 120% of the maximum human loading dose or higher on a mg/m² basis) to pregnant rabbits.

PRECAUTIONS

GENERAL: (FOSPHENYTOIN SODIUM INJECTION SPECIFIC)

SENSORY DISTURBANCES

Severe burning, itching, and/or paresthesia were reported by 7 of 16 normal volunteers administered IV fosphenytoin sodium injection at a dose of 1200 mg PE at the maximum rate of administration (150 mg PE/min). The severe sensory disturbance lasted from 3 to 50 minutes in 6 of these subjects and for 14 hours in the seventh subject. In some cases, milder sensory disturbances persisted for as long as 24 hours. The location of the discomfort varied among subjects with the groin mentioned most frequently as an area of discomfort. In a separate cohort of 16 normal volunteers (taken from 2 other studies) who were administered IV fosphenytoin sodium injection at a dose of 1200 mg PE at the maximum rate of administration (150 mg PE/min), none experienced severe disturbances, but most experienced mild to moderate itching or tingling.

Patients administered fosphenytoin sodium injection at doses of 20 mg PE/kg at 150 mg PE/min are expected to experience discomfort of some degree. The occurrence and intensity of the discomfort can be lessened by slowing or temporarily stopping the infusion.

The effect of continuing infusion unaltered in the presence of these sensations is unknown. No permanent sequelae have been reported thus far. The pharmacologic basis for these positive sensory phenomena is unknown, but other phosphate ester drugs, which deliver smaller phosphate loads, have been associated with burning, itching, and/or tingling pred.

PHOSPHATE LOAD

The phosphate load provided by fosphenytoin sodium injection (0.0037 mmol phosphate/mg PE fosphenytoin sodium injection) should be considered when treating patients who require phosphate restriction, such as those with severe renal impairment.

IV LOADING IN RENAL AND/OR HEPATIC DISEASE OR IN THOSE WITH HYPOALBUMINEMIA

After IV administration to patients with renal and/or hepatic disease, or in those with hypoalbuminemia, fosphenytoin clearance to phenytoin may be increased without a similar increase in phenytoin clearance. This has the potential to increase the frequency and severity of adverse events (see [CLINICAL PHARMACOLOGY, Special Populations](#), and [DOSAGE AND ADMINISTRATION, Dosing in Special Populations](#)).

GENERAL: (PHENYTOIN ASSOCIATED)

Fosphenytoin sodium injection is *not* indicated for the treatment of *absence seizures*.

A small percentage of individuals who have been treated with phenytoin have been shown to metabolize the drug slowly. *Slow metabolism* may be due to limited enzyme availability and lack of induction; it appears to be genetically determined.

Phenytoin and other hydantoin are contraindicated in patients who have experienced phenytoin hypersensitivity. Additionally, caution should be exercised if using structurally similar (eg, barbiturates, succinimides, oxazolidinediones, and other related compounds) in these same patients.

Phenytoin has been infrequently associated with the exacerbation of *porphyria*. Caution should be exercised when fosphenytoin sodium injection is used in patients with this disease.

Hyperglycemia, resulting from phenytoin's inhibitory effect on insulin release, has been reported. Phenytoin may also raise the serum glucose concentrations in diabetic patients. Plasma concentrations of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely, irreversible cerebellar dysfunction. Accordingly, at the first sign of *acute toxicity*, determination of plasma phenytoin concentrations is recommended (see [PRECAUTIONS, Laboratory Tests](#)). Fosphenytoin sodium injection dose reduction is indicated if phenytoin concentrations are excessive; if symptoms persist, administration of fosphenytoin sodium injection should be discontinued.

The liver is the primary site of biotransformation of phenytoin; patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

Phenytoin and other hydantoins are not indicated for seizures due to hypoglycemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.

Phenytoin has the potential to lower serum folate levels.

LABORATORY TESTS

Phenytoin doses are usually selected to attain therapeutic plasma total phenytoin concentrations of 10 to 20 µg/mL, (unbound phenytoin concentrations of 1 to 2 µg/mL). Following fosphenytoin sodium injection administration, it is recommended that phenytoin concentrations not be monitored until conversion to phenytoin is essentially complete. This occurs within approximately 2 hours after the end of IV infusion and 4 hours after IM injection.

Prior to complete conversion, commonly used immunoanalytical techniques, such as TDx®/TDxFLx™ (fluorescence polarization) and Emit® 2000 (enzyme multiplied), may significantly overestimate plasma phenytoin concentrations because of cross-reactivity with fosphenytoin. The error is dependent on plasma phenytoin and fosphenytoin concentration (influenced by fosphenytoin sodium injection dose, route and rate of administration, and time of sampling relative to dosing), and analytical method. Chromatographic assay methods accurately quantitate phenytoin concentrations in biological fluids in the presence of fosphenytoin. Prior to complete conversion, blood samples for phenytoin monitoring should be collected in tubes containing EDTA as an anticoagulant to minimize *ex vivo* conversion of fosphenytoin to phenytoin. However, even with specific assay methods, phenytoin concentrations measured before conversion of fosphenytoin is complete will not reflect phenytoin concentrations ultimately achieved.

DRUG INTERACTIONS

No drugs are known to interfere with the conversion of fosphenytoin to phenytoin. Conversion could be affected by alterations in the level of phosphatase activity, but given the abundance and wide distribution of phosphatases in the body it is unlikely that drugs would affect this activity enough to affect conversion of fosphenytoin to phenytoin. Drugs highly bound to albumin could increase the unbound fraction of fosphenytoin. Although, it is unknown whether this could result in clinically significant effects, caution is advised when administering fosphenytoin sodium injection with other drugs that significantly bind to serum albumin.

The pharmacokinetics and protein binding of fosphenytoin, phenytoin, and diazepam were not altered when diazepam and fosphenytoin sodium injection were concurrently administered in single submaximal doses.

The most significant drug interactions following administration of fosphenytoin sodium injection are expected to occur with drugs that interact with phenytoin. Phenytoin is extensively bound to serum plasma proteins and is prone to competitive displacement. Phenytoin is metabolized by hepatic cytochrome P450 enzymes and is particularly susceptible to inhibitory drug interactions because it is subject to saturable metabolism. Inhibition of metabolism may produce significant increases in circulating phenytoin concentrations and enhance the risk of drug toxicity. Phenytoin is a potent inducer of hepatic drug-metabolizing enzymes.

The most commonly occurring drug interactions are listed below:

- Drugs that may increase plasma phenytoin concentrations include: acute alcohol intake, amiodarone, chloramphenicol, chlordiazepoxide, cimetidine, diazepam, dicumarol, disulfiram, estrogens, ethosuximide, fluoxetine, H2-antagonists, halothane, isoniazid, methylphenidate, phenothiazines, phenylbutazone, salicylates, succinimides, sulfonamides, tolbutamide, trazodone.
- Drugs that may decrease plasma phenytoin concentrations include: carbamazepine, chronic alcohol abuse, reserpine.
- Drugs that may either increase or decrease plasma phenytoin concentrations include: phenobarbital, valproic acid, and sodium valproate. Similarly, the effects of phenytoin on phenobarbital, valproic acid and sodium plasma valproate concentrations are unpredictable.
- Although not a true drug interaction, tricyclic antidepressants may precipitate seizures in susceptible patients and fosphenytoin sodium injection dosage may need to be adjusted.
- Drugs whose efficacy is impaired by phenytoin include: anticoagulants, corticosteroids, coumarin, digitoxin, doxycycline, estrogens, furosemide, oral contraceptives, rifampin, quinidine, theophylline, vitamin D.

Monitoring of plasma phenytoin concentrations may be helpful when possible drug interactions are suspected (see [PRECAUTIONS, Laboratory Tests](#)).

DRUG/LABORATORY TEST INTERACTIONS

Phenytoin may decrease serum concentrations of T4 . It may also produce artifactually low results in dexamethasone or metyrapone tests. Phenytoin may also cause increased serum concentrations of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase (GGT).

Care should be taken when using immunoanalytical methods to measure plasma phenytoin concentrations following fosphenytoin sodium injection administration (see [PRECAUTIONS, Laboratory Tests](#)).

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

The carcinogenic potential of fosphenytoin has not been studied. Assessment of the carcinogenic potential of phenytoin in mice and rats is ongoing.

Structural chromosome aberration frequency in cultured V79 Chinese hamster lung cells was increased by exposure to fosphenytoin in the presence of metabolic activation. No evidence of mutagenicity was observed in bacteria (Ames test) or Chinese hamster lung cells *in vitro*, and no evidence for clastogenic activity was observed in an *in vivo* mouse bone marrow micronucleus test.

No effects on fertility were noted in rats of either sex given fosphenytoin. Maternal toxicity and altered estrous cycles, delayed mating, prolonged gestation length, and developmental toxicity were observed following administration of fosphenytoin during mating, gestation, and lactation at doses of 50 mg PE/kg or higher (approximately 40% of the maximum human loading dose or higher on a mg/m² basis).

PREGNANCY

PREGNANCY CATEGORY D

(see [WARNINGS](#))

USE IN NURSING MOTHERS

It is not known whether fosphenytoin is excreted in human milk.

Following administration of Dilantin, phenytoin appears to be excreted in low concentrations in human milk. Therefore, breast-feeding is not recommended for women receiving fosphenytoin sodium injection.

PEDIATRIC USE

THE SAFETY OF FOSPHENYTOIN SODIUM INJECTION IN PEDIATRIC PATIENTS HAS NOT BEEN ESTABLISHED.

GERIATRIC USE

No systematic studies in geriatric patients have been conducted. Phenytoin clearance tends to decrease with increasing age (see [CLINICAL PHARMACOLOGY, Special Populations](#)).

ADVERSE REACTIONS

The more important adverse clinical events caused by the IV use of fosphenytoin sodium injection or phenytoin are cardiovascular collapse and/or central nervous system depression. Hypotension can occur when either drug is administered rapidly by the IV route. The rate of administration is very important; for fosphenytoin sodium injection, it should not exceed 150 mg PE/min.

The adverse clinical events most commonly observed with the use of fosphenytoin sodium injection in clinical trials were nystagmus, dizziness, pruritus, paresthesia,

headache, somnolence, and ataxia. With two exceptions, these events are commonly associated with the administration of IV phenytoin. Paresthesia and pruritus, however, were seen much more often following fosphenytoin sodium injection administration and occurred more often with IV fosphenytoin sodium injection administration than with IM fosphenytoin sodium injection administration. These events were dose and rate related; most alert patients (41 of 64; 64%) administered doses of ≥ 15 mg PE/kg at 150 mg PE/min experienced discomfort of some degree. These sensations, generally described as itching, burning, or tingling, were usually not at the infusion site. The location of the discomfort varied with the groin mentioned most frequently as a site of involvement. The paresthesia and pruritus were transient events that occurred within several minutes of the start of infusion and generally resolved within 10 minutes after completion of fosphenytoin sodium injection infusion. Some patients experienced symptoms for hours. These events did not increase in severity with repeated administration. Concurrent adverse events or clinical laboratory change suggesting an allergic process were not seen (see [PRECAUTIONS, Sensory Disturbances](#)).

Approximately 2% of the 859 individuals who received fosphenytoin sodium injection in premarketing clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal were pruritus (0.5%), hypotension (0.3%), and bradycardia (0.2%).

DOSE AND RATE DEPENDENCY OF ADVERSE EVENTS FOLLOWING IV FOSPHENYTOIN SODIUM INJECTION

The incidence of adverse events tended to increase as both dose and infusion rate increased. In particular, at doses of ≥ 15 mg PE/kg and rates ≥ 150 mg PE/min, transient pruritus, tinnitus, nystagmus, somnolence, and ataxia occurred 2 to 3 times more often than at lower doses or rates.

INCIDENCE IN CONTROLLED CLINICAL TRIALS

All adverse events were recorded during the trials by the clinical investigators using terminology of their own choosing. Similar types of events were grouped into standardized categories using modified COSTART dictionary terminology. These categories are used in the tables and listings below with the frequencies representing the proportion of individuals exposed to fosphenytoin sodium injection or comparative therapy.

The prescriber should be aware that these figures cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses or investigators. An inspection of these frequencies, however, does provide the prescribing physician with one basis to estimate the relative contribution of drug and nondrug factors to the adverse event incidences in the population studied.

INCIDENCE IN CONTROLLED CLINICAL TRIALS - IV ADMINISTRATION TO PATIENTS WITH EPILEPSY OR NEUROSURGICAL PATIENTS

Table 2 lists treatment-emergent adverse events that occurred in at least 2% of patients treated with IV fosphenytoin sodium injection at the maximum dose and rate in a randomized, double-blind, controlled clinical trial where the rates for phenytoin and fosphenytoin sodium injection administration would have resulted in equivalent systemic exposure to phenytoin.

Table 2. Treatment-Emergent Adverse Event Incidence Following IV Administration at the Maximum Dose and Rate to Patients With Epilepsy or Neurosurgical Patients (Events in at Least 2% of Fosphenytoin Sodium Injection-Treated Patients)

BODY SYSTEM	IV Fosphenytoin Sodium Injection	IV Phenytoin
Adverse Event	N=90	N=22
BODY AS A WHOLE		
Pelvic Pain	4.4	0.0
Asthenia	2.2	0.0
Back Pain	2.2	0.0
Headache	2.2	4.5
CARDIOVASCULAR		
Hypotension	7.7	9.1
Vasodilatation	5.6	4.5
Tachycardia	2.2	0.0
DIGESTIVE		
Nausea	8.9	13.6
Tongue Disorder	4.4	0.0
Dry Mouth	4.4	4.5
Vomiting	2.2	9.1
NERVOUS		
Nystagmus	44.4	59.1
Dizziness	31.1	27.3
Somnolence	20.0	27.3

Ataxia	11.1	18.2
Stupor	7.7	4.5
Incoordination	4.4	4.5
Paresthesia	4.4	0.0
Extrapyramidal Syndrome	4.4	0.0
Tremor	3.3	9.1
Agitation	3.3	0.0
Hypesthesia	2.2	9.1
Dysarthria	2.2	0.0
Vertigo	2.2	0.0
Brain Edema	2.2	4.5

SKIN AND APPENDAGES

Pruritus	48.9	4.5
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SPECIAL SENSES

Tinnitus	8.9	9.1
Diplopia	3.3	0.0
Taste Perversion	3.3	0.0
Amblyopia	2.2	9.1
Deafness	2.2	0.0

INCIDENCE IN CONTROLLED TRIALS - IM ADMINISTRATION TO PATIENTS WITH EPILEPSY

Table 3 lists treatment-emergent adverse events that occurred in at least 2% of fosphenytoin sodium injection-treated patients in a double-blind, randomized, controlled clinical trial of adult epilepsy patients receiving either IM fosphenytoin sodium injection substituted for oral Dilantin or continuing oral Dilantin. Both treatments were administered for 5 days.

TABLE 3. Treatment-Emergent Adverse Event Incidence Following Substitution of IM Fosphenytoin Sodium Injection for Oral Dilantin in Patients With Epilepsy (Events in at Least 2% of Fosphenytoin Sodium Injection-Treated Patients)

BODY SYSTEM	IM Fosphenytoin Sodium Injection	Oral Dilantin
Adverse Event	N=179	N=61
BODY AS A WHOLE		
Headache	8.9	4.9
Asthenia	3.9	3.3
Accidental Injury	3.4	6.6
DIGESTIVE		
Nausea	4.5	0.0
Vomiting	2.8	0.0
HEMATOLOGIC AND LYMPHATIC		
Ecchymosis	7.3	4.9
NERVOUS		
Nystagmus	15.1	8.2
Tremor	9.5	13.1
Ataxia	8.4	8.2
Incoordination	7.8	4.9
Somnolence	6.7	9.8
Dizziness	5.0	3.3
Paresthesia	3.9	3.3
Reflexes Decreased	2.8	4.9
SKIN AND APPENDAGES		
Pruritus	2.8	0.0

ADVERSE EVENTS DURING ALL CLINICAL TRIALS

Fosphenytoin sodium injection has been administered to 859 individuals during all clinical trials. All adverse events seen at least twice are listed in the following, except those already included in previous tables and listings. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in greater than 1/100 individuals; infrequent adverse events are those occurring in 1/100 to 1/1000 individuals.

BODY AS A WHOLE

Frequent: fever, injection-site reaction, infection, chills, face edema, injection-site pain; *Infrequent:* sepsis, injection-site inflammation, injection-site edema, injection-site hemorrhage, flu syndrome, malaise, generalized edema, shock, photosensitivity reaction, cachexia, cryptococcosis.

CARDIOVASCULAR

Frequent: hypertension; *Infrequent:* cardiac arrest, migraine, syncope, cerebral hemorrhage, palpitation, sinus bradycardia, atrial flutter, bundle branch block, cardiomegaly, cerebral infarct, postural hypotension, pulmonary embolus, QT interval prolongation, thrombophlebitis, ventricular extrasystoles, congestive heart failure.

DIGESTIVE

Frequent: constipation; *Infrequent:* dyspepsia, diarrhea, anorexia, gastrointestinal hemorrhage, increased salivation, liver function tests abnormal, tenesmus, tongue edema, dysphagia, flatulence, gastritis, ileus.

ENDOCRINE

Infrequent: diabetes insipidus.

HEMATOLOGIC AND LYMPHATIC

Infrequent: thrombocytopenia, anemia, leukocytosis, cyanosis, hypochromic anemia, leukopenia, lymphadenopathy, petechia.

METABOLIC AND NUTRITIONAL

Frequent: hypokalemia; *Infrequent:* hyperglycemia, hypophosphatemia, alkalosis, acidosis, dehydration, hyperkalemia, ketosis.

MUSCULOSKELETAL

Frequent: myasthenia; *Infrequent:* myopathy, leg cramps, arthralgia, myalgia.

NERVOUS

Frequent: reflexes increased, speech disorder, dysarthria, intracranial hypertension, thinking abnormal, nervousness, hypesthesia; *Infrequent:* confusion, twitching, Babinski sign positive, circumoral paresthesia, hemiplegia, hypotonia, convulsion, extrapyramidal syndrome, insomnia, meningitis, depersonalization, CNS depression, depression, hypokinesia, hyperkinesia, brain edema, paralysis, psychosis, aphasia, emotional lability, coma, hyperesthesia, myoclonus, personality disorder, acute brain syndrome, encephalitis, subdural hematoma, encephalopathy, hostility, akathisia, amnesia, neurosis.

RESPIRATORY

Frequent: pneumonia; *Infrequent:* pharyngitis, sinusitis, hyperventilation, rhinitis, apnea, aspiration pneumonia, asthma, dyspnea, atelectasis, cough increased, sputum increased, epistaxis, hypoxia, pneumothorax, hemoptysis, bronchitis.

SKIN AND APPENDAGES

Frequent: rash; *Infrequent:* maculopapular rash, urticaria, sweating, skin discoloration, contact dermatitis, pustular rash, skin nodule.

SPECIAL SENSES

Frequent: taste perversion; *Infrequent:* deafness, visual field defect, eye pain, conjunctivitis, photophobia, hyperacusis, mydriasis, parosmia, ear pain, taste loss.

UROGENITAL

Infrequent: urinary retention, oliguria, dysuria, vaginitis, albuminuria, genital edema, kidney failure, polyuria, urethral pain, urinary incontinence, vaginal moniliasis.

OVERDOSAGE

Nausea, vomiting, lethargy, tachycardia, bradycardia, asystole, cardiac arrest, hypotension, syncope, hypocalcemia, metabolic acidosis, and death have been reported in cases of overdosage with fosphenytoin.

The median lethal dose of fosphenytoin given intravenously in mice and rats was 156 mg PE/kg and approximately 250 mg PE/kg, or about 0.6 and 2 times, respectively, the maximum human loading dose on a mg/m² basis. Signs of acute toxicity in animals included ataxia, labored breathing, ptosis, and hypoactivity.

Because fosphenytoin sodium injection is a prodrug of phenytoin, the following information may be helpful. Initial symptoms of acute phenytoin toxicity are nystagmus, ataxia, and dysarthria. Other signs include tremor, hyperreflexia, lethargy, slurred speech, nausea, vomiting, coma, and hypotension. Depression of respiratory and circulatory systems leads to death. There are marked variations among individuals with respect to

plasma phenytoin concentrations where toxicity occurs. Lateral gaze nystagmus usually appears at 20 µg/mL, ataxia at 30 µg/mL, and dysarthria and lethargy appear when the plasma concentration is over 40 µg/mL. However, phenytoin concentrations as high as 50 µg/mL have been reported without evidence of toxicity. As much as 25 times the therapeutic phenytoin dose has been taken, resulting in plasma phenytoin concentrations over 100 µg/mL, with complete recovery.

Treatment is nonspecific since there is no known antidote to fosphenytoin sodium injection or phenytoin overdose. The adequacy of the respiratory and circulatory systems should be carefully observed, and appropriate supportive measures employed. Hemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been used in the treatment of severe intoxication in children. In acute overdose the possibility of other CNS depressants, including alcohol, should be borne in mind.

Formate and phosphate are metabolites of fosphenytoin and therefore may contribute to signs of toxicity following overdose. Signs of formate toxicity are similar to those of methanol toxicity and are associated with severe anion-gap metabolic acidosis. Large amounts of phosphate, delivered rapidly, could potentially cause hypocalcemia with paresthesia, muscle spasms, and seizures. Ionized free calcium levels can be measured and, if low, used to guide treatment.

DOSAGE AND ADMINISTRATION

The dose, concentration in dosing solutions, and infusion rate of IV fosphenytoin sodium injection is expressed as phenytoin sodium equivalents (PE) to avoid the need to perform molecular weight-based adjustments when converting between fosphenytoin and phenytoin sodium doses. Fosphenytoin sodium injection should always be prescribed and dispensed in phenytoin sodium equivalent units (PE). Fosphenytoin sodium injection has important differences in administration from those for parenteral phenytoin sodium (see below).

Products with particulate matter or discoloration should not be used. Prior to IV infusion, dilute fosphenytoin sodium injection in 5% dextrose or 0.9% saline solution for injection to a concentration ranging from 1.5 to 25 mg PE/mL.

STATUS EPILEPTICUS

- The loading dose of fosphenytoin sodium injection is 15 to 20 mg PE/kg administered at 100 to 150 mg PE/min.
- Because of the risk of hypotension, fosphenytoin should be administered no faster than 150 mg PE/min. Continuous monitoring of the electrocardiogram, blood pressure, and respiratory function is essential and the patient should be observed throughout the period where maximal serum phenytoin concentrations occur, approximately 10 to 20 minutes after the end of fosphenytoin sodium injection infusions.

- Because the full antiepileptic effect of phenytoin, whether given as fosphenytoin sodium injection or parenteral phenytoin, is not immediate, other measures, including concomitant administration of an IV benzodiazepine, will usually be necessary for the control of status epilepticus.
- The loading dose should be followed by maintenance doses of fosphenytoin sodium injection, or phenytoin either orally or parenterally.

If administration of fosphenytoin sodium injection does not terminate seizures, the use of other anticonvulsants and other appropriate measures should be considered.

IM fosphenytoin sodium injection should not be used in the treatment of status epilepticus because therapeutic phenytoin concentrations may not be reached as quickly as with IV administration. If IV access is impossible, loading doses of fosphenytoin sodium injection have been given by the IM route for other indications.

NONEMERGENT LOADING AND MAINTENANCE DOSING

The loading dose of fosphenytoin sodium injection is 10 - 20 mg PE/kg given IV or IM. The rate of administration for IV fosphenytoin sodium injection should be no greater than 150 mg PE/min. Continuous monitoring of the electrocardiogram, blood pressure, and respiratory function is essential and the patient should be observed throughout the period where maximal serum phenytoin concentrations occur, approximately 10 to 20 minutes after the end of fosphenytoin sodium injection infusions.

The initial daily maintenance dose of fosphenytoin sodium injection is 4 - 6 mg PE/kg/day.

IM OR IV SUBSTITUTION FOR ORAL PHENYTOIN THERAPY

Fosphenytoin sodium injection can be substituted for oral phenytoin sodium therapy at the same total daily dose.

Dilantin capsules are approximately 90% bioavailable by the oral route. Phenytoin, supplied as fosphenytoin sodium injection, is 100% bioavailable by both the IM and IV routes. For this reason, plasma phenytoin concentrations may increase modestly when IM or IV fosphenytoin sodium injection is substituted for oral phenytoin sodium therapy.

The rate of administration for IV fosphenytoin sodium injection should be no greater than 150 mg PE/min.

In controlled trials, IM fosphenytoin sodium injection was administered as a single daily dose utilizing either 1 or 2 injection sites. Some patients may require more frequent dosing.

DOSING IN SPECIAL POPULATIONS

PATIENTS WITH RENAL OR HEPATIC DISEASE

Due to an increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminemia, the interpretation of total phenytoin plasma concentrations should be made with caution (see [CLINICAL PHARMACOLOGY, Special Populations](#)). Unbound phenytoin concentrations may be more useful in these patient populations. After IV fosphenytoin sodium injection administration to patients with renal and/or hepatic disease, or in those with hypoalbuminemia, fosphenytoin clearance to phenytoin may be increased without a similar increase in phenytoin clearance. This has the potential to increase the frequency and severity of adverse events (see [PRECAUTIONS](#)).

ELDERLY PATIENTS

Age does not have a significant impact on the pharmacokinetics of fosphenytoin following fosphenytoin sodium injection administration. Phenytoin clearance is decreased slightly in elderly patients and lower or less frequent dosing may be required.

PEDIATRIC

The safety of fosphenytoin sodium injection in pediatric patients has not been established

8.11.2 PHENYTOIN

In Box: IMPORTANT NOTE

This drug must be administered slowly. In adults, do not exceed 50 mg per minute intravenously.

In neonates, the drug should be administered at a rate not exceeding 1-3 mg/kg/min.

INDICATIONS AND USAGE

Phenytoin Sodium Injection is indicated for the control of status epilepticus of the grand mal type and prevention and treatment of seizures occurring during neurosurgery.

CONTRAINDICATIONS

Phenytoin is contraindicated in patients with a history of hypersensitivity to hydantoin products. Because of its effect on ventricular automaticity, phenytoin is contraindicated in sinus bradycardia, sinoatrial block, second- and third-degree A-V block, and patients with Adams-Stokes syndrome.

WARNINGS

Intravenous administration should not exceed 50 mg per minute in adults.

In neonates, the drug should be administered at a rate not exceeding 1-3 mg/kg/min.

Severe cardiotoxic reactions and fatalities have been reported with atrial and ventricular conduction depression and ventricular fibrillation. Severe complications are most commonly encountered in elderly or gravely ill patients.

Phenytoin should be used with caution in patients with hypotension and severe myocardial insufficiency. Hypotension usually occurs when the drug is administered rapidly by the intravenous route. The intramuscular route is not recommended for the treatment of status epilepticus since blood levels of phenytoin in the therapeutic range cannot be readily achieved with doses and methods of administration ordinarily employed. There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma and Hodgkin's Disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness, e.g., fever, rash and liver involvement. In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs. Acute alcoholic intake may increase phenytoin serum levels while chronic alcoholic use may decrease serum levels.

PRECAUTIONS

General

The addition of Phenytoin Sodium Injection to intravenous infusion is not recommended due to lack of solubility and resultant precipitation. Phenytoin Sodium Injection should be injected slowly (not exceeding 50 mg per minute in adults), directly into a large vein through a large-gauge needle or intravenous catheter. Each injection of intravenous Phenytoin Sodium Injection should be followed by an injection of sterile saline through the same needle or intravenous catheter to avoid local venous irritation due to the alkalinity of the solution. Continuous infusion should be avoided. Soft tissue irritation and inflammation has occurred at the site of injection with and without extravasation of intravenous phenytoin. Soft tissue irritation may vary from slight tenderness to extensive necrosis, sloughing, and in rare instances has led to amputation. Improper administration including subcutaneous or perivascular injection should be avoided to help prevent the possibility of the above. Edema, discoloration and pain of the distal limb (described as "purple glove syndrome") have been reported following peripheral intravenous phenytoin sodium injection. This may or may not be associated with extravasation. Although resolution of symptoms may be spontaneous, skin necrosis and limb ischemia have occurred and required such interventions as fasciotomies, skin grafting and amputation. Therefore, Phenytoin Sodium Injection should be administered as described above. The liver is the site of biotransformation. Patients with impaired liver function, elderly patients, or those who are gravely ill may show early toxicity. A small percentage of individuals who have been treated with phenytoin have been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined. Phenytoin should be discontinued if a skin rash appears (see WARNINGS section regarding drug discontinuation). If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus or Stevens-Johnson syndrome is suspected, use of this drug should not be resumed and alternative therapy should be considered. (See ADVERSE REACTIONS.) If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated. Hyperglycemia, resulting from the drug's inhibitory effects on insulin release, has been reported. Phenytoin may also raise the serum glucose level in diabetic patients. Phenytoin is not indicated for seizures due to hypoglycemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated. Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and absence (petit mal) seizures are present, combined drug therapy is needed. Serum levels of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely irreversible cerebellar dysfunction. Accordingly, at the first sign of acute toxicity, plasma levels are recommended. Dose reduction of phenytoin therapy is indicated if plasma levels are excessive; if symptoms persist, termination is recommended. (See WARNINGS.)

Drug Interactions

There are many drugs which may increase or decrease phenytoin levels or which phenytoin may affect. The most commonly occurring drug interactions are listed below:

1. Drugs which may increase phenytoin serum levels include: Chloramphenicol, dicumarol, disulfiram, tolbutamide, isoniazid, phenylbutazone, acute alcohol intake, salicylates, chlordiazepoxide, phenothiazines, diazepam, estrogens, ethosuximide, halothane, methylphenidate, sulfonamides, cimetidine, trazodone.
2. Drugs which may decrease phenytoin levels include: Carbamazepine, chronic alcohol abuse, reserpine. Moban® brand of Molindone Hydrochloride contains calcium ions which interfere with the absorption of phenytoin. Ingestion times of phenytoin and antacid preparations containing calcium should be staggered in patients with low serum phenytoin levels to prevent absorption problems.
3. Drugs which may either increase or decrease phenytoin serum levels include: Phenobarbital, valproic acid and sodium valproate. Similarly, the effect of phenytoin on phenobarbital, valproic acid and sodium valproate serum levels is unpredictable.
4. Although not a true drug interaction, tricyclic antidepressants may precipitate seizures in susceptible patients and phenytoin dosage may need to be adjusted.
5. Drugs whose efficacy is impaired by phenytoin include: Corticosteroids, coumarin anticoagulants, oral contraceptives, quinidine, vitamin D, digitoxin, rifampin, doxycycline, estrogens, furosemide. Serum level determinations are especially helpful when possible drug interactions are suspected.

Drug and/or Laboratory Test Interactions

Phenytoin may cause decreased serum levels of protein-bound iodine (PBI). It may also produce lower than normal values for dexamethasone or metyrapone tests. Phenytoin may cause increased serum levels of glucose, alkaline phosphatase and gamma glutamyl transpeptidase (GGT).

ADVERSE REACTIONS

The most notable signs of toxicity associated with the intravenous use of this drug are cardiovascular collapse and/or central nervous system depression. Hypotension does occur when the drug is administered rapidly by the intravenous route. The *rate* of administration is very important; it should not exceed 50 mg per minute in adults, and 1-3 mg/kg/min in neonates. At this rate, toxicity should be minimized.

Cardiovascular

Severe cardiotoxic reactions and fatalities have been reported with atrial and ventricular conduction depression and ventricular fibrillation. Severe complications are most commonly encountered in elderly or gravely ill patients.

Central Nervous System

The most common manifestations encountered with phenytoin therapy are referable to this system and are usually dose-related. These include nystagmus, ataxia, slurred speech, decreased coordination and mental confusion. Dizziness, insomnia, transient nervousness, motor twitchings and headaches have also been observed. There have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, tremor and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs. A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy.

Gastrointestinal System

Nausea, vomiting and constipation.

Integumentary System

Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) is the most common; other types of dermatitis are seen more rarely. Other more serious forms which may be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, Stevens-Johnson syndrome, and toxic epidermal necrolysis (see PRECAUTIONS).

Hemopoietic System

Hemopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis and pancytopenia with or without bone marrow suppression. While macrocytosis and megaloblastic anemia have occurred, these conditions usually respond to folic acid therapy. Lymphadenopathy including benign lymph node hyperplasia, pseudolymphoma, lymphoma and Hodgkin's Disease have been reported (see WARNINGS).

Connective Tissue System

Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, hypertrichosis and Peyronie's Disease.

Injection Site

Local irritation, inflammation, tenderness, necrosis and sloughing have been reported with or without extravasation of intravenous phenytoin.

Other

Systemic lupus erythematosus, periarteritis nodosa, toxic hepatitis, liver damage, immunoglobulin abnormalities and purple glove syndrome may occur. (See PRECAUTIONS.)

OVERDOSAGE

The lethal dose in children is not known. The lethal dose in adults is estimated to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia and dysarthria. Other signs are tremor, hyperflexia, lethargy, slurred speech, nausea, vomiting. The patient may become comatose and hypertensive. Death is due to respiratory and circulatory depression. There are marked variations among individuals with respect to phenytoin plasma levels where toxicity may occur. Nystagmus, on lateral gaze, usually appears at 20 mcg/mL, ataxia at 30 mcg/mL, dysarthria and lethargy appear when the plasma concentration is over 40 mcg/mL, but as high a concentration as 50 mcg/mL has been reported without evidence of toxicity. As much as 25 times the therapeutic dose has been taken to result in a serum concentration over 100 mcg/mL with complete recovery.

DOSAGE AND ADMINISTRATION

The addition of Phenytoin Sodium Injection to intravenous infusion is not recommended due to the lack of solubility and resultant precipitation. **Not to exceed 50 mg per minute, intravenously in adults, and not exceeding 1-3 mg/kg/min in neonates.** There is a relatively small margin between full therapeutic effect and minimally toxic doses of this drug. The solution is suitable for use as long as it remains free of haziness and precipitate. Upon refrigeration or freezing, a precipitate might form; this will dissolve again after the solution is allowed to stand at room temperature. The product is still suitable for use. Only a clear solution should be used. A faint yellow coloration may develop; however, this has no effect on the potency of the solution. In the treatment of status epilepticus, the intravenous route is preferred because of the delay in absorption of phenytoin when administered intramuscularly. Serum concentrations should be monitored and care should be taken when switching a patient from the sodium salt to the free acid form.

Phenytoin Sodium Injection is formulated with the sodium salt of phenytoin. Because there is approximately an 8% increase in drug content with the free acid form over that of the sodium salt, dosage adjustments and serum level monitoring may be necessary when switching from a product formulated with the sodium salt and vice versa.

Status Epilepticus

In adults, a loading dose of 10 to 15 mg/kg should be administered slowly intravenously, at a rate not exceeding 50 mg per minute (this will require approximately 20 minutes in a 70 kg patient). The loading dose should be followed by maintenance doses of 100 mg orally or intravenously every 6-8 hours. Recent work in neonates and pediatric patients has shown that absorption of phenytoin is unreliable after oral administration, but a loading dose of 15-20 mg/kg of phenytoin intravenously will usually produce plasma concentrations of phenytoin within the generally accepted therapeutic range (10-20 mcg/mL). The drug should be injected slowly intravenously at a rate not exceeding 1-3 mg/kg/min. Phenytoin Sodium Injection should be injected *slowly* and directly into a large vein through a large-gauge needle or intravenous

catheter. Each injection of intravenous phenytoin should be followed by an injection of sterile saline through the same needle or

catheter to avoid local venous irritation due to alkalinity of the solution. Continuous infusion should be avoided; the addition of

Phenytoin Sodium Injection to intravenous infusion fluids is not recommended because of the likelihood of precipitation.

Continuous monitoring of the electrocardiogram and blood pressure is essential. The patient should be observed for signs of respiratory depression. Determination of phenytoin plasma levels is advised when using phenytoin in the management of status epilepticus and in the subsequent establishment of maintenance dosage.

Other measures, including concomitant administration of an intravenous benzodiazepine such as diazepam, or an intravenous shortacting barbiturate, will usually be necessary for rapid control of seizures because of the required slow rate of administration of phenytoin.

If administration of Phenytoin Sodium Injection does not terminate seizures, the use of other anticonvulsants, intravenous barbiturates, general anesthesia and other appropriate measures should be considered.

Intramuscular administration should not be used in the treatment of status epilepticus because the attainment of peak plasma levels may require up to 24 hours.

Neurosurgery

Prophylactic dosage—100 to 200 mg (2 to 4 mL) intramuscularly at approximately 4-hour intervals during surgery and continued

during the postoperative period. When intramuscular administration is required for a patient previously stabilized orally, compensating

dosage adjustments are necessary to maintain therapeutic plasma levels. An intramuscular dose 50% greater than the oral dose is

necessary to maintain these levels. When returned to oral administration, the dose should be reduced by 50% of the original oral dose

for one week to prevent excessive plasma levels due to sustained release from intramuscular tissue sites.

If the patient requires more than a week of IM phenytoin, alternative routes should be explored, such as gastric intubation. For time

periods less than one week, the patient shifted back from IM administration should receive one half the original oral dose for the same

period of time the patient received IM phenytoin. Monitoring plasma levels would help prevent a fall into the subtherapeutic range.

Serum blood level determinations are especially helpful when possible drug interactions are suspected.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

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/s/

JASMINE C GATTI
10/05/2010

ALLEN D BRINKER
10/05/2010

MARK I AVIGAN
10/05/2010



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: October 1, 2010

To: Russell Katz, MD, Director
Division of Neurology Products

Thru: Melina Griffis, RPh, Team Leader
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Anne Crandall, PharmD, Safety Evaluator
Division of Medication Error Prevention

Subject: Medication Error Review

Drug Name: Cerebyx (Fosphenytoin Sodium) Injection, 100 mg PE/2 mL,
500 mg PE/10 mL
Phenytoin Sodium Injection, 100 mg/2 mL, 250 mg/5 mL

Application Type/Number: NDA 020450 ANDA 089521
ANDA 077481 ANDA 089744
ANDA 078126 ANDA 040573
ANDA 078137 ANDA 084307
ANDA 078277 ANDA 040781
ANDA 076886
ANDA 077989
ANDA 078158
ANDA 078417
ANDA 078765
ANDA 078052
ANDA 078476
ANDA 078736

Applicant/sponsor: Eisai Inc., Bedford, Apotex Inc., Wockhardt, Pharmaforce, Teva
Parenteral, Baxter Healthcare, Hospira, Sun Pharma Global, Hikma
Farmaceutica, App Pharms, Akorn Strides, Strides Arcolab

OSE RCM #: 2010-571

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EXECUTIVE SUMMARY

This review evaluates 494 cases of medication errors involving fosphenytoin and phenytoin injection. The Division of Neurology Products requested this review to determine the types of errors reported with each product and the comparative safety of these products in the medication use process.

We found that although some errors relate to practice issues (for example, errors in transcription, errors in calculation, infusion pump programming errors, administration of multiple loading doses), confusion related to product labels and labeling for fosphenytoin and phenytoin caused the majority of errors.

Consequently, DMEPA recommends revisions to the insert labeling for both fosphenytoin and phenytoin injection to clarify the rate of administration, product preparation, storage and administration, dose adjustments, and duplication of therapy. Additionally, we recommend that container labels of all fosphenytoin products reflect consistent storage recommendations, improve the display of total drug content, and better differentiate between the 2 mL and 10 mL vials. The phenytoin injection container label needs to delete the statement “no infusion” and include the maximum rate of administration.

Furthermore, DMEPA plans to further review confusion regarding phenytoin equivalency nomenclature used for dosing fosphenytoin and the source of concomitant therapy. (See Section 5 of this review for full recommendations).

1 BACKGROUND

1.1 INTRODUCTION

The Division of Neurology Products (DNP) requested that DMEPA assess fosphenytoin and phenytoin injection medication errors comparing and contrasting the types of medication errors, populations affected, and the frequency at which they occur. DNP requested that DMEPA provide a summary of all errors for both products with a focus on fosphenytoin errors related to phenytoin equivalents, total volume of vial/concentration issues, and refrigeration storage requirements of fosphenytoin, and then compare errors among both products to determine overall safety. This review is in preparation for an Advisory Committee Meeting planned for November 3, 2010. Two other assessments will be provided by the Agency. The Division of Pharmacovigilance will provide an analysis of the incidence of purple glove syndrome with both fosphenytoin and phenytoin injection and the Division of Neurology products will provide background regarding the clinical pharmacology issues of using fosphenytoin for unapproved uses in the pediatric population. These analyses will provide context to aid in the Advisory Committee’s deliberations.

1.2 FOSPHENYTOIN AND PHENYTOIN INJECTION PRODUCT INFORMATION

Both fosphenytoin and phenytoin injection share identical indications of use, but also have several important differences. Table 1 provides a summary of the product characteristics and labeled recommendations of each product.

Table 1: Fosphenytoin and Phenytoin Labeled Recommendations for Use

Labeled Recommendations	Cerebyx (Fosphenytoin) (50 mg PE*/mL)	Phenytoin Injection, USP (50 mg/mL)
Indications	<ul style="list-style-type: none"> - Generalized status epilepticus - Prevention and treatment of seizures during neurosurgery - Safety and effectiveness not evaluated for more than 5 days of therapy 	<ul style="list-style-type: none"> - Control of status epilepticus of the grand mal type - Prevention and treatment of seizures occurring during neurosurgery - No time limit for use
Patient population	Adults	Neonates, pediatric and adult patients
Rate of administration	100 to 150 mg PE/minute	Phenytoin must be injected slowly and directly into a large vein and should be followed by an injection of sterile saline through the same needle <ul style="list-style-type: none"> - Adults: 50 mg per minute - Neonates: 1-3 mg/kg/min
Loading dose	<ul style="list-style-type: none"> - Status epilepticus: 15 to 20 mg PE/kg - Nonemergent: 10 to 20 mg PE/kg 	<u>Status epilepticus (does not differentiate between emergent and nonemergent):</u> <ul style="list-style-type: none"> - 10 to 15 mg/kg (adults) - 15 to 20 mg/kg (neonates and pediatric patients) <u>Neurosurgery:</u> <ul style="list-style-type: none"> - 100 mg to 2000 mg intramuscularly
Maintenance dose and Frequency of administration	4 to 6 mg PE/kg/day N/A	<u>Status epilepticus:</u> <ul style="list-style-type: none"> - 100 mg every 6 hours to 8 hours (adult) - N/A (neonates and pediatric patients) <u>Neurosurgery:</u> <ul style="list-style-type: none"> - 100 mg to 2000 mg every 4 hours during surgery and postoperative period (population not specified)
Monitoring	<ul style="list-style-type: none"> - electrocardiogram, respiratory depression and blood pressure after administration - phenytoin concentrations of 10 to 20 mcg/mL 	<ul style="list-style-type: none"> - electrocardiogram, respiratory depression blood pressure, and plasma levels of phenytoin after administration - phenytoin concentrations of 10 to 20 mcg/mL
Recommended plasma level of product	10 to 20 mcg/mL	10 to 20 mcg/mL

* Fosphenytoin's milligram weight is expressed as phenytoin equivalents "mg PE"

Labeled Recommendations	Cerebyx (Fosphenytoin) (50 mg PE*/mL)	Phenytoin Injection, USP (50 mg/mL)
Diluent	0.9% saline solution or 5% dextrose	N/A (per label, addition to intravenous infusion is not recommended)
Dilution concentration	1.5 mg to 25 mg PE/mL	N/A
How supplied	100 mg PE/2 mL, 500 mg PE/10 mL vial	100 mg/2 mL, 500 mg/10 mL
Storage	Undiluted: refrigerator Diluted: N/A	Undiluted: room temperature Diluted: N/A

1.2.1 Fosphenytoin Injection

Fosphenytoin is available from Pfizer as Cerebyx and marketed by multiple generic firms. Fosphenytoin is indicated for short-term (five days or less) parenteral administration when other means of phenytoin administration are unavailable, inappropriate, or deemed less advantageous.

Fosphenytoin, a phosphate ester prodrug of phenytoin, was developed to overcome complications associated with parenteral phenytoin[†]. Fosphenytoin has greater water solubility and normal pH. These attributes allow for more rapid intravenous administration and according to the prescriber information is associated with greater infusion tolerance. Fosphenytoin, like phenytoin injection, may also be administered intramuscularly. The active metabolite of fosphenytoin is phenytoin, and the product is dosed based on phenytoin equivalents. Because the product dosing recommendations are based on phenytoin equivalents, fosphenytoin's milligram weight is expressed as phenytoin equivalents "mg PE" to avoid the need for practitioners to perform molecular weight-based adjustments when converting between fosphenytoin and phenytoin injection doses. Additionally, the laboratory measurements used to monitor fosphenytoin levels in the body are based on the amount of phenytoin (mcg/mL) in the blood. Fosphenytoin is labeled for use only in the adult population and currently offers no dosing recommendations for pediatric patients.

1.2.2 Phenytoin Injection

Phenytoin is available in oral and intravenous formulations. Phenytoin injection should be injected slowly and directly into a large vein and should be followed by an injection of sterile saline through the same needle. Because of the risk of adverse reactions that can occur from rapid administration, phenytoin injection contains a black box warning in the package insert which cautions practitioners about the need to slowly administer phenytoin injection via the intravenous route. The black box warning explicitly states that the adult rate of administration should not exceed 50 mg per minute and in neonates the rate should not exceed 1 to 3 mg/kg/minute.

[†] Eriksson, Kai. Keranen, Tapani. Kalvianen, Reetta. Fosphenytoin. Expert Opin Drug Metab Toxicol. 2009 Jun; 5(6):695-701

1.3 REGULATORY HISTORY

Cerebyx (fosphenytoin) solution was approved in 1996, and generics were approved in 2007. DMEPA previously evaluated errors concerning: 1) Presentation of total drug content on the container label, and 2) Name confusion between Cerebyx and Celebrex and 3) Confusion with the “mg PE” expression. To address these issues DMEPA previously recommended the following:

- Express the strength in terms of total drug content per total volume followed by concentration per mL to avoid confusion over total drug content in the vial.
- Change the proprietary name of Celebrex (celecoxib) because this name was being confused with both Cerebyx and Celexa (citalopram) and it was the newest approved of all three medications.
- The phenytoin equivalency issue has been debated since the products approval in 1996. The DMEPA review completed in 2000 (review # 00-0167) determined that the level of confusion surrounding phenytoin equivalency could not be assessed solely on spontaneous reporting of medication errors. DMEPA concluded that based on the available information submitted to the Agency that they would not recommend the removal or change the expression of strength using phenytoin sodium equivalents because it could cause more confusion. DMEPA recommended the applicant conduct a survey to determine the level of confusion that might still exist for phenytoin equivalence (mg PE) dosing and suggest revisions based on the results of that survey.

Dilantin (phenytoin injection) was approved in 1956 and is now only available in generic form. A review of medication errors involving wrong rate of administration (OSE review # 2008-876) was already underway by DMEPA when DNP requested this expanded review.

2 METHODS AND MATERIALS

2.1 INTRODUCTION

DMEPA used two data sources, FDA Adverse Event Reporting System (AERS) and the Institute of Safe Medication Practice Databases (ISMP) ***, for identification of medication errors involving fosphenytoin and phenytoin injection. All included reports describing medication errors were screened for duplicates and combined into cases which were further categorized by error type. Reports that did not describe a medication error or described errors relating to oral administration of phenytoin, intentional overdose, adverse events unrelated to a medication error, administration of drug to the wrong patient, and system-related errors (i.e., infusion pump programming errors and administration of a second dose because the first dose was not documented) were excluded from further analysis.

Additionally, DMEPA evaluated the labels and labeling for fosphenytoin and phenytoin injection for aspects that may have contributed to the reported medication errors.

2.2 AERS SEARCH STRATEGY

DMEPA conducted two searches of the FDA Adverse Event Reporting System (AERS) database to identify post-marketing reports of medication errors associated with fosphenytoin and with phenytoin.

The first AERS database search conducted on April 30, 2010 for medication error reports involving phenytoin injection used the following search criteria:

Product Names: Dilantin (trade name) and Phenytoin and phenytoin sodium (active ingredient)

Reaction Terms: medication errors (HLGT) and product quality issues (HLGT)

Search Limitations: The search also limited the route of administration to intra-arterial, intra-articular, intramuscular, intravenous, intravenous bolus, intravenous drip, other, parenteral, and unknown in order to exclude medication errors associated with the oral administration of phenytoin.

The second AERS database search conducted on April 26, 2010 for medication errors involving fosphenytoin used the following search criteria:

Product Names: Cerebyx (trade name) and Fosphenytoin and fosphenytoin sodium (active ingredient)

Reaction Terms: medication errors (HLGT) and product quality issues (HLGT).
We limited the time frame to the last ten years, April 26, 2000 to April 26, 2010.

2.3 INSTITUTE OF SAFE MEDICATION PRACTICE DATABASES (ISMP) ***

The Institute of Safe Medication Practices searched two inpatient data sources, Quantros*** and the Pennsylvania Patient Safety Reporting System (PA-PSRS) *** for medication errors involving fosphenytoin and phenytoin injection.

For phenytoin injection, Quantros*** was searched using the timeframe of March 25, 2001 to April 2, 2010. For fosphenytoin, two separate Quantros*** searches were combined to cover the time period of March 25, 2001 to March 25, 2010.

The Pennsylvania Patient Safety Reporting System (PA-PSRS)*** was searched for both fosphenytoin and phenytoin injection medication errors starting with year the surveillance system began (2004) to April 5, 2010.

2.4 LABELS, LABELING AND PACKAGING

The labels and labeling for fosphenytoin and phenytoin injection were evaluated with particular attention paid to aspects in the labeling that may have contributed to the medication error cases that were deemed relevant to the review (see Section 2 above). For this review DMEPA reviewed the following labels (see Appendices A and B for images):

Cerebyx (fosphenytoin):

- Container Labels: 100 mg PE/ 2 mL. 500 mg PE/10 mL (Akorn, Apotex, Appn Phar, Baxter, Bedford, Hospira, Parke Davis, Pharmforce, Sun Pharm, Teva, Wockhardt)
- Cerebyx (fosphenytoin) Injection Prescribing Information. No image available.

Phenytoin injection:

- Container Labels : 100 mg/2 mL, 250 mg/5 mL (Hospira, Hikma, Baxter, Pharmforce)
- Phenytoin Injection Prescribing Information (Baxter). No image available.

3 RESULTS

In total, 494 cases were deemed relevant to this review. Table 2 provides a summary for the types and number of errors for each product. Of the 494 cases, fosphenytoin accounted for 290 cases while phenytoin accounted for 60 cases. The remaining 144 medication error cases involved concurrent administration of fosphenytoin and phenytoin (n=62) and confusion between fosphenytoin and phenytoin injection (n=82).

Table 2: Fosphenytoin and Phenytoin Injection Medication Errors

ERROR TYPES	SUBTYPE OF ERROR	FOSPHENYTOIN	PHENYTOIN INJECTION
WRONG TECHNIQUE (N=33)	WRONG DILUENT	-----	17
	WRONG DILUENT RATIO	16	-----
WRONG FREQUENCY (N=17)		13	4
WRONG ROUTE (N=18)	INTRA-ARTERIAL	-----	4
	INTRAVENTRICULAR	-----	1
	PARAVASCULAR	-----	1
	ORAL FORMULATION GIVEN INTRAVENOUSLY		6
	INTRAVENOUS FORMULATION PRESCRIBED/ADMINISTERED ORALLY	5	1
WRONG DRUG (N=144)	FOSPHENYTOIN	-----	19
	PHENYTOIN	63	-----
	OTHER	62 (CELEBREX)	
DUPLICATE/CONCOMITANT THERAPY (N=62)		62	
WRONG DOSE (N=203)	OVERDOSE	124	14
	UNDERDOSE	46	4
	UNSPECIFIED WRONG DOSE	15	0

ERROR TYPES	SUBTYPE OF ERROR	FOSPHENYTOIN	PHENYTOIN INJECTION
WRONG RATE OF ADMINISTRATION (N=12)	EXCEEDED RECOMMENDED RATE	4	8
DELAY IN THERAPY (N=5)	KNOWLEDGE DEFICIT REGARDING STORAGE REQUIREMENT	5	-----

3.1 FOSPHENYTOIN ERRORS

The types of errors occurring with fosphenytoin include: wrong dose, wrong drug, wrong route of administration, monitoring errors, wrong rate of administration and errors associated with delay in therapy because of storage requirements, as well as wrong technique and wrong frequency of administration.

3.1.1 Wrong Dose

Wrong dose errors accounted for the majority of medication errors reported with fosphenytoin. The most serious and often fatal errors occurred when healthcare providers administered two and ten fold overdoses to pediatric and adult patients. The lack of pediatric dosing information in the insert, expression of strength, and phenytoin equivalency are contributing factors to these wrong dose errors.

Lack of Pediatric Dosing in Insert Labeling

Fosphenytoin is not approved for use in pediatrics and currently offers no dosing recommendations for pediatric patients in the insert labeling. However, drug use data indicates that fosphenytoin use in the pediatric population has been increasing since 2007 (which coincides with approval of generic fosphenytoin formulations) and now exceeds the use of phenytoin in the pediatric population[‡].

Expression of Strength

The majority of the two fold and 10 fold overdoses are attributed to the expression of strength on the labels and labeling as well as electronic and printed displays of automated dispensing cabinets within healthcare institutions. The product vials expressed the strength of fosphenytoin in terms of 50 mg PE/mL, rather than the total drug content, 500 mg PE/10 mL or 100 mg PE/2 mL. In response to these errors, the Agency previously recommended that Cerebyx labels be modified to prominently display the total drug content followed by the concentration. However, some healthcare institutions continued to display fosphenytoin in terms of 50 mg PE/mL, 10 mL, instead of displaying the total drug content in electronic and printed displays. Therefore, FDA disseminated another “Dear Healthcare Professional” letter to warn practitioners of the overdose risk associated with electronic and printed displays and to request these systems be revised to display the drug strength in terms of total drug content.

[‡] OSE review 2010-571, IV Phenytoin and Fosphenytoin Utilization Review. Grace Chai. May 17, 2010

Phenytoin Equivalency (mg PE) dosing

A greater number of wrong dosing errors related to confusion over phenytoin equivalency which is not as easily remedied as changing the expression of product strength. The expression of strength for Cerebyx, mg PE, was chosen to avoid confusion with molecular weight-based adjustments when converting between fosphenytoin and phenytoin. However, cases describe inconsistent use of the mg PE nomenclature by physicians and pharmacists did not know whether to interpret the physician's order as converted to mg PE or to convert it themselves during the transcription process. Nurses also confused the amount of fosphenytoin in the vial and administered the dose based on fosphenytoin mg rather than mg PE. Since the previous review OSE/DMEPA completed in 2000, thirty-seven cases of mg PE dosing confusion have been reported with only seven cases occurring between 2006 and 2009. As found in the previous Cerebyx reviews, no cases reported death relating to this type of error.

3.1.2 Monitoring Errors

Because fosphenytoin is a prodrug of phenytoin, and is dosed based on phenytoin equivalents, fosphenytoin is monitored regularly by checking phenytoin levels (mcg/mL) in the blood to determine if the drug is at therapeutic levels, as well as to determine that the drug level is not toxic. These lab values in conjunction with the clinical response help practitioners evaluate if a dosage adjustment is required. Although the drug fosphenytoin appears on the patient's drug profile, the lab value is designated as phenytoin mg/L. This inconsistency in lab value terminology versus the drug name (fosphenytoin/phenytoin) that appears on the patients profile is unique to fosphenytoin/phenytoin. One example of this documented medication error describes a pharmacist requesting the MD consider decreasing the fosphenytoin dose because of elevated lab values. An order was written to "D/C Dilantin". Neither the nurse nor pharmacist who reviewed the order understood the relationship between Dilantin (phenytoin) and Cerebyx (fosphenytoin) and thus did not discontinue the fosphenytoin.

3.1.3 Wrong Technique

Healthcare practitioners failed to dilute fosphenytoin prior to administration in several cases. In most cases fosphenytoin was administered intravenous push despite the instructions in the package insert labeling stating that fosphenytoin should be diluted in a ratio of 1.5 to 25 mg PE to 1 mL of diluent ratio.

3.1.4 Wrong Drug

A large number of reported errors with fosphenytoin were associated with proprietary name confusion involving Cerebyx and Celebrex. Previous DMEPA reviews concluded that the occurrence of these errors was related to the orthographic and phonetic similarities between these names and overlapping product characteristics. Based on the assessment of these errors, DMEPA recommended in March 1999, a name change for Celebrex because of the number of wrong drug errors occurring between Celebrex, Celexa and Cerebyx. However, instead of a name change an educational campaign was implemented. The last review that DMEPA conducted on this issue occurred in December 2000 and concluded that name confusion continued to occur despite the educational efforts that targeted healthcare practitioners. Thus, we reiterated our recommendation to change the name for Celebrex.

3.1.5 Wrong Storage

Few errors were reported because of the different storage requirements (i.e., refrigeration) for fosphenytoin versus phenytoin injection. Most cases describe a delay in therapy because of confusion over product location (i.e., refrigerator or med cart).

3.2 PHENYTOIN ERRORS

The types of errors occurring with phenytoin include: wrong dose, wrong technique, wrong frequency, and wrong rate of administration. Errors associated with phenytoin were related to the type of product formulation and limited diluent that can be used prior to administration, the time period in which the product must be used following dilution and inherent molecular characteristics that require a slow rate of administration.

3.2.1 Wrong Route of Administration

Wrong routes of administration included intra-arterially, paravascularly, intra-ventricularly or intravenous administration of phenytoin oral suspension.

3.2.2 Wrong Rate of Administration

Healthcare practitioners reported administration of phenytoin injection at a rate that exceeds the recommended 50 mg/minute. Although most of the cases do not explicitly identify the contributing factor, one case did note that confusion arose from the statement “no infusion” which appears on the principal display panel of the currently marketed vials of intravenous phenytoin. The reporter noted that the “no infusion” statement appeared on the previous intravenous phenytoin product that was used in their hospital. The reporter wrongfully assumed that the product could now be pushed and proceeded to rapidly inject the intravenous phenytoin. They also noted that the “outer package” (we assume to be carton labeling) and the package insert state “Do not exceed 50 mg per minute”. However neither of these was available to the reporter at the time of product administration.

One other case indicates that the nurse knew that the rate of administration should be slow, so the intravenous phenytoin was administered at a rate of 500 mg over 5 minutes (100 mg per minute). However, this rate is still double the recommended rate of 50 mg/minute.

3.2.3 Wrong Technique

A large number of reported errors involving phenytoin injection dealt with the use of an incorrect diluent prior to administration. Phenytoin injection can not be diluted in dextrose containing products.

3.2.4 Wrong Dose

Most wrong dose errors reported with phenytoin injection were practice-related (i.e., dose transcribed incorrectly or prescribed incorrectly).

3.3 COMMON CAUSES OF ERROR TO BOTH PRODUCTS

Common causes of error for both products include the following.

3.3.1 Hypoalbuminemia

The majority of these cases led to an overdose. In all cases, the prescriber maintained the same dose, even though the albumin level was decreased or increased.

3.3.2 Incorrect Frequency of Administration

Several medication error cases reported an incorrect frequency of fosphenytoin and phenytoin administration. Once daily was the most commonly reported wrong frequency for both products which typically occurred during prescribing. The fosphenytoin prescriber information recommends 4 to 6 mg PE/kg/day. Multiple errors indicate that the full dose was prescribed once rather than in divided frequencies, such as 300 mg at bedtime or 6 mg/kg/day. On many occasions, the pharmacist intercepted errors such as these; however one error did reach the patient.

3.3.3 Duplicate Therapy

Multiple patients were administered both medications which resulted in adverse events. In some cases one product was confused for the other. There has been no change in the frequency of occurrence of duplicate therapy over the last 10 years; six cases were reported in 2000 and five cases were reported in 2009. These errors mostly occurred because of the way orders for these drugs are written.

Fosphenytoin and phenytoin injection share the same indication and often the determination for product selection is based on whether the patient is capable of taking oral medications or whether they are restricted to intravenous medications. Physicians often write contingency orders with a change of product if the patient is able to swallow medications. We identified orders that specifically stated; “Dilantin po or Cerebyx iv if unable to swallow” or “Cerebyx iv switch to Dilantin when iv d/c”. In these cases, the nurses overlooked the “or” and administered both. Additionally, physicians often fail to discontinue one product when a new therapy is initiated and pharmacists fail to recognize the duplicate therapy.

3.3.4 Fosphenytoin and Phenytoin Injection Confusion

Wrong drug medication errors between fosphenytoin and phenytoin injection occurred throughout the medication use process and occurred bi-directionally. Physicians wrote the order as fosphenytoin but intended to write phenytoin and vice versa. Pharmacists and technicians also sent or delivered fosphenytoin when phenytoin injection was prescribed and vice versa.

3.4 POPULATIONS AFFECTED

Patient age was reported in only 274 cases. Table 3 provides a summary of patient age by the drug associated with the error. The majority of medication errors occurred in patients >16 years of age. However, fifty eight cases did involve medication errors with either fosphenytoin (n=49) or phenytoin injection (n=9) in the pediatric population.

Table 3: Age Distribution of reported errors (only available in AERS and PaPSRS*)**

Age	Fosphenytoin	Phenytoin injection	Fosphenytoin and Phenytoin injection
0- < 2 years	19	3	---
> 2 years to < 16 years	30	6	1
Adult > 16 years	131	50	34

3.4.1 Errors Associated with Death (n=16)

Ten deaths were associated with fosphenytoin wrong dose errors. Seven can be positively associated with confusion related to total drug content. Six phenytoin deaths were associated with wrong route and wrong rate errors. Table 4 summarizes the deaths by error type, drug, and patient age.

Table 4: Errors Associated With Death

Error Type	Fosphenytoin	Phenytoin injection	Patient Age
Wrong Dose	10	---	Seven patients out of 10 were ≤ 3y.o.
Wrong Route	---	5	> 16y.o.
Wrong Rate	---	1	> 16y.o.

3.5 CONTRIBUTING FACTORS OF ERROR IDENTIFIED FROM THE LABEL AND LABELING

Our review of the current container labels, carton labeling, and prescriber information for fosphenytoin and phenytoin injection identified several sources that may be contributing to the medication errors evaluated in this review.

3.5.1 Fosphenytoin Container Label

- The 2 mL vials do not consistently state the storage recommendations across all currently approved and marketed fosphenytoin products.
- The presentation of total drug content is not consistently presented across all currently approved and marketed fosphenytoin products.
- The 2 mL and 10 mL Cerebyx vials are not well differentiated.
- The container labels lack a statement that communicates the need to dilute fosphenytoin prior to administration.

3.5.2 Fosphenytoin Insert Labeling

In reviewing the insert labeling we noted that important information is absent from the Dosage and Administration which may be contributing to errors:

- The recommended frequency of administration is not stated.
- Instructions for proper dilution and recommended ratios of drug to diluent are absent.
- Information pertaining to the effect of hypoalbuminemia and the equation that can be used to determine free phenytoin levels are absent.
- A statement which informs practitioners of storage requirements after dilution is absent.
- The insert does not provide guidelines for pediatric dosing.

3.5.3 Phenytoin Injection Container Label

- The container label contains the statement, “no infusion”.
- The immediate container label does not convey the correct rate of administration.

3.5.4 Phenytoin Injection Insert Labeling

There are several areas of vulnerability that were noted during analysis of the insert labeling for phenytoin sodium injection, including the following:

- The Prescriber Information does not have updated drug interactions information, e.g. Caspofungin (we retrieved two cases that describe errors related to this drug-drug interaction).
- Information on the effect of hypoalbuminemia and the equation that can be used to determine free phenytoin levels is absent.
- The insert labeling does not state what type to diluent to use for phenytoin.
- The insert labeling does not state what ratio of diluent and active drug product should be used to dilute phenytoin sodium injection.
- The insert labeling does not provide rate of administration recommendations for pediatric patients.

4 DISCUSSION

We did not conduct a comparative safety analysis between fosphenytoin and phenytoin injections as requested by DNP. There is no value in comparing rates of medication error to determine incidence and comparative safety among these drug products using this data because it is based on voluntary, spontaneous reports. Moreover, many factors influence the ability to determine a medication error reporting rate such as product usage and reporting differences among health care organizations (i.e., differences in culture among health care organizations, differences in the definition of a medication error among health care organizations, differences in the patient populations served by various health care organizations, differences in the type(s), passive or active, of reporting and detection systems for medication errors among health care organizations reporting systems)[§]. The information contained in each report is more informative than the number of reports because it allows us to identify the contributing factors to the error and apply lessons learned to improve the safe use of each product within the medication use system.

Examination of the medication error data revealed similar types of error common to both products (wrong dose, wrong technique, wrong frequency, wrong route, wrong drug, wrong rate and duplicate therapy) with serious and sometimes fatal outcomes. Causality for these errors is multi-factorial and somewhat different because of the products' formulation and design of their labels and labeling. No particular stage in the medication use system appears most vulnerable because the errors occurred throughout the entire medication use system (i.e., prescribing, dispensing and administering, stocking, and monitoring). Although some errors were related to practice issues (e.g. errors in transcription, errors in calculation, infusion pump programming errors, administration of multiple loading doses, etc.) the majority occurred because of confusion related to the product's label and labeling. As such, DMEPA recommends revisions to each product's labels and labeling to ensure their safe use.

4.1 FOSPHENYTOIN ERRORS

Although there are many factors contributing to the medication errors reported with fosphenytoin, the container and insert labeling revisions discussed in the following subsections may minimize the occurrence of the two broadly categorized types of wrong dose and wrong route of administration errors.

Additionally, DNP specifically requested an assessment of errors involving confusion with fosphenytoin's proprietary name and storage requirements. Although there were few reported errors because of storage requirements, evaluation of the fosphenytoin container labels revealed inconsistencies across products. The labels and labeling can be revised to uniformly display the statement of required storage. Confusion still occurs between the two proprietary names; Cerebyx and Celebrex. However, it is unclear as to the impact a name change might have on such errors given the length of time Celebrex has been marketed.

4.1.1 *Wrong Dose*

Although fosphenytoin is not indicated for use in the pediatric population the most serious outcomes occurred in this age group. Overdoses resulting in death were attributed to confusion over the total drug content contained in each fosphenytoin vial. Although the brand product, Cerebyx, revised their container labels to prominently display the strength in terms of total drug content, some of the generic manufacturer's labels are not consistent with the prominence to which this statement of strength is expressed. The generic manufacturers should be brought into compliance with these recommendations

[§] NCCMERP Statement on the use of medication error rates to compare health care organizations - <http://www.nccmerp.org/council/council2002-06-11.html>

to ensure safe use. Additionally, because this product is widely used in pediatric patients because of its perceived safety in comparison to that of phenytoin, which is based upon its safety profile in adults, studying dosing in the pediatric population should be considered so that dosing recommendations can be added to the insert labeling. Currently practitioners are, presumably, dosing this product based on the phenytoin dose recommendations. However even the phenytoin dose recommendations are vague. Analysis of the phenytoin package insert found a loading dose recommendation for neonates and pediatric patients; however, there are no dosing recommendations for an intravenous maintenance dose. Additionally, there is a boxed warning on the rate of administration for neonates and adults and is silent regarding the rate for pediatric patients. A brief search of the web displays even credible sources can provide poor dosing guidelines and, without guidance from the package insert, dosing errors are certain to continue in this vulnerable population. Additionally, a search of internet references for fosphenytoin dosing often stated the dosing incorrectly because the mg PE nomenclature was dropped as stated in the Massachusetts General hospital for Children Handbook “give phenytoin or fosphenytoin 20 mg/kg IV” which was published in 2009**.

Inclusion of explicit directions for use in the package inserts of both fosphenytoin and phenytoin could mitigate confusion that occurs when practitioners attempt to dose these products in the pediatric population.

Additionally, using the measurement of phenytoin plasma levels has contributed to errors in dosing during drug monitoring. Confusion arises from the inconsistency between drug therapy name (i.e., fosphenytoin) and monitoring lab value (phenytoin). As a result patients are continued on fosphenytoin therapy without requisite dose adjustments. Improved labeling and prescriber education which describes the need to monitor phenytoin levels may help avoid this confusion.

Another area leading to wrong dose errors with fosphenytoin relates to the phenytoin equivalency nomenclature. We speculate that medication errors involving phenytoin equivalency exhibited a downward trend because of several factors such as the provider’s acclimation to the usage of the mg PE nomenclature and procedures or protocols implemented in facilities which require fosphenytoin to be presented in a manner which clearly designates the strength. Fosphenytoin may also be limited to providers in the emergency department or specialized floors, which would preclude usage by practitioners who are less accustomed to the nomenclature. Additionally, computer programs may have automatic conversions built into the programs with messages alerting practitioners about the conversion. Decreased reporting or reporting fatigue may also have caused the downward trend, rather than a true decrease in the number of errors. However, two of the reported cases resulted in adverse events and multiple cases described a delay in treatment. The most recent case, reported in 2009, states, “many physicians and nurses do not understand phenytoin equivalents (PE) which has led to patients receiving improper doses”. This leads us to believe there is still some confusion with this nomenclature.

In order to fully understand the relative confusion remaining with phenytoin equivalency, we recommend the applicant survey health care practitioners as to their understanding of how the equivalency is used in dosing and monitoring of fosphenytoin. Based on the findings of this survey further consideration needs to be given to whether or not a change is required and what impact this may have on errors given the length of time the product has been marketed.

4.1.2 Wrong Route

In several cases fosphenytoin was administered intravenous push rather than the recommended intravenous infusion. Healthcare practitioners failed to properly dilute fosphenytoin to a concentration

** <http://www2.massgeneral.org/neurology/epilepsy/PDFs/Status%20Epilepticus%20Review.pdf>

ranging from 1.5 to 25 mg PE/mL prior to intravenous administration as recommended in the Dosage and Administration section of the fosphenytoin insert labeling. Although the insert recommends this dilution there is no explanation or clear equation to determine what exactly mg PE signifies in the Dosage and Administration section. Descriptions of the conversion are only offered at the beginning of the prescriber information. However, the dilution instructions are based on mg PE nomenclature that is not adequately described next to the dilution information. This can perpetuate confusion or add to the confusion associated with how to translate the dose and proper dilution. This ambiguity may have contributed to errors in dilution.

Moreover, because fosphenytoin is available as a solution unlike some other intravenous medications, there is a tendency to believe that a solution can be administered without further dilution because it is already available in a form (solution) that can be administered intravenously (as opposed to powder). A statement on the container label that indicates fosphenytoin must be diluted prior to administration could help communicate this information more clearly to practitioners at the point of patient care. It may also be helpful to state the dilution requirements in terms of the vial in addition to mg PE. Revisions to the package insert to include dilution directions that describe mg PE and how much diluent can be used for each 2 mL or 10 mL vial for proper dilution technique could mitigate these dilution errors.

4.2 PHENYTOIN ERRORS

Administration of phenytoin via the wrong route or by a wrong rate accounted for the most serious reported outcomes, including death. These types of errors are particularly disconcerting for a product that plays a role in emergency medicine, as it requires quick action and little time to investigate proper route, dilution and administration.

4.2.1 *Wrong Route*

Phenytoin wrong route errors involve intravenous administration of phenytoin oral suspension. Phenytoin has the distinct disadvantage of being available in multiple formulations and can, depending on the formulation, be administered either orally or intravenously. Because the oral phenytoin solution is often drawn up in syringes and dispensed to the nursing unit, it presents opportunity for this type of error. Healthcare practitioners assume products in syringes should be administered intravenously. This type of error is not specific to phenytoin, but rather a practice related error that could occur with many drug products that are available in both oral and intravenous formulations.

4.2.2 *Wrong Rate of Administration*

Phenytoin wrong rate errors involve administration that exceeds the recommended rate of 50 mg/minute. Phenytoin sodium injection has a boxed warning which states that phenytoin should not be administered in adults at a rate to exceed 50 mg per minute intravenously and should not exceed the rate of 1-3 mg/kg/min in neonates. Because phenytoin injection has a high predilection for precipitation, intravenous infusions are not recommended. However phenytoin injection also cannot be given at a rapid rate or what is often referred to in the medical community as “pushed”. These contradictions in administration directions contribute to these administration errors. Because phenytoin injection is often used in acute care situations or emergencies, and product labeling other than the container may not always be readily available. Therefore the rate of administration, greater than 50 mg per minute, if clearly communicated on the container label could help mitigate future rate of administration confusion.

4.2.3 *Wrong Technique*

Incorrect dilution of phenytoin prior to product administration is another and more commonly reported error. Analysis of these cases reveals that most can be attributed to a knowledge deficit. The insert labeling does not describe the interaction between dextrose and dextrose containing solutions,

although the interaction between dextrose and phenytoin injection is documented on reference websites. According to global RPh, a pharmacist website, phenytoin injection should be diluted with normal saline, although this is not stated in the prescribing information^{††}. Mixing phenytoin injection with dextrose containing solutions causes precipitation in intravenous solutions and administration sets, which increases the risk of vein damage.^{**}

Practitioners who are unaccustomed to phenytoin injection administration may also not be aware that dextrose can be problematic and may use the prescriber information as a reference for proper dilution. There is no description in the Warning section of the prescriber information, nor is it located in dosage and administration. A statement in the insert labeling reads “The addition of phenytoin injection to intravenous infusion is not recommended due to lack of solubility and resultant precipitation”. However, this statement is ambiguous because it does not specify what type of intravenous infusion the product is not compatible with (i.e. dextrose or normal saline). Although precipitants may occur with most solutions, clearly stating that diluting with dextrose results in rapid precipitation may help decrease medication errors such as this from occurring. Explicit instructions in the package insert regarding proper product dilution could help mitigate these errors and result in less confusion during the dilution process.

4.3 COMMON CAUSES OF ERROR

Common causality led to certain types of errors among both products (i.e., wrong dose, wrong frequency of administration, wrong drug and concomitant therapy).

4.3.1 Failure to Understand the Relationship of Dose to Serum Albumin Levels

These errors resulted in wrong dose errors because a dose reduction based on plasma albumin levels did not occur. An evaluation of the fosphenytoin prescriber information reveals that there is a brief description in the Special Population section that describes how unbound phenytoin concentrations may be more useful in patients with renal or hepatic disease. However, there is no mention of the equation^{§§} that can be used to determine the appropriate dose and there is no mention in the Dosage and Administration section regarding renal or liver dosing. An evaluation of the prescriber information for phenytoin injection reveals that although there is a laboratory test section; however there is no mention of monitoring albumin or how albumin levels affect phenytoin levels and how the phenytoin dose should be altered based on these changes.

4.3.2 Frequency of Administration not Clear in the Labeling

A once daily frequency of administration was common to both products. We suspect physicians think fosphenytoin must be administered once daily because the insert labeling only states the total daily dose and does not state the frequency of administration. Literature sources vary in the dosing recommendations from daily to three times daily. Presumably, the fosphenytoin package insert assumes practitioners will refer to the phenytoin insert which does state that phenytoin should be administered every 6 to 8 hours. The errors with phenytoin once daily administration could be because of the confusion among these products.

^{††} http://www.globalrph.com/phenytoin_dilution.htm

^{**} <http://www.ismp.org/newsletters/acuteare/articles/19961023.asp>

^{§§} <http://www.mdcalc.com/phenytoin-dilantin-correction-for-albumin-or-renal-failure>

4.3.3 Similarity in Product Names Leading to Concomitant Therapy

We cannot ascertain whether all of these errors occurred when the products were ordered by their proprietary names; however some did state that the orders used Cerebyx and Dilantin. The proprietary names have no similarities and thus a nurse or practitioner might not recognize that they are virtually identical products. It seems that institutions or physicians that use established names are more likely to recognize that fosphenytoin and phenytoin sodium injection are similar. With the increased use of established names in ordering, confusion resulting in duplicate therapy may decrease. However one error was noted in which the practitioner complained that the ‘fos’ prefix increases duplicate therapy errors because it looks less similar then if it were a suffix on the end of the name. This issue requires further investigation before a definitive cause can be established.

5 CONCLUSIONS AND RECOMMENDATIONS

Medication errors with fosphenytoin and phenytoin sodium injection are equally deleterious because their use in emergency situations and vulnerable patient populations. Although the products have identical indications and are used in similar settings of care, each product has unique formulation issues that contribute to these medication errors. It is extremely difficult to quantify the incidence or comparative safety among these drug products as this analysis is based on spontaneously reported data, and other factors that influence the ability to determine a medication error reporting rate such as product usage and differences in health care organizations. In order to improve the safe use of these products we recommend revisions to the insert labeling for both fosphenytoin and phenytoin to provide clarity as it relates to the rate of administration, product preparation, storage and administration, dose adjustments, and duplication of therapy. Additionally, we recommend the container labels of all fosphenytoin products reflect consistent storage recommendations, improve the display of total drug content, communicate the need for dilution and better differentiate between the 2 mL and 10 mL vials. The phenytoin container label should be revised to delete the statement “no infusion” and include the maximum rate of administration. Furthermore, there is also a need to gain a better understanding as to the continued extent of confusion that remains with the phenytoin equivalency nomenclature used for dosing fosphenytoin and the source of concomitant therapy. We provide the following recommendations that address the contributing factors to these errors.

If you have further questions or need clarifications, please contact Laurie Kelley, Project Manager, at 301-796-5068.

RECOMMENDATIONS TO DNP

A. Fosphenytoin

Update the package insert to contain the following pertinent information:

- Frequency of administration.
- Update the Dosage and Administration section to include dosing recommendations in liver and renal failure and consider including the equation that can be used for phenytoin correction for altered albumin levels.
- Detailed instructions for proper dilution and recommended ratio of drug to diluent.
- A statement which informs practitioners of storage requirements after product dilution.
- Dosing guidelines for pediatric patients.
- Updated Drug Interaction section.

B. *Phenytoin Sodium Injection*

Update the package insert to contain the following pertinent information:

- Include a “Laboratory Test” section that includes the recommended phenytoin laboratory levels that should be used for monitoring (in conjunction with patient response) and a section devoted to phenytoin and albumin and include the equation that can be used for phenytoin correction for altered albumin levels.
- Recommended diluent to be used for diluting phenytoin sodium injection.
- Detailed instructions for proper dilution and recommended ratio of diluent and active drug.
- Include rate of administration recommendations for pediatric patient population in the boxed warning.

RECOMMENDATIONS TO APPLICANTS

A. *Fosphenytoin Container Labels and Carton Labeling*

- Revise either the 2 mL or 10 mL container labels to incorporate colors that are not used in the other volume, thereby allowing for improved visual differentiation between the 2 mL and 10 mL Cerebyx and fosphenytoin vials.
- Revise the 2 mL container vials to ensure that the storage statement is displayed on immediate container label. This revision should be implemented by all manufacturers of Cerebyx and fosphenytoin.
- The presentation of total drug content should be consistently presented in accordance with USP. The total drug content should be the most prominent and the mg per mL concentration should appear less prominent.
- Include the statement “Dilute prior to administration” on the principal display panel of all container labels and carton labeling.

B. *Phenytoin Sodium Injection Container Label/Carton Labeling*

- Remove the ‘no infusion’ statement and replace it with the recommended rate of administration, “Maximum rate for adults should not exceed 50 mg/minute or 1-3 mg/kg/min in neonates” on the container labels and carton labeling.

REFERENCES

Reviews

OPDRA review #000009-005, Chan Park, April 13, 1999.

OPDRA review # 99-003-5. Celebrex. Carol Holquist. December 18, 2000.

OPDRA review #00-0167, Carol Holquist, February 11, 2002.

OSE review #2008-876, Anne Crandall, October 1, 2010.

Databases

1. Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential postmarketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

2. ISMP

ISMP is a quality improvement tool, which facilitates productive and efficient documentation, reporting, analysis, tracking, trending, and prevention of adverse drug events. ISMP provides both PA-PSRS and MedMarx medication error reports.

- a. Quantros is a national, Internet-accessible database that hospitals and health care systems use to track and trend adverse drug reactions and medication errors. Hospitals and health care systems participate in ISMP voluntarily and subscribe to it on an annual basis.
- b. Pennsylvania Patient Safety Reporting System (PaPSRS) was established under Act 13 of 2002, the Medical Care Availability and Reduction of Error Act as an independent state agency. Consistent with Act 13 of 2002, the Authority developed the Pennsylvania Patient Safety Reporting System, a confidential web-based system that both receives and analyzes reports of what the Act calls Serious Events (actual occurrences) and Incidents (so-called "near-misses"). The Authority analyzes and evaluates all reports and makes recommendations for changes in health care practices and procedures which may be instituted to reduce the number and severity of Serious Events and Incidents in Pennsylvania's healthcare instructions.
<http://patientsafetyauthority.org/Pages/Default.aspx>

Articles

- 1) Eriksson K, Keränen T, Kälviäinen R. Fosphenytoin. Expert Opin Drug Metab Toxicol. 2009 Jun;5(6):695-701
- 2) ISMP Medication Safety Alert, Acute Care. FDA Advise-ERR: Medication errors associated with Cerebyx. <http://www.ismp.org/newsletters/acutecare/articles/19961023.asp>
- 3) Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, Handforth A, Faught E, Calabrese VP, Uthman BM, Ramsay RE, Mamdani MB. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med. 1998 Sep 17;339(12):792-8
- 3) Adams BD, Buckley NH, Kim JY, Tipps LB. J Emerg Med. Fosphenytoin may cause hemodynamically unstable bradydysrhythmias. 2006 Jan;30(1):75-9.
- 4) Horowitz BZ. Fosphenytoin farewell? Ann Emerg Med. 2004 Mar;43(3):398-400.

5) Trinka E. What is the relative value of the standard anticonvulsants: Phenytoin and fosphenytoin, phenobarbital, valproate, and levetiracetam? *Epilepsia*. 2009 Dec;50 Suppl 12:40-3.

APPENDICES

Appendix A: Cerebyx and Fosphenytoin Labels and Labeling

Pfizer/Eisai : NDA 20450

Each vial contains fosphenytoin sodium 150 mg equivalent to 100 mg phenytoin sodium.
Usual Dosage- See package insert.

NDC 0071-4007-05

Cerebyx®
 (Fosphenytoin Sodium Injection)
100 mg PE in 2 mL
 (PE = phenytoin sodium equivalents)
**For IM or IV use
 2 mL Vial**

 055986361

EXP. LOT

NDC 0071-4007-05
 STERI-VIAL®
Cerebyx®
 (Fosphenytoin Sodium Injection)
100 mg PE in 2 mL
 (PE = phenytoin sodium equivalents)
 Rx only
 25 VIALS (2 mL each)

For IM or IV use.
 Each vial contains fosphenytoin sodium 750 mg equivalent to 500 mg phenytoin sodium.
Usual Dosage- See package insert for full prescribing information.
Note-Administration differs from parenteral phenytoin. See Dosage and Administration.
Store under refrigeration at 2°C to 8°C (36°F to 46°F).
Distributed by
Parke-Davis
 Division of Pfizer Inc, NY, NY 10017
Marketed by
Eisai Inc.
 Traneck, NJ 07086

NDC 0071-4008-10

Cerebyx®
 (Fosphenytoin Sodium Injection)
500 mg PE in 10 mL
 (PE = phenytoin sodium equivalents)
 Rx only

 055994361

10 mL Vial

EXP. LOT


MADE IN IRELAND

TEVA : ANDA 76886

TEVA
NDC 0703-7101-01
Fosphenytoin
Sodium Injection, USP

100 mg PE in 2 mL
(50 mg PE/mL)
(PE=phenytoin sodium equivalents)
2 mL Single Dose Vial
For IM or IV Use

Rx only
Teva Parenteral Medicines
Irvine, CA 92618




00212C

TEVA
NDC 0703-7101-04 **Rx only** Each vial contains fosphenytoin sodium, USP 150 mg equivalent to 100 mg phenytoin sodium, tromethamine, USP (TRIS) as a buffer, hydrochloric acid, NF or sodium hydroxide, NF to adjust the pH to 8.6 to 9.0, and sufficient water for injection, USP. Store under refrigeration at 2° to 8°C (36° to 46°F).
Fosphenytoin
Sodium Injection, USP
Usual Dosage: See Package Insert.

100 mg PE in 2 mL
(50 mg PE/mL)
(PE=phenytoin sodium equivalents)
2 mL Single Dose Vials
For IM or IV Use
25 Vials

DOSES OF FOSPHENYTOIN SODIUM INJECTION, USP ARE EXPRESSED AS THEIR PHENYTOIN SODIUM EQUIVALENTS (PE=phenytoin sodium equivalents).
NOTE: Administration differs from parenteral phenytoin. See Dosage and Administration.
Mfd. by: Teva Parenteral Medicines, Inc.
Irvine, CA 92618



00213C

TEVA

NDC 0703-7105-01 **Rx only**

Fosphenytoin
Sodium Injection, USP

500 mg PE in 10 mL
(50 mg PE/mL)
(PE=phenytoin sodium equivalents)
10 mL Single Dose Vial
For IM or IV Use


Note: Administration differs from parenteral phenytoin. See Dosage and Administration.

Store under refrigeration
2° to 8°C
(36° to 46°F).

Teva Parenteral Medicines
Irvine, CA 92618

Each vial contains fosphenytoin sodium, USP 750 mg equivalent to 500 mg phenytoin sodium.

Usual Dosage:
See Package Insert.

 00214C

TEVA

NDC 0703-7105-03 **Rx only**

Fosphenytoin
Sodium Injection, USP

500 mg PE in 10 mL
(50 mg PE/mL)
(PE=phenytoin sodium equivalents)
10 mL Single Dose Vials
For IM or IV Use
10 Vials

Each vial contains fosphenytoin sodium, USP 750 mg equivalent to 500 mg of phenytoin sodium, tromethamine, USP (TRIS) as a buffer, hydrochloric acid, NF or sodium hydroxide, NF to adjust the pH to 8.6 to 9.0, and sufficient water for injection, USP.


Store under refrigeration at 2° to 8°C (36° to 46°F).

NOTE: Administration differs from parenteral phenytoin. See Dosage and Administration.

DOSES OF FOSPHENYTOIN SODIUM INJECTION, USP ARE EXPRESSED AS THEIR PHENYTOIN SODIUM EQUIVALENTS (PE=phenytoin sodium equivalents).

Usual Dosage: See Package Insert.

Manufactured by: Teva Parenteral Medicines, Inc., Irvine, CA 92618

 00215C

Bedford Laboratories : ANDA 77481

FOSPHENYTOIN
SODIUM INJECTION USP

NDC 55390-175-10


2 mL Single Dose Vial
FOR IM OR IV USE.

100 mg PE/2 mL
(50 mg PE/mL)
(PE = phenytoin sodium equivalents)

Usual Dosage - See package insert.
Rx ONLY

Manufactured for:
Bedford Laboratories™
Bedford, OH 44146

FPY-V00



NDC 55390-175-10 10 x 2 mL Single Dose Vials

FOSPHENYTOIN SODIUM INJECTION USP

FOR IM OR IV USE

Rx ONLY **100 mg PE/2 mL** **BEDEORD**
LABORATORIES™

(50 mg PE/mL)
(PE = phenytoin sodium equivalents)

FOSPHENYTOIN SODIUM INJECTION USP

NDC 55390-176-10
10 mL Single Dose Vial
FOR IM OR IV USE.

Each vial contains fosphenytoin sodium 750 mg equivalent to 500 mg phenytoin sodium.

Usual Dosage - See package insert.

Note - Administration differs from parenteral phenytoin. See Dosage and Administration.

Store under refrigeration at 2° to 8°C (36° to 46°F).

Manufactured for:
Bedford Laboratories™
Bedford, OH 44146

500 mg PE/10 mL
(50 mg PE/mL)
(PE = phenytoin sodium equivalents)

Rx ONLY

FPY-VA00

NDC 55390-176-10 10 x 10 mL Single Dose Vials

FOSPHENYTOIN SODIUM INJECTION USP

FOR IM OR IV USE

Rx ONLY **500 mg PE/10 mL** **BEDEORD**
LABORATORIES™

(50 mg PE/mL)
(PE = phenytoin sodium equivalents)

Baxter Healthcare : ANDA 077989

NDC 10019-263-17

Fosphenytoin
Sodium Injection, USP

150 mg equivalent to
100 mg PE in 2 mL
(50 mg PE/mL) **Rx only**
(PE = phenytoin sodium equivalents)
FOR IM OR IV USE
2 mL Vial
Mfd. by Baxter Healthcare
Deerfield, IL 60015 USA

482-439-0000
(01)00310019263175

Lot: _____
Exp.: _____

LOT _____

EXP. _____

To open—Cut seal along dotted line.

NDC 10019-263-01

Fosphenytoin
Sodium Injection, USP

150 mg equivalent to
100 mg PE in 2 mL **Rx only**
(50 mg PE/mL)
(PE = phenytoin sodium equivalents)
FOR IM OR IV USE
25 x 2 mL Single Dose Vials
Baxter
Manufactured by Baxter Healthcare Corporation
Deerfield, IL 60015 USA 462-440-01

Each vial contains fosphenytoin sodium 150 mg equivalent to 100 mg phenytoin sodium, Tromethamine (TRIS) as a buffer, Hydrochloric Acid or Sodium Hydroxide to adjust the pH to 8.6 to 9.0, and sufficient Water for Injection.

Non-latex.
Usual Dosage: See package insert.
Note: Administration differs from parenteral phenytoin. See Dosage and Administration.
Store under refrigeration at 2°C to 8°C (36°F to 46°F).
DOSES OF FOSPHENYTOIN SODIUM INJECTION ARE EXPRESSED AS THEIR PHENYTOIN SODIUM EQUIVALENTS (PE = phenytoin sodium equivalents).

(01)00310019263014

NDC 10019-263-71 **Rx only**

Fosphenytoin
Sodium Injection, USP

750 mg equivalent to
500 mg PE in 10 mL
(50 mg PE/mL)
(PE = phenytoin sodium equivalents)
FOR IM OR IV USE 10 mL Vial

Each vial contains fosphenytoin sodium 750 mg equivalent to 500 mg phenytoin sodium, Tromethamine (TRIS) as a buffer, Hydrochloric Acid or Sodium Hydroxide to adjust the pH to 8.6 to 9.0, and sufficient Water for Injection.

Usual Dosage: See package insert.
Note: Administration differs from parenteral phenytoin. See Dosage and Administration.
Store under refrigeration at 2°C to 8°C (36°F to 46°F).

Manufactured by
Baxter Healthcare Corporation
Deerfield, IL 60015 USA
462-440-01

(01)00310019263717

LOT: _____
EXP.: _____

NDC 10019-263-03 **Rx only**

Fosphenytoin
Sodium Injection, USP

750 mg equivalent to
500 mg PE in 10 mL
(50 mg PE/mL)
(PE = phenytoin sodium equivalents)
FOR IM OR IV USE
10 x 10 mL Single Dose Vials

Manufactured by
Baxter Healthcare Corporation
Deerfield, IL 60015 USA 462-482-00

Each vial contains fosphenytoin sodium 750 mg equivalent to 500 mg phenytoin sodium, Tromethamine (TRIS) as a buffer, Hydrochloric Acid or Sodium Hydroxide to adjust the pH to 8.6 to 9.0, and sufficient Water for Injection.


Non-latex.

Usual Dosage: See package insert.

Note: Administration differs from parenteral phenytoin. See Dosage and Administration.


Store under refrigeration at 2°C to 8°C (36°F to 46°F).

DOSES OF FOSPHENYTOIN SODIUM INJECTION ARE EXPRESSED AS THEIR PHENYTOIN SODIUM EQUIVALENTS
(PE = phenytoin sodium equivalents).



(01)033 100 19263 033

LOT: EXP:



APP Pharmaceuticals : ANDA 078052

NDC 63323-403-02 400302


FOSPHENYTOIN SODIUM
INJECTION, USP

100 mg PE/2 mL
(50 mg PE/mL)
(PE=Phenytoin sodium equivalents).
For IM or IV use
Usual Dosage: See Insert.
2 mL Single Use Vial

APP Pharmaceuticals, LLC
Schaumburg, IL 60173

402314A

LOT/EXP



NDC 63323-403-02 400302

FOSPHENYTOIN
SODIUM
INJECTION, USP

100 mg PE/2 mL
(50 mg PE/mL)
(PE = phenytoin sodium equivalents)
For IM or IV use Rx only
2 mL Single Use Vials

Sterile.

Each vial contains fosphenytoin sodium 150 mg equivalent to 100 mg phenytoin sodium, Tromethamine (TRIS) as a buffer, Hydrochloric Acid or Sodium Hydroxide to adjust the pH to 8.6 to 9, and sufficient Water for Injection.


Usual Dosage: See insert.

Note- Administration differs from parenteral phenytoin. See Dosage and Administration.

Store under refrigeration at 2°C to 8°C (36°F to 46°F).

DOSES OF FOSPHENYTOIN SODIUM INJECTION ARE EXPRESSED AS THEIR PHENYTOIN SODIUM EQUIVALENTS (PE = phenytoin sodium equivalents)

Vial stoppers do not contain natural rubber latex.



APP Pharmaceuticals, LLC
Schaumburg, IL 60173

42799A

NDC 63323-403-10 400310

**FOSPHENYTOIN
SODIUM**
INJECTION, USP

500 mg PE/10 mL ||

(50 mg PE/mL)
(PE = phenytoin sodium equivalents)
For IM or IV use Rx only
10 mL Single Use Vial

Sterile.
Each vial contains fosphenytoin sodium 750 mg equivalent to 500 mg phenytoin sodium.

Usual Dosage: See insert.
Note- Administration differs from parenteral phenytoin. See Dosage and Administration.
Store under refrigeration at 2°C to 8°C (36°F to 46°F).
Vial stoppers do not contain natural rubber latex.

APP
APP Pharmaceuticals, LLC
Schaumburg, IL 60173

402315A
LOT/EXP



NDC 63323-403-10 400310

**FOSPHENYTOIN
SODIUM**
INJECTION, USP

500 mg PE/10 mL ||

(50 mg PE/mL)
(PE = phenytoin sodium equivalents)
For IM or IV Use
10 mL Single Use Vial
10 VIALS Rx only

Sterile.
Each vial contains fosphenytoin sodium 750 mg equivalent to 500 mg phenytoin sodium, Tromethamine (TRIS) as a buffer, Hydrochloric Acid, or Sodium Hydroxide to adjust the pH to 8.6 to 9, and sufficient Water for Injection.

Usual Dosage: See insert.
Note- Administration differs from parenteral phenytoin. See Dosage and Administration.
Store under refrigeration at 2°C to 8°C (36°F to 46°F).

DOSES OF FOSPHENYTOIN SODIUM INJECTION ARE EXPRESSED AS THEIR PHENYTOIN SODIUM EQUIVALENTS (PE = phenytoin sodium equivalents)
Vial stoppers do not contain natural rubber latex.

APP
APP Pharmaceuticals, LLC
Schaumburg, IL 60173



Apotex : ANDA 078126

(01) (003) 60505074655

NDC 60505-0746-5 2 mL Vial

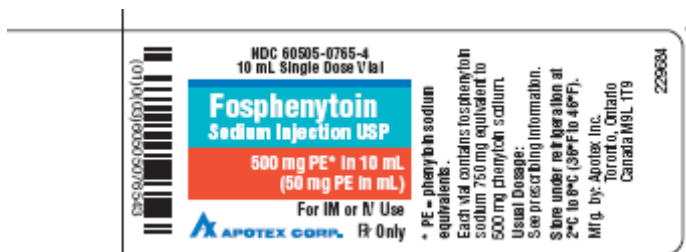
**Fosphenytoin
Sodium Injection USP**

100 mg PE (PE = phenytoin sodium equivalents) in 2 mL

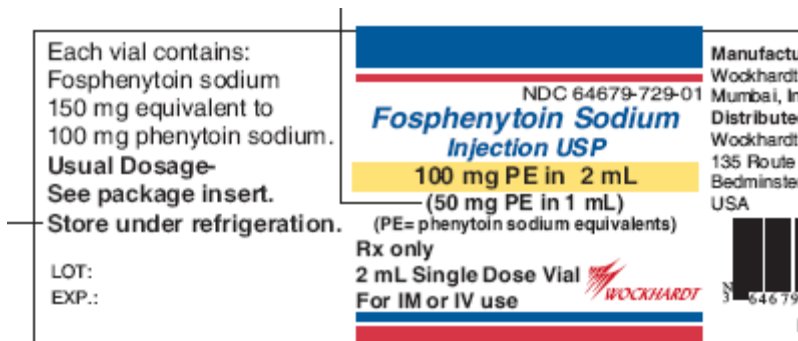
For IM or IV Use
Rx Only

APOTEX CORP.

Mfg. by: Apotex Inc.
Toronto, Ontario
Canada M9L 1T9 229682



Wockhardt : ANDA 078137




NDC 64679-729-01

Fosphenytoin Sodium
Injection USP

100 mg PE in 2 mL

(50 mg PE in 1 mL)
(PE = phenytoin sodium equivalents)
For IM or IV Use

Rx only
25 VIALS
2 mL Single Dose Vials




NDC 64679-730-01

Fosphenytoin Sodium
Injection USP

500 mg PE in 10 mL
(50 mg PE in 1 mL)
(PE= phenytoin sodium equivalents)

Rx only
10 mL Single Dose Vial
For IM or IV use



Each vial contains fosphenytoin sodium 750 mg equivalent to 500 mg phenytoin sodium.

Usual Dosage: See package insert for full prescribing information.
Note - Administration differs from parenteral phenytoin. See Dosage and administration.

Store under refrigeration at 2° to 8°C (36° to 46°F).

Manufactured by:
Wockhardt Limited, Mumbai, India.

Distributed by:
Wockhardt USA Inc.
135 Route 202/206, Bedminster, NJ 07921, USA.

LOT:

NDC 64679-730-01

***Fosphenytoin Sodium
Injection USP***

500 mg PE in 10 mL

(50 mg PE in 1 mL)

(PE = phenytoin sodium equivalents)

For IM or IV Use

Rx only



10 VIALS



10 mL Single Dose Vials



Appendix B : Phenytoin Labels and Labeling

Hospira : ANDA 089744, 089521

2 mL NDC 0409-1317-01
Phenytoin Sodium
Injection, USP Rx only
100 mg in 2 mL
IM/IV (no infusion)
RL-0636 (10/04)
Hospira, Inc.
Lake Forest, IL 60045 USA



5 mL NDC 0409-1317-02
Phenytoin Sodium
Injection, USP Rx only
250 mg in 5 mL
IM/IV (no infusion)
RL-0638 (10/04)
Hospira, Inc.
Lake Forest, IL 60045 USA



2 mL Single-dose
5 Ampuls

NDC 0409-1317-01

PHENYTOIN SODIUM Inj., USP 100 mg in 2 mL

For I.M. or I.V. use (no infusion)

Rx only

Each mL contains phenytoin sodium 50 mg; propylene glycol 40% and alcohol 10%. Also contains sodium hydroxide for pH adjustment, pH 11.5 (10.0 to 12.3). Administer slowly. Do not exceed 50 mg per minute intravenously. Usual dosage: See insert. Note: Do not use injection if it is hazy or contains a precipitate.

The addition of Phenytoin Sodium Injection to an intravenous infusion is not recommended due to the lack of solubility and resultant precipitation. Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

©Hospira 2004 Printed in USA
HOSPIRA, INC., LAKE FOREST, IL 60045 USA



RL-0637 (10/04)



5 mL Single-dose
5 Ampuls

NDC 0409-1317-02

PHENYTOIN SODIUM Inj., USP 250 mg in 5 mL

For I.M. or I.V. use (no infusion)

Rx only

Each mL contains phenytoin sodium 50 mg; propylene glycol 40% and alcohol 10%. Also contains sodium hydroxide for pH adjustment, pH 11.5 (10.0 to 12.3). Administer slowly. Do not exceed 50 mg per minute intravenously. Usual dosage: See insert. Note: Do not use Injection if it is hazy or contains a precipitate.

The addition of Phenytoin Sodium Injection to an intravenous infusion is not recommended due to the lack of solubility and resultant precipitation.

The solution is suitable for use as long as it remains free of haziness and precipitate. Only a clear solution should be used. A faint yellow coloration may develop; however, this has no effect on the potency of the solution. Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

©Hospira 2004
HOSPIRA, INC., LAKE FOREST, IL 60045 USA


Printed in USA



RL-0639 (10/04)



Hikma: ANDA 040573

 NDC 62778-040-01
HIKMA FARMACÉUTICA


PHENYTOIN
SODIUM INJECTION, USP

100 mg/2 mL (50 mg/mL)
For IV (no infusion) or IM Use
2 mL Single Dose Vial
Rx Only

Usual Dosage: See package insert.
Store at 20° - 25°C (68° - 77°F).
[See USP, Controlled Room Temperature].


Do not use if hazy or has a precipitate.

Iss. Nov. 2004



NDC 62778-040-01

Lot:
Exp.:

 NDC 62778-041-01 NOTE: Administer slowly. Do not exceed 50 mg per minute intravenously. **SINGLE USE - DISCARD UNUSED CONTENTS.**
HIKMA FARMACÉUTICA

PHENYTOIN
SODIUM INJECTION, USP


250 mg/5 mL (50 mg/mL)
For IV (no infusion) or IM Use
5 mL Single Dose Vial
Rx Only

Each mL contains phenytoin sodium 50 mg, propylene glycol 0.4 mL and alcohol 0.1 mL in Water for Injection, pH 10.0-12.3; sodium hydroxide added, if needed, for pH adjustment.

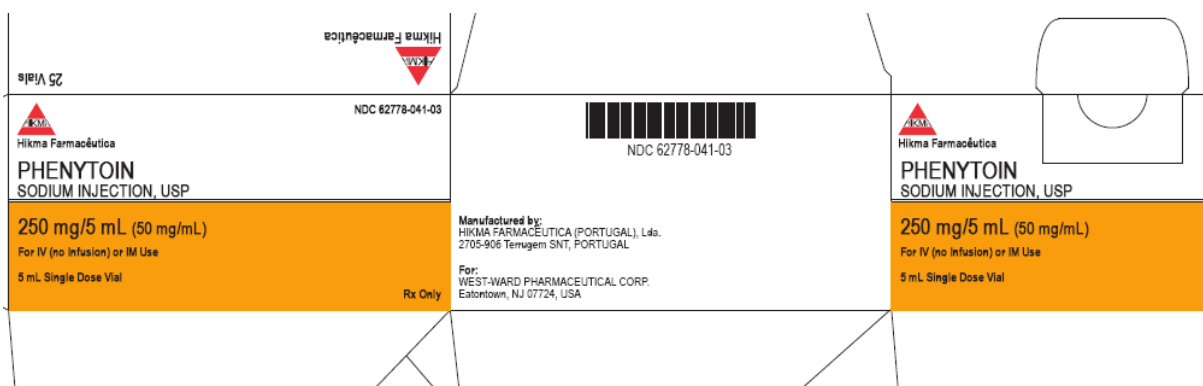
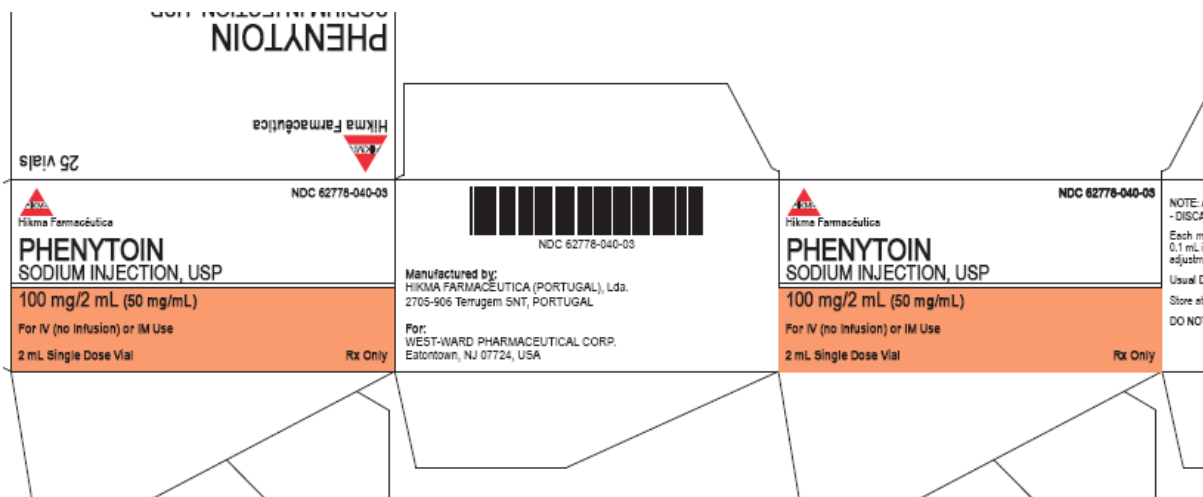
Usual Dosage: See package insert.
Store at 20° - 25°C (68° - 77°F). [See USP, Controlled Room Temperature].

HIKMA FARMACÉUTICA (PORTUGAL), Lda.
2705-905 Terrugem SNT, PORTUGAL

Iss. Nov. 2004



NDC 62778-041-01
Exp.:
Lot:



Pharmaforce : ANDA 040781

<p>5mL Single Use Vial</p> <p>PHENYTOIN SODIUM INJECTION, USP 250 mg / 5 mL (50 mg/mL) For intravenous (no infusion) or intramuscular use</p>	<p>NOTE: Administer slowly. Do not exceed 50 mg per minute intravenously. SINGLE USE - DISCARD UNUSED CONTENTS. Each mL contains phenytoin sodium 50 mg, propylene glycol 0.4 mL and alcohol 0.1 mL in Water for Injection, pH 10.0 to 12.3; sodium hydroxide added, if needed, for pH adjustment.</p> <p>USUAL DOSAGE: See package insert for complete prescribing information.</p> <p>Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. DO NOT USE IF SOLUTION IS HAZY OR HAS A PRECIPITATE.</p> <p>Rx only</p> <p>Rev. 07/07 Mfd. by: PharmaForce, Inc. Hilliard, OH 43026</p>
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2mL Single Use Vial
 Rx only

PHENYTOIN
 SODIUM INJECTION, USP

100 mg / 2 mL
 (50 mg/mL)

**For intravenous
 (no infusion) or
 intramuscular use
 Do not use if hazy
 or has a precipitate**

Mfd. by: PharmaForce, Inc.
 Hilliard, OH 43026 Rev. 07/07

25 x 5 mL Single Use Vials	Rx Only	<p>NOTE: Administer slowly. Do not exceed 50 mg per minute intravenously. SINGLE USE - DISCARD UNUSED CONTENTS.</p> <p>Each mL contains phenytoin sodium 50 mg, propylene glycol 0.4 mL and alcohol 0.1 mL in Water for Injection, pH 10.0 to 12.3; sodium hydroxide added, if needed, for pH adjustment.</p> <p>USUAL DOSAGE: See package insert for complete prescribing information.</p> <p>Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. DO NOT USE IF SOLUTION IS HAZY OR HAS A PRECIPITATE.</p> <p>Rx Only</p>
<p>PHENYTOIN SODIUM INJECTION, USP</p> <p>250 mg / 5 mL (50 mg/mL)</p> <p>For intravenous (no infusion) or intramuscular use</p> <p>Mfd. by: PharmaForce, Inc. Hilliard, OH 43026</p>		Rev. 07/07

25 x 2 mL Single Use Vials

PHENYTOIN
SODIUM INJECTION, USP

100 mg / 2 mL

(50 mg/mL)

For intravenous (no infusion) or intramuscular use

Rx only

Each contains 2mL

NOTE: Administer slowly. Do not exceed 50 mg per minute intravenously.

SINGLE USE - DISCARD UNUSED CONTENTS.

Each mL contains phenytoin sodium 50 mg, propylene glycol 0.4 mL and alcohol 0.1 mL in Water for Injection, pH 10.0 to 12.5; sodium hydroxide added, if needed, for pH adjustment.

USUAL DOSAGE: See package insert for complete prescribing information.

Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. DO NOT USE IF SOLUTION IS HAZY OR HAS A PRECIPITATE.

Rx only

Rev. 07/07

Mfg. by: Pharmforce, Inc., Hurd, OH 43026

Baxter: ANDA 084307

NDC 0641-0493-21

Phenytoin
Sodium Inj., USP

100 mg/2 mL

(50 mg/mL) **Rx only**
FOR IV (No Infusion)
OR IM USE
2 mL DOSETTE Vial
DO NOT USE IF HAZY OR
HAS A PRECIPITATE
Mfd. by Baxter Healthcare Corp.
Deerfield, IL 60015 USA
462-344-01

Lot: _____
Exp.: _____



NDC 0641-2555-41

Phenytoin
Sodium Inj., USP

250 mg/5 mL **Rx only**
(50 mg/mL)
5 mL Single Use Vial
FOR IV (No Infusion) OR IM USE

NOTE: Administer slowly. Do not exceed 50 mg per minute intravenously. SINGLE USE – DISCARD UNUSED CONTENTS. Each mL contains phenytoin sodium 50 mg, propylene glycol 0.4 mL and alcohol 0.1 mL in Water for Injection, pH 10.0-12.3; sodium hydroxide added, if needed, for pH adjustment.

Usual Dosage: See package insert. Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]. DO NOT USE IF SOLUTION IS HAZY OR HAS A PRECIPITATE.

Mfd. by Baxter Healthcare Corp.
Deerfield, IL 60015 USA
462-346-00

Lot: _____
Exp.: _____



Lot: _____
Exp.: _____

To open—Cut seal along dotted line.

NDC 0641-0493-25

Phenytoin
Sodium Injection, USP

100 mg/2 mL **Rx only**
(50 mg/mL)
FOR INTRAVENOUS (NO INFUSION)
OR INTRAMUSCULAR USE
25 x 2 mL DOSETTE Vials
Baxter
Manufactured by Baxter Healthcare Corporation
Deerfield, IL 60015 USA 462-345-01

NOTE: Administer slowly. Do not exceed 50 mg per minute intravenously.

Each mL contains phenytoin sodium 50 mg, propylene glycol 0.4 mL and alcohol 0.1 mL in Water for Injection, pH 10.0-12.3; sodium hydroxide added, if needed, for pH adjustment.

Usual Dosage: See package insert for complete prescribing information.

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]. DO NOT USE IF SOLUTION IS HAZY OR HAS PRECIPITATE.

3 0641-0493-25 9



Exp.:



To open—Cut seal along dotted line.

NDC 0641-2555-45

Phenytoin Sodium Injection, USP

250 mg/5 mL

Rx only

(50 mg/mL)

25 x 5 mL Single Use Vial
FOR INTRAVENOUS (NO INFUSION)
OR INTRAMUSCULAR USE

Baxter

Manufactured by

Baxter Healthcare Corporation

Deerfield, IL 60015 USA

462-347-00

NOTE: Administer slowly. Do not exceed
50 mg per minute intravenously.

SINGLE USE - DISCARD UNUSED CONTENTS.

Each mL contains phenytoin sodium 50 mg,
propylene glycol 0.4 mL and alcohol 0.1 mL
in Water for Injection. pH 10.0-12.3;
sodium hydroxide added, if needed, for
pH adjustment.

Usual Dosage: See package insert for
complete prescribing information.

Store at 20°-25°C (68°-77°F) [see USP
Controlled Room Temperature].

**DO NOT USE IF SOLUTION IS HAZY OR
HAS A PRECIPITATE.**



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0641-2555-45

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Appendix C: AERS Cases

Fosphenytoin

ISRNUM	CK	CSENUM	RECVDATE
3534613		6 3506805	25-Jul-00
3539680		1 4059643	2-Aug-00
3566985		0 5598625	6-Sep-00
3625660		4 3581380	11-Dec-00
3656826		5 3594214	25-Jan-01
3667856		1 5785719	21-Feb-01
3694047		0 3634958	2-Apr-01
3705939		8 3642996	17-Apr-01
3714306		2 3647121	30-Apr-01
3714520		6 3648916	1-May-01
3724369		6 3655883	#####
3732114		3 3662432	1-Jun-01
3782020		3 3703747	23-Aug-01
3788156		5 3705782	31-Aug-01
3796495		7 3713733	21-Sep-01
3800381		3 3718578	26-Sep-01
3800406		5 3718579	26-Sep-01
3800411		9 3718567	26-Sep-01
3818090		3 3726935	1-Nov-01
3847953		8 3754592	2-Jan-02
3899891		2 3783268	15-Apr-02
3912554	X	3790271	6-May-02
3953139		9 3788936	23-Jul-02
4057956		9 3906991	13-Feb-03
4077140		2 3921413	19-Mar-03
4098280		8 3621334	17-Apr-03
4099715		7 3938983	21-Apr-03
4110178		5 3946042	8-May-03
4110495		9 3946432	8-May-03
4115734		6 4059552	#####
4116400		3 3951683	#####
4116454		4 3951499	#####
4144158		0 3453874	7-Jul-03
4161238		4 3982902	4-Aug-03
4161242		6 3982797	4-Aug-03
4161576		5 3985787	4-Aug-03
4168366		8 3988686	14-Aug-03
4168463		7 3988344	14-Aug-03
4173246		8 6942020	18-Aug-03
4181125		5 3998586	4-Sep-03
4186122		1 3999878	11-Sep-03
4189624		7 4005363	11-Sep-03
4279277		1 4005145	22-Jan-04
4333671		9 4123647	6-Apr-04
4333672		0 4123648	6-Apr-04
4345207		7 4133516	20-Apr-04

4457951		1	4219738	23-Sep-04
4493978		1	5662901	4-Nov-04
4506781		0	5679380	22-Nov-04
4591669	X		5711148	18-Feb-05
4754321		3	5870273	26-Aug-05
4780432		2	5890043	26-Sep-05
4860889		9	5771076	16-Dec-05
5084280		8	6115378	17-Aug-06
5109786		4	6134752	15-Sep-06
5113338	X		6140449	20-Sep-06
5231737		2	6232254	6-Feb-07
5377760		9	6348726	3-Jul-07
5421904		7	6517769	20-Aug-07
5455656		1	6422992	13-Sep-07
5467088		0	6431104	21-Sep-07
5519067		2	6474298	14-Nov-07
5523434		0	6476822	19-Nov-07
5565304		8	6508279	18-Dec-07
5585602		1	6526944	8-Jan-08
5610687		3	6549429	31-Jan-08
5639774		0	6572520	25-Feb-08
5640646		6	6571228	26-Feb-08
5679082		5	6602685	24-Mar-08
5705875		1	6620171	14-Apr-08
5735538		8	6609234	#####
5940485		2	6808005	3-Nov-08
6220353		1	6971894	10-Jun-09
6282813		7	6984192	24-Jul-09
6332908		4	7102023	27-Aug-09

Phenytoin AERS

ISRNUM	CK	CSENUM	RECVDATE	
3487889		8	3456838	11-Apr-00
3490775		0	3463428	20-Apr-00
3524085	X		3495901	3-Jul-00
3548686		8	3440207	29-Feb-00
3606186		0	3564580	1-Nov-00
3708497		7	3631400	20-Apr-01
3746484		3	3673604	25-Jun-01
3820134	X		3728261	6-Nov-01
3852061		6	3752693	14-Jan-02
3853216		7	3748730	15-Jan-02
3873504		8	3761483	21-Feb-02
3876541		2	3730652	27-Feb-02
3892619		1	3778298	29-Mar-02
3944011		9	3805810	1-Jul-02
3955079		8	3811883	24-Jul-02
3969648		2	3837159	3-Sep-02
3993084		6	3853188	15-Oct-02

4019135		0	3827325	29-Nov-02
4020948	X		7082525	4-Dec-02
4055134		0	3904297	7-Feb-03
4061120		7	3910267	14-Feb-03
4098872		6	3938392	18-Apr-03
4118056		2	3953672	#####
4175722		0	3994610	20-Aug-03
4208566		1	4062063	22-Sep-03
4333671		9	4123647	6-Apr-04
4346237		1	3612848	26-Apr-04
4353264		7	4132199	30-Apr-04
4369839		5	4152399	#####
4400514		4	4173353	16-Jul-04
4450676		8	4213749	13-Sep-04
4493978		1	5662901	4-Nov-04
4558459		5	5723933	19-Jan-05
4592192		9	5713842	26-Feb-05
4594848		0	5722049	23-Feb-05
4618331		9	5714244	23-Mar-05
4627475		7	5774316	5-Apr-05
4696242		0	5828519	21-Jun-05
4699098		5	5830850	22-Jun-05
4731540		3	5851943	19-Jul-05
4802402		8	5905464	13-Oct-05
4816072		6	5880637	26-Oct-05
4846283		5	5936338	6-Dec-05
4879210		5	5961356	9-Dec-05
4922203	X		5760630	24-Feb-06
4967095		8	6027413	3-Apr-06
4980859	X		6022611	18-Apr-06
4996421		9	5999206	5-May-06
5026214		8	5998502	8-Jun-06
5072826		5	6105330	2-Aug-06
5074834		7	6102029	9-Aug-06
5080055		4	6112919	10-Aug-06
5082152		6	6115398	15-Aug-06
5083768		3	6110455	18-Aug-06
5086010		2	5948718	17-Aug-06
5095106		0	6106965	1-Sep-06
5128155		4	6012310	11-Oct-06
5170661		0	6202813	5-Dec-06
5222336		7	6225723	29-Jan-07
5327529		6	6314564	#####
5380831		4	6254902	6-Jul-07
5406827		1	6376648	7-Aug-07
5472087		9	6436886	25-Sep-07
5491045		1	6445588	19-Oct-07
5579054		5	6520012	28-Dec-07
5648333		5	6582154	3-Mar-08
5661211		0	6331205	12-Mar-08

5696202		7	6614786	3-Apr-08
5795570		5	6672945	30-Jun-08
5871336		2	6748631	5-Sep-08
5923034		4	6790905	18-Oct-08
5929740	X		6795791	24-Oct-08
6050101	X		6892561	21-Jan-09
6054364		6	6893906	27-Jan-09
6057096		3	6903344	26-Jan-09
6059127		3	6896988	30-Jan-09
6059139	X		6896993	30-Jan-09
6085757		9	6926362	17-Feb-09
6126522		3	6947288	20-Mar-09
6129590		8	6949682	24-Mar-09
6135234		1	6954375	27-Mar-09
6136291		9	6950816	30-Mar-09
6176074		7	6885122	1-May-09
6303662		7	7084070	7-Aug-09
6535195		7	7244252	13-Jan-10
6545370		3	7251600	21-Jan-10
6583088		1	7238698	16-Feb-10
6605217		3	7297546	26-Feb-10
6680104		3	7342725	13-Apr-10
6687958		5	7359753	20-Apr-10
6690054		4	7361294	21-Apr-10

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/s/

ANNE CRANDALL
10/01/2010

MELINA N GRIFFIS
10/01/2010

CAROL A HOLQUIST
10/01/2010