
MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration

Date: June 20, 2005
From: Eric Bastings, MD.
To: Advisory Committee
Subject: MT100

Introduction

As you know, the committee will discuss new drug application (NDA) 21-645, proposed trade name MT100 (naproxen sodium 500 mg and metoclopramide hydrochloride 16 mg) Tablets, Pozen, Inc., for the proposed indication of acute treatment of migraine headache with or without aura. The division issued a Not Approvable (NA) letter because, among other issues, Pozen did not establish the contribution of metoclopramide to the efficacy of the combination.

The main safety concern of the combination drug product is related to the risk of tardive dyskinesia associated with metoclopramide, a neuroleptic dopamine receptor antagonist, currently marketed in the US (trade name Reglan) for short-term therapy (4 to 12 weeks) of gastroesophageal reflux, only when conservative treatment fails, and for treatment of diabetic gastroparesis (2-8 weeks). The recommended dose is 5 to 20 mg four times daily. Tardive dyskinesia is a potentially permanent movement disorder, often very disabling to the patient (see below for further description). Metoclopramide is also reported to cause drug-induced parkinsonism, akathisia and acute dystonia.

Pozen presented at a post-NA action meeting in late 2004 a post-hoc analysis in which, for the subgroup of patients with no nausea at baseline, metoclopramide seems to provide a significant contribution. Efficacy only in patients with no nausea is somewhat contra-intuitive for an antiemetic drug, but the division agreed to consider that if Pozen prospectively replicates that finding, an indication of treatment of migraine in that subpopulation may be granted, if the clinical benefit outweighs the risk of tardive dyskinesia (TD) and other risks associated with the combination.

The goal of the AC meeting is to determine – before Pozen conducts an additional efficacy study - if the risk of TD with the expected use of metoclopramide in the migraine population is low enough to consider approval of MT100, for use in the subpopulation of non-nauseated migraine patients. Of note, there are a number of treatments already approved for that indication, with no limitation to a subpopulation of patients with no nausea.

It is important to emphasize that the issue we would like to discuss is to whether the risk of tardive dyskinesia is acceptable in regard to the limited efficacy of metoclopramide (which will be discussed below). The division has already taken the position that the TD

risk could be managed by labeling if a robust and significant clinical effect was demonstrated (e.g. large effect size on a clinically meaningful outcome measure, or efficacy in populations refractory to other migraine drugs). There are also two other safety issues to consider with MT100: a carcinogenic signal seen with metoclopramide in animal studies, and the vascular risk recently associated with naproxen.

Metoclopramide contribution to MT100 efficacy

My discussion here is focused on the issue of the relative contribution of metoclopramide to the efficacy of MT100. I will not discuss the issue of the efficacy of MT100 as a whole, which is not the object of the advisory meeting. The reader can find a detailed discussion of these topics in the medical and statistical reviews of MT100, and in the supervisory memoranda.

According to the combination policy [CFR 300.50 (a)], two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug. The division concluded that Pozen has not met the combination policy requirement for MT100, and has not established that both active drug components make a contribution to the claimed effects.

Two factorial studies explored the contribution of individual components to the safety and efficacy of the combination: Study MT100-301 and -304. The division agreed that both studies demonstrate a clear benefit of the combination over metoclopramide (which establishes the contribution of naproxen) for sustained headache pain response, but both studies failed to demonstrate a benefit of the combination over naproxen (which therefore failed to establish a contribution of metoclopramide).

The primary endpoint for the two factorial studies was sustained headache response (defined as moderate to severe headache pain at baseline going to no or mild pain at 2 hours which did not relapse or require rescue medication up to hour 24). Table 1 summarizes the primary endpoint results for the metoclopramide contribution to sustained pain response in the factorial studies, according to FDA analyses:

Table 1: Sustained Pain Response in MT100-301 and MT100-304

Trial	MT100 n(%)	Naproxen 500 mg n(%)	Metoclopramide contribution to MT100 response [‡]	p value
MT100-301 (n=1067)	150 (35.6%)	128 (29.8%)	5.8%	NS* (p=0.064)
MT100-304 (n=2627)	328 (31.8%)	295 (27.9%)	3.9%	NS* (p=0.063)

*NS = non significant; [‡] Metoclopramide contribution to MT100 response = MT100 response minus naproxen response.

Both studies failed to reach statistical significance for the primary endpoint analysis in the comparison of MT100 and naproxen. It is important to briefly discuss here the differences between the analyses conducted by the sponsor and those conducted by FDA. For Study 301, Pozen relied on a post-hoc “refinement analysis” (ordered logistic regression with baseline pain and investigator site as the covariates) instead of the a priori designated logistic regression. The use of the “refined” analysis led to a statistically significant difference between MT100 and naproxen ($p=0.025$). In a 3/27/00 telecon, the division notified Pozen that FDA does not agree that Study 301 is positive on its primary endpoint, “sustained response”, because Pozen performed a “refinement” to the analysis which was not prespecified, and was performed after the data were unblinded. Pozen proposed using an “almost positive” Study 301 and a positive second study to demonstrate superiority over its components and then using other trials to demonstrate efficacy over placebo. The division agreed to this approach but also reminded Pozen that the division would be looking at improvements in the secondary outcome measures of nausea, photophobia, and phonophobia in order to establish efficacy.

For Study 304, Pozen relied in the NDA on ordered logistic regression (with baseline pain and investigator site as covariates) to test MT100 versus naproxen, and MT100 versus metoclopramide. However, as discussed in detail in the FDA statistical review, the review team found that ordered logistic regression was not Pozen’s protocol specified primary method. Using the protocol specified method (extended Mantel Haenszel statistic), there was no statistically significant difference between MT100 and naproxen for sustained headache response ($p=0.063$). To further evaluate the robustness of the analysis results by the originally protocol specified method, the FDA statistician also analyzed the data by stratifying the center factor only, which is the only factor usually stratified. This led to a non significant difference between MT100 and naproxen ($p=0.09$).

In addition to the lack of a statistically significant difference between MT100 and naproxen in the factorial studies, the treatment effect size (for sustained relief) of MT100 over naproxen is very modest (4-6%), and the trend for statistical significance is probably explained by very large sample sizes (i.e. $n=2627$ in Study 304), much larger than for typical migraine studies. In that sense, the studies (and especially Study 304) were apparently overpowered. The lack of benefit of MT100 over naproxen is further supported by the fact that MT100 was not statistically different from naproxen for key symptoms at the 2-hour endpoints typically used in migraine trials (as detailed in Table 2, copied from the FDA medical officer’s review).

Table 2: Selected Secondary Endpoint Results from Trials MT100-301 and MT100-304

Parameter	MT100-301		MT100-304	
	MT100	NAP	MT100	NAP
2-hr pain response (%)	48.1	46.6 p=0.665	49.8	46.7 p=0.143
2-hr pain free (%)	18.7	14.0 p=0.053	16.8	16.0 p=0.604
2-hr Nausea (%)	23.7	26.6 p=0.333	33.7	36.7 p=0.138
2-hr Photophobia (%)	54.5	52.2 p=0.504	54.8	53.9 p=0.721
2-hr Phonophobia (%)	45.7	48.0 p=0.504	48.0	48.1 p=0.983
Sustained Nausea Free (%)	45.3	39.4 p=0.100	37.0	33.5 p=0.083
Sustained Photophobia Free (%)	32.2	29.8 p=0.409	27.9	27.0 p=0.584
Sustained Phonophobia Free (%)	35.3	30.3 p=0.174	32.3	29.3 p=0.135

Subpopulation of migraine patients with no nausea at baseline

After the division issued a Not Approvable (NA) letter on May 28, 2004, Pozen met with the division on October 6, 2004, to present arguments that the requirements of the Combination rule had been met in the two factorial studies. At that meeting, Pozen presented subgroup analyses for the population of patients with no nausea at baseline. These analyses were presented in the study protocol among several other subgroup analyses, and there was no pre-specified plan to correct for multiple comparisons, so they are considered as exploratory. I reproduce here below Pozen's results, as presented in NDA 21-465.

Table 3: Subgroup analyses in Study 301 (nausea present or absent at baseline)

Parameter	All patients		Subgroup with no nausea at baseline		Subgroup with nausea at baseline	
	MT100 (n=423)	Naproxen (n=430)	MT100 (n=231)	Naproxen (n=233)	MT100 (n=192)	Naproxen (n=197)
Sustained pain response (%)	35.6	29.8 p=0.077	38.4	28.4 p=0.009	32.2	31.5 p=0.78
2-hr pain response (%)	48.1	46.6 p=0.665	50.7	45.3 p=0.40	45.3	48.2 p=0.59

Table 4: Subgroup analyses in Study 304 (nausea present or absent at baseline)

Parameter	All patients		Subgroup with no nausea at baseline		Subgroup with nausea at baseline	
	MT100 (n=1036)	Naproxen (n=1062)	MT100 (n=342)	Naproxen (n=361)	MT100 (n=694)	Naproxen (n=701)
Sustained pain response (%)	31.8	27.9 p=0.063	36.7	26.7 p=0.004	29.6	28.5 p=0.622
2-hr pain response (%)	49.8	46.7 p=0.143	54.6	47.2 p=0.56	47.6	46.5 p=0.47

These analyses show that, in patients with no nausea at baseline, sustained pain response rates were higher for MT100 than for naproxen (again, these comparisons were not pre-specified as key primary or secondary analyses, and correction for multiple comparisons was not presented in the analysis plan). However, Table 3 and Table 4 also show that for the subgroup of patients with no nausea at baseline, 2-hour response rates were not significantly better for MT100 than for naproxen (even without correcting for multiple comparisons), so these subgroup analyses failed to establish a contribution of metoclopramide to the 2-hour response rate, which is a key migraine endpoint. Moreover, the metoclopramide contribution suggested in patients with no nausea at baseline must be mitigated against the lack of contribution in patients with nausea at baseline, where MT100 sustained pain response rates were essentially identical to naproxen response rates, and the 2-hour response rate was numerically better for naproxen than for MT100 in one study (Study 301), and similar in the second study (Study 304).

Before considering granting an indication limited to the subpopulation of migraine with no nausea at baseline, it is important to determine if this represents a meaningful indication.

In a survey of 500 self-reported migraineurs, Silberstein noted that nausea occurred in more than 90% of all migraineurs, and that nearly one third of these experienced nausea during every attack. So the Silberstein survey suggests that most migraine patients do experience nausea, with the majority of these patients only experiencing nausea for some but not all of their attacks. The survey also suggests that only a minority of patients (less than 10%) consistently have migraine with no nausea at baseline, which is the indication for which MT100 is being considered¹. The incidence of nausea at baseline in migraine trials typically varies between 45% and 80%, with usually at least half of patients nauseated. For example, in MT100 phase III studies, nausea incidence varied from 45% (MT100 group) in study MT100-301 to 69% (metoclopramide group) in study MT100-306.

If MT100 is only shown to be effective and indicated for attacks with no nausea, those patients would either need to have a separate treatment prescribed for those attacks with nausea at baseline, or would take MT100 for a condition for which metoclopramide has not demonstrated its contribution, hence they would be exposed to the risks of adverse events associated with metoclopramide without any demonstrated benefit. Some patients

¹ Silberstein SD. Migraine symptoms: results of a survey of self-reported migraineurs. *Headache*. 1995 Jul-Aug;35(7):387-96.

may also have no nausea at the time they initially seek treatment, but develop nausea later.

Tardive dyskinesia and other extrapyramidal symptoms

Tardive dyskinesia is characterized by repetitive stereotypical movements, usually more pronounced in the orolingual region. These include chewing and smacking of the mouth and lips, rolling the tongue in the mouth or pushing against the inside of the cheek, and periodic protrusion or flycatcher movements of the tongue². The predominant hypothesis for their genesis is denervation supersensitivity of the striatal dopamine receptors following chronic blockade. Risk factors for the development of TD include old age, female gender, presence of affective disorders, history of neuroleptic-induced parkinsonism, presence of organic brain disease, high-potency neuroleptics, sufficient duration of treatment with neuroleptics, and possibly the use of anticholinergic medications, previous electroconvulsive treatment, and drug holidays. Once TD has appeared, its peak severity is reached rapidly, and is often maintained. TD resolves in up to 33% of patients within 2 years after discontinuation of the offending agent³. Metoclopramide-induced tardive dyskinesia can be permanent⁴. Tardive tremor⁵ and tardive dystonia⁶ due to metoclopramide were also recently described.

The exact incidence of metoclopramide-induced tardive dyskinesia remains unclear, but movement disorder experts have stated that to prevent persistent and disabling movement disorders, long-term use of metoclopramide should be avoided⁷. No case of TD was observed in the MT100 NDA. However, rare side effects can only be expected to be observed when large populations are exposed to a drug for a sufficient period of time, and may not occur during the pre-marketing drug development program; the absence of TD cases in the MT100 NDA is not unexpected and does not eliminate the concern for TD occurrence in the post-marketing period.

Other extrapyramidal symptoms, mainly acute dystonic reactions, are reported to occur in approximately 0.2% of patients receiving oral metoclopramide at doses between 30 to 40 mg per day and in 2% of patients receiving intravenous metoclopramide. Akathisia has also been reported with metoclopramide⁸, sometime leading to a suicide attempt⁹. Dr. Prohaska noted that during the clinical development program for MT100, there were two subjects reporting acute dystonic reactions.

² Neurology in Clinical Practice, 4th Edition.

³ Textbook of Clinical Neurology. Goetz and Pappert. 1st Edition.

⁴ Jeste DV, Caligiuri MP. Tardive dyskinesia. Schizophr Bull. 1993; 19(2):303-15.

⁵ Tarsy D et al. Mov Disord 2002. 17 (3): 620-621.

⁶ Skidmore F, Reich SG. Tardive Dystonia. Curr Treat Options Neurol. 2005; 7(3):231-236.

⁷ Miller LG, Jankovic J. Metoclopramide-induced movement disorders. Clinical findings with a review of the literature. Arch Intern Med. 1989; 149:2486-92.

⁸ Akagi H, Kumar TM. Lesson of the week: Akathisia: overlooked at a cost. BMJ. 2002 22; 324(7352):1506-7.

⁹ Chow LY, Cung D, Leung V, Leung TF, Leung CM. Suicide attempt due to metoclopramide-induced akathisia. Int J Clin Pract 1997; 51: 330-331

Some of the key issues in evaluating the risk of tardive dyskinesia in the migraine population are to determine if the recommended chronic/intermittent use (up to 6 doses per month) and the relatively low dose of metoclopramide eliminate or substantially lower the risk.

Metoclopramide treatment duration before TD occurrence

Metoclopramide is approved for short-term use (12 weeks maximum) and only when conservative treatment fails (for GERD). For the migraine indication, the use of MT100 would be chronic-intermittent (i.e., episodic based on occurrence of migraine symptoms—one dose per migraine, up to 6 times per month). The risk associated with metoclopramide given as chronic-intermittent treatment is currently unknown. In this section, I will first discuss what is known of the risk of TD with chronic metoclopramide treatment, with an emphasis of chronic treatment duration before TD occurs, and then I will discuss the risk associated with chronic-intermittent treatment.

TD Risk associated with chronic treatment

The package insert for Reglan (Schwarz Pharma is the current sponsor) states that "The use of Reglan® tablets is recommended for adults only. Therapy should not exceed 12 weeks in duration". The label also warns against potential adverse side effects of the drug. With respect to tardive dyskinesia, the label says, in the "Warnings" section, that "Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with metoclopramide. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients are likely to develop the syndrome. Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase with the duration of treatment and the total cumulative dose. Less commonly, the syndrome can develop **after relatively brief treatment periods at low doses (emphasis added)**; in these cases, symptoms appear more likely to be reversible."

In a published analysis of 67 cases of metoclopramide associated tardive dyskinesia, the mean (\pm SD) length of treatment with metoclopramide before the onset of symptoms was 20 ± 15 months¹⁰, with several patients experiencing TD after short durations of treatment (2-6 months). In that study, the symptoms were still present 6 months or more after discontinuation of metoclopramide in 71% of patients on whom long-term follow-up was provided. There are also a number of reports in the literature in which TD were described after short durations of treatment (e.g. 1 week¹¹, 17 days¹², 4 months¹³).

¹⁰ Sewell DD, Jeste DV. Metoclopramide-associated tardive dyskinesia. An analysis of 67 cases. Arch Fam Med. 1992 Nov; 1(2): 271-8.

¹¹ Santos A et al. Metoclopramide Neurotoxicity, J South Carolina Med Assoc. November 1988; 542-45.

¹² Mejia NI, et al. Metoclopramide-induced Tardive Dyskinesia in an Infant, Movement Disorders 2005. 20: 86-89

¹³ Wiholm BE et al. Tardive dyskinesia associated with metoclopramide, BMJ. 1984; 228: 545-47.

FDA also reviewed the Adverse Event Reporting System¹⁴ database for cases of TD with metoclopramide. Mary Ross Southworth, PharmD, Safety Evaluator in the Division of Drug Risk Evaluation, searched AERS for cases that were coded as tardive dyskinesia, parkinsonism, akathisia, and acute dystonia (see reviews included in this briefing package). She identified 68 unique cases of metoclopramide associated-TD. In general, tardive dyskinesia associated with metoclopramide use occurred in an older population (mean age 57.2 years). The range of doses in the case series was 5 to 80 mg daily with a mean of 35 mg (within the recommended range of 20 to 80 mg daily). That range includes the proposed dose of metoclopramide in MT100 (16 mg). TD was associated with chronic treatment (mean duration of treatment 638 days). However, the distribution of treatment duration was apparently skewed because of outliers with a very long duration of treatment, since the median duration of treatment was only 180 days. The 25th percentile of duration of treatment before the occurrence of TD was only 29.5 days, which suggest that TD may occur after a relatively short duration of treatment. It is also important to emphasize that there is probably a vast underreporting of tardive dyskinesia (TD) to AERS, since TD represents a well-known adverse event of metoclopramide, already presented as a warning in labeling.

FDA also looked at the patterns of use of metoclopramide. Sigal Kaplan, Ph.D, B.Pharm, Pharmacoepidemiologist in the Division of Surveillance, Research and Communication Support, examined outpatient prescribing and drug use patterns for metoclopramide in the U.S., as well as the duration of therapy for this drug using longitudinal patient level data (this review is also included in this briefing package). She notes that over the ten-year period from 1995 to 2004, there was a two-fold increase in the number of outpatient prescriptions dispensed for metoclopramide in the U.S., to 7 million prescriptions. During the last five years, from 2000 through 2004, more than 50% of metoclopramide uses were for gastroenterology-related diagnoses. Less than 2% of use was for a migraine indication. Dr. Kaplan notes that for the majority of the patients in the study (68%), the length of cumulative therapy for metoclopramide was 1 to 30 days. The frequency of patients decreased as the total cumulative therapy for metoclopramide increased. Nonetheless, the proportion of patients who had cumulative therapy for metoclopramide for more than 6 months exceeded 10%. Dr. Kaplan concludes that physicians as well as patients did not follow the labeled recommendation for limited duration of therapy. She also concludes that a similar label recommendation for a new combination product that contains metoclopramide is not likely to be followed, especially if the product contains naproxen, which is frequently used without restrictions on duration.

Risk associated with chronic/intermittent use of metoclopramide

In her review of the FDA AERS database, Dr Southworth did not identify cases in AERS which described movement disorders after intermittent, short term use of

¹⁴ The Adverse Event Reporting System (AERS) database is a computerized repository for spontaneous reports of adverse events for both drug and therapeutic biologic products. AERS receives approximately 250,000 reports yearly. There are two primary reporter sources, pharmaceutical companies and consumers. The pharmaceutical company (predominate reporter source) who is mandated under the Code of Federal Regulations (CFR) 314.80 must submit adverse event reports to FDA that they have receive from health professionals, and consumers of which both may report directly to FDA, or have reviewed from published peer analyzed medical literature.

metoclopramide. She could not determine whether this is because this dosing regimen typically does not occur, or, if it does, whether very few adverse events have occurred (or been reported) because of it. As noted above in the outpatient prescribing pattern study, only 2% of the use of metoclopramide was for migraine. There is no current indication for chronic/intermittent use, which may explain the absence of cases in AERS. AERS does not specifically capture whether a treatment is chronic or intermittent. Dr. Southworth also noted that from the information that has been provided in the AERS reports, it is not possible to differentiate risk associated with chronic (frequent) intermittent treatment compared to chronic continuous treatment.

Two ways to appreciate the risk of TD with a recommended chronic/intermittent use are first to determine if existing clinical or preclinical data offer some clues on the risk difference compared to chronic use, and then to predict if patients will indeed follow the recommended pattern of use (chronic/intermittent). Historically, it has been observed that some part of the population is expected to exceed the recommended maximum number of monthly doses, and take the drug chronically instead.

Existing evidence regarding the risk of TD with intermittent use

Although post-marketing data do not allow us to definitely assess if intermittent use of metoclopramide is less risky than chronic use, some animal and some human data suggest that intermittent use of neuroleptics may be no safer than chronic use.

In a rat study in which animals were treated either discontinuously or continuously with haloperidol, only discontinuous treatment caused a long-lasting abnormal rise in the number of mouth movements. The authors hypothesize that a kindling-like sensitization to the dyskinetic-inducing side-effects of neuroleptic drugs may occur following intermittent antidopaminergic treatment¹⁵.

Van Harten et al. examined the association between three lifetime medication variables (cumulative amount of neuroleptics, number of interruptions in neuroleptic treatment, cumulative amount of anticholinergics) and the occurrence and severity of tardive dyskinesia¹⁶. In that study, the risk of tardive dyskinesia was three times as great for patients with more than two neuroleptic interruptions as for patients with two or fewer interruptions, and the number of interruptions in neuroleptic treatment was the second factor after the well-known risk factor of age in predicting TD. The authors argued that repeated “on-off” manipulations of some dopaminergic systems may have a greater negative impact than continuous dopaminergic activity.

¹⁵ Birte Glenthøj and Ralf Hemmingsen. Intermittent neuroleptic treatment induces long-lasting abnormal mouthing in the rat. *European Journal of Pharmacology* Volume 164, Issue 2, 19 May 1989, Pages 393-396.

¹⁶ Peter N. van Harten et al. Intermittent Neuroleptic Treatment and Risk for Tardive Dyskinesia: Curaçao Extrapryamidal Syndromes Study III. (*Am J Psychiatry* 1998; 155:565–567).

After a literature review, Goldman and Luchins also concluded that intermittent neuroleptic therapy may increase the risk of persistent tardive dyskinesia and increase dopaminergic sensitivity¹⁷.

Although the pattern of use in these psychiatric studies is different from the proposed chronic-intermittent pattern proposed in migraine, the psychiatric experience suggests that intermittent neuroleptic treatment is not necessarily safer than chronic treatment for the risk of TD.

Predicted compliance with recommended chronic-intermittent use

An important question is to predict how likely it is that migraine patients would exceed the recommended limit of six doses of MT100 per month. As Dr. Southworth noted in her review, “Although the proposed labeling for Myzan [MT100] allows for only intermittent dosing of the drug (one tablet per migraine, no second dosing, up to 6 doses per month), it is possible that patients may use the drug in a (off-label) manner similar to some other migraine treatments (chronically, for prophylaxis). The data from AERS suggests that movement disorders would be a valid risk associated with this type of treatment.”

A wealth of information is available in the literature regarding the “overuse” of acute medications by migraine patients. Recognizing the frequency of the problem, the IHS (International Headache Society) has included in its last classification¹⁸ “Medication-overuse headache” (MOH - 8.2), with, as subcategories, ergotamine-overuse headache, triptan-overuse headache, analgesic-overuse headache, opioid-overuse headache, and combination medication-overuse headache (all of these drugs are acute treatments of migraine and have recommended limits in the number of monthly doses). The IHS notes that “by far the most common cause of migraine-like headache occurring on ≥ 15 days per month and of a mixed picture of migraine-like and tension-type-like headaches on ≥ 15 days per month is overuse of symptomatic migraine drugs and/or analgesics”.

The issue of medication-overuse headache was recently reviewed by Diener and Limmroth¹⁹. They note that epidemiological data suggest that up to 4% of the population overuse analgesics and other drugs for the treatment of pain conditions such as migraine and that about 1% of the general population in Europe, North America, and Asia have MOH. Bigal, Lipton et al.²⁰ note that “Studies suggest that a substantial proportion of headache sufferers presenting to headache clinics may overuse acute medications”. Gladstone and Dodick²¹ note that “Chronic daily headache (CDH) is a significant public

¹⁷ Morris B. Goldman and Daniel J. Luchins. Intermittent Neuroleptic therapy and Tardive Dyskinesia: A Literature Review. *Hospital and Community Psychiatry*, 1984; 35:1215-1219.

¹⁸ The International Classification of Headache Disorders. 2nd Edition. *Headache Classification Subcommittee of the International Headache Society*. *Cephalalgia* 2004; Vol 24.

¹⁹ Diener HC, Limmroth V. Medication-overuse headache: a worldwide problem. *Lancet Neurol.* 2004; 8: 475-83.

²⁰ Bigal ME, Rapoport AM, Sheftell FD, Tepper SJ, Lipton RB. Transformed migraine and medication overuse in a tertiary headache centre--clinical characteristics and treatment outcomes. *Cephalalgia.* 2004; 24: 483-90.

²¹ Gladstone J, Eross E, Dodick D. Chronic daily headache: a rational approach to a challenging problem.

health problem with 3 to 5% of the population worldwide experiencing daily or near-daily headaches”, and that “Medication overuse is common in patients with CDH who present to physicians.” Silberstein and Liu²² note that “Medication overuse-induced headache represents one of the most common iatrogenic disorders. It is the reason that most patients visit headache subspecialty clinics worldwide and often is the cause of an intractable or worsening headache in primary headache sufferers.” Pascual et al.²³ note that around 40% of patients attending a specialized headache clinic meet CDH diagnostic criteria, and that 80% of these overuse symptomatic medications. Since MT100 includes an analgesic as one of its components, it is not unreasonable to suggest that the drug could be overused by part of the migraine population exposed to it, as so many other acute migraine drugs are in the US and abroad.

Carcinogenicity

Pozen was required to conduct a rat carcinogenicity study to support approval of MT100. MT 100 caused increased incidences of mammary tumors, adrenocortical tumors, pheochromocytomas, and pancreatic islet cell tumors. Pozen postulated that all of these tumors result from the increased levels of prolactin known to be produced by metoclopramide, but we believe that there are inadequate data to support this assertion, with the possible exception of mammary tumors. The pivotal type of study needed to test the proposed mechanism, i.e. determining if interfering with the mechanism prevents the tumor increase, was not performed.

Even if prolactin as a mechanism is accepted, there is no evidence that it would not be operative in humans. Most dopamine-blocking antipsychotic drugs produce mammary tumors in rodents but as a class are not thought to produce mammary tumors in humans. However, a more recent study suggests a small but significant risk of breast cancer with dopamine antagonists in the human²⁴. Metoclopramide increases prolactin at therapeutic doses in humans, and is cited as the galactagogue (medications that aid in initiating and maintaining adequate milk production) of choice²⁵.

We have concluded that the increase in tumors by MT 100 in the rat study is presumably due to metoclopramide. Assuming a non-genotoxic mechanism, however, there is a somewhat reasonable safety margin with respect to expected human plasma levels (except for female mammary tumors, where there was no clear no effect level established). However, if prolactin is indeed the cause of the tumors, its levels are increased by therapeutic doses of metoclopramide. On the other hand, the proposed

Semin Neurol. 2003; 23(3): 265-76.

²² Silberstein SD, Liu D. Drug overuse and rebound headache. *Curr Pain Headache Rep.* 2002;6(3):240-7.

²³ Pascual J, Colas R, Castillo J. Epidemiology of chronic daily headache. *Curr Pain Headache Rep.* 2001(6):529-36.

²⁴ Wang PS, et al. Dopamine antagonists and the development of breast cancer. *J. Arch Gen Psychiatry.* 2002 Dec; 59(12): 1147-54.

²⁵ Gabay MP. Galactogogues: medications that induce lactation. *J Hum Lact.* 2002; Aug; 18(3): 274-9.

human administration will be intermittent, which lowers the risk for a non-genotoxic carcinogen (with the caveat that some patients will probably use the drug chronically even if labeling recommends intermittent use). Also, it must be noted that several other migraine drugs have carcinogenicity findings described in the labeling.

Vascular risk

Based on a review of available data from long-term placebo- and active-controlled clinical trials of non-steroidal anti-inflammatory drugs (NSAIDs), the Food and Drug Administration has concluded that an increased risk of serious adverse cardiovascular (CV) events may be a class effect for NSAIDs (excluding aspirin). The Food and Drug Administration issued in June 2005 supplemental request letters to sponsors of all non-steroidal anti-inflammatory drugs (NSAID) requesting that they make labeling changes to their products. These letters include recommended proposed labeling for both the prescription and over-the-counter (OTC) NSAIDs and a medication guide for the entire class of prescription products. All sponsors of marketed prescription Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have been asked to revise the labeling (package insert) for their products to include a boxed warning, highlighting the potential for increased risk of cardiovascular (CV) events and the well described, serious, potential life-threatening gastrointestinal (GI) bleeding associated with their use.

Questions for the Committee

1. All currently approved acute treatments of migraine are indicated without restriction regarding the presence or absence of nausea at baseline. Does an indication limited to the subpopulation of migraine patients with no nausea at baseline represent a clinically meaningful and acceptable indication? Is the subpopulation of patients with no nausea at baseline a well defined population?
2. Is there sufficient evidence that the chronic-intermittent administration of metoclopramide does not carry the same risk of tardive dyskinesia as the chronic administration?
-If yes, what is the maximum recommended number of monthly doses to avoid the risk of tardive dyskinesia?
3. Do you believe that, based on the existing data on medication-overuse headache, there is evidence that a proportion of patients prescribed MT100 will likely take a number of monthly doses higher than recommended?
4. In a September 10, 2004 amendment to NDA 21-645, Pozen estimated an incidence of tardive dyskinesia of 0.002% or less for persons taking MT100 according to label. For a US migraine population in excess of 28,000,000 patients, MT100 marketing would lead to up to 20 cases of tardive dyskinesia per million patients prescribed the drug (without consideration to the increased risk in patients overusing the drug). Is that risk acceptable if the only benefit demonstrated is a less than 6% improvement on sustained headache relief, with no benefit on acute relief, relapse rate, and use of rescue medication?

5. If Pozen confirms prospectively in a clinical study a statistically significant improvement in sustained headache pain relief of the magnitude seen in earlier trials (i.e. 4-6%), with no effect on typical 2-hours outcome measures (pain, nausea, photophobia, phonophobia), and no effect on relapse rate or rescue medication use in the 2-24 hour period, limited to the subpopulation of patients with no nausea at baseline, would the demonstrated benefit outweigh the risks related to tardive dyskinesia?
 - If no, what additional data (or desired primary outcome, or desired effect on sustained pain relief) are needed to provide evidence of safety and efficacy?

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