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

**Pediatric Postmarketing Pharmacovigilance Review**

| | |
|---|---|
| **Date:** | January 23, 2017 |
| **Safety Evaluator:** | Office of Surveillance and Epidemiology<br>Page Crew, PharmD, MPH, BCPS<br>Division of Pharmacovigilance II |
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| **Product Name:** | Aleve PM® (naproxen sodium 220 mg and diphenhydramine hydrochloride 25 mg) |
| **Pediatric Labeling Approval Date:** | January 17, 2014 |
| **Application Type/Number:** | NDA205352 |
| **Applicant/Sponsor:** | Bayer HealthCare, LLC |
| **OSE RCM #:** | RCM 2016-1631 |

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## EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA), the Division of Pharmacovigilance (DPV) within the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports for Aleve PM (diphenhydramine hydrochloride 25 mg and naproxen sodium 220 mg) in pediatric patients. This pharmacovigilance review was triggered by PREA for the original approval of Aleve PM for "use in adults and children 12 years and older."

Aleve PM was approved on January 17, 2014 for over-the-counter (OTC) use in patients ages 12 and over. The medication has two indications: "for relief of occasional sleeplessness when associated with minor aches and pains" and "helps you fall asleep and stay asleep". The safety of Aleve PM in children under age 12 has not been established.

For the purpose of this review, DPV searched the FDA Adverse Event Reporting System (FAERS) database for adverse event reports associated with Aleve PM in all patients. DPV identified six non-serious pediatric cases. There were no deaths associated with the use of Aleve PM.

Five of the six cases describe unintentional exposure to Aleve PM in children under the age of 12. Four of the five cases contain the PT "*Accidental exposure to product*" or "*Accidental exposure to product by child*". The fifth case contains the PT "*Product use issue*", but upon further review was determined to be a possible unintentional exposure case. Two cases note that the child opened the bottle independently (ages 22 months and two years). Because factors other than type of container closure system can impact access to medication by children (e.g., incorrect closure of a child resistant cap), it is challenging to draw conclusions from this limited information. None of the five cases contained information on the outcome after the unintentional exposure to Aleve PM. DPV did not identify any safety signals given the limited information provided within these five cases.

The sixth pediatric adverse event case in the case series reported incorrect drug administration duration in a 14 year old male with a past medical history of autism and "sleep issue". The reporter stated the patient was using Aleve PM every night. The start date of Aleve PM is listed in the report as 2014, and the FAERS report was received by FDA on January 30, 2015, but the total duration of therapy by the patient was not expressly stated in the narrative. No information on outcome was provided. DPV did not identify a safety signal given the limited information provided within this case.

Overall, DPV did not identify any safety signals or pediatric safety concerns during review of this pediatric post-marketing case series. DPV will continue routine pharmacovigilance monitoring of Aleve PM.

# 1 INTRODUCTION

## 1.1 PEDIATRIC REGULATORY HISTORY

Aleve PM (diphenhydramine 25 mg and naproxen sodium 220 mg) was approved on January 17, 2014 under NDA 205352 for over-the-counter (OTC) use in pediatric patients ages 12 and over for 1) relief of occasional sleeplessness when associated with minor aches and pains and 2) helps you fall asleep and stay asleep. This pharmacovigilance review was triggered by the Pediatric Research Equity Act (PREA) for the original approval of Aleve PM for "use in adults and children 12 years and older." The drug facts label directs adults and children 12 years and older to take two caplets at bedtime. The safety of Aleve PM in children under age 12 has not been established.[1]

### Pediatric Research Equity Act (PREA) Requirements

In the Aleve PM approval letter[2], the Division of Nonprescription Clinical Evaluation (DNCE) addressed PREA requirements stating, "We are waiving the pediatric study requirement for age birth to less than 12 years because there is evidence suggesting that the drug product would be ineffective and unsafe in this population. This is because insomnia does not routinely occur in children except when it is associated with other disorders. A waiver is not required for adolescents aged 12 to 17 years because the product is labeled for use in this population." The sponsor provided data for use in pediatric patients ages 12 and over in the Aleve PM NDA.[3]

### Clinical Trials for Aleve PM in Pediatric Patients, Ages 12 - 17

On January 16, 2014, the Division Director of DNCE completed a Summary Review of Aleve PM. In total, 243 subjects between the ages of 12-17 years were enrolled in Aleve PM clinical trials.[3] None of the study participants were younger than 12 years of age. Of note, due to the overall small number of pediatric subjects in the clinical trials, the sponsor did not conduct a subgroup analysis of safety among children ages 12 to 17. Per the Division Director of DNCE Summary Review, "Efficacy was demonstrated in adolescents, with significant benefit on both sleep latency and WASO [wake after sleep onset]. The age distribution of adolescent patients is primarily in the 16 and 17 year old age groups, with very few patients enrolled in the younger age groups. However, based on the age range for diphenhydramine under the monograph for sleep aids and the age range down to 12 years for other approved OTC naproxen products (Aleve), it is appropriate to approve this combination product for the same age range."[4]

**Table 1.1.1 Number of Pediatric Subjects by Age in the Clinical Studies**

| | Number of Subjects Enrolled | | | | |
|---|---|---|---|---|---|
| **Age (years)** | **Study 13053** | **Study 14837** | **Study 15881** | **Study 15560** | **Total** |
| 17 | 37 | 56 | 19 | 2 | 114 |
| 16 | 35 | 59 | 13 | 0 | 107 |
| 15 | 0 | 0 | 6 | 2 | 8 |
| 14 | 0 | 0 | 5 | 1 | 6 |
| 13 | 0 | 0 | 4 | 1 | 5 |
| 12 | 0 | 0 | 2 | 1 | 3 |
| Total | 72 | 115 | 49 | 7 | **243** |

Adapted from Yang L. Aleve PM Cross Discipline Team Leader Review (Application number: 205352Orig1s000). U.S. Food and Drug Administration. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205352Orig1s000CrossR.pdf. Accessed on December 16, 2016

| Table 1.1.2 Number of Pediatric Subjects by Study Treatment in the Clinical Studies | | | | | |
|---|---|---|---|---|---|
| | Number of Subjects | | | | |
| Study Treatment | Study 13053 | Study 14837 (Pivotal) | Study 15881 (Pivotal) | Study 15560 (Multi-Dose) | Total |
| NP 440 / DPH 50 | 13 | 28 | - | 3 | 44 |
| NP 440 / DPH 25 | - | - | 22 | - | 22 |
| NP 220 / DPH 50 | 12 | 31 | - | - | 43 |
| NP 440 alone | 10 | 36 | 16 | - | 62 |
| DPH 220 alone | 8 | - | - | - | 8 |
| DPH 50 alone | 13 | 20 | 11 | - | 44 |
| Advil PM | 16 | - | - | - | 16 |
| Placebo | 0 | - | - | 4 | 4 |
| Total | 72 | 115 | 49 | 7 | **243** |

NP = Naproxen, DPH = diphenhydramine

Adapted from Yang L. Aleve PM Cross Discipline Team Leader Review (Application number: 205352Orig1s000). U.S. Food and Drug Administration. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205352Orig1s000CrossR.pdf. Accessed on December 16, 2016

The Division Director of DNCE Summary Review also summarized clinical safety data. Overall, this safety data did not highlight any safety issues that were unique to the pediatric population relative to the adult population.[4] The review states:

"As an NSAID, this product is expected to have the typical class effects of GI bleeding risk, cardiovascular risk (anti-platelet effects), hepatic and renal effects. The Drug Facts label will carry standard warnings and will be consistent with that for Aleve."

The Medical Review[5] from January 10, 2014, also provided further data from the Poison Control Centers regarding diphenhydramine (DPH) overdosage in pediatric patients:

- More than half of all DPH exposures (52+34717+113331, 53.4%) occurred in children under the age of 13. In the pediatric age ranges up to 13 years, there was an approximately equal distribution of females and males, whereas in all older age ranges females outnumbered males in approximately the ratio 1.7:1 (63% female, 37% male).
- The route of exposure was oral ingestion in 98.9% of reports. The majority of cases involved exposure to a single substance (71.6%, 198,583/277,322), whereas 17.8% (49,357/277,322) involved two substances and 10.6% (29,382/277,322) involved three or more substances. Single substance exposures predominated in all age ranges and in both genders.
- Unintentional exposures accounted for 39.5% of reports (109481/277322) and were the largest category, followed by Intentional – Suspected suicide (25.7%, 71202/277322) and Unintentional – therapeutic error (22.8%, 63103/277322).
- The reasons for exposure depended on age, where unintentional exposures were more frequent for infants and children, while intentional and suspected suicide reports accounted for the majority of reports for adolescents and adults.
- There were 346 reported deaths, including one death in a neonate less than one month of age, eight deaths among children age one month to less than two years, six deaths among children age two years to less than 13 years, and seven deaths among children age 13 years to less than 18 years .

**FDA Section 915 Non-New Molecular Entity Postmarket Safety Summary**

On March 9, 2016, the Division of Nonprescription Drug Products (DNDP) within the Office of New Drugs (OND) and DPV within OSE completed an FDA Section 915 Non-New Molecular Entity Postmarket Safety Summary of Aleve PM.[6] The review identified the possible intentional misuse of Aleve PM for sleeplessness without pain, resulting in inappropriate exposure to nonsteroidal anti-inflammatory drugs (NSAIDs). OSE's Division of Medication Error Prevention and Analysis (DMEPA) reviewed the reports of medication errors associated with Aleve PM and concluded that "sleeplessness without pain…could be intentional misuse or consumers neglecting to mention pain when reporting adverse events or medication errors." FDA is currently working with Bayer Healthcare to collect additional data about the use of this product for sleeplessness to evaluate if regulatory action would be useful to prevent intentional misuse.[7]

## 1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

Aleve PM carries the following labeled safety warnings[1]:

**Warnings**

**Allergy alert**
Naproxen sodium may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:

- hives
- facial swelling
- asthma (wheezing)
- shock
- skin reddening
- rash
- blisters

If an allergic reaction occurs, stop use and seek medical help right away.

**Stomach bleeding warning**
This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if you:

- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others)
- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed

**Do not use**

- if you have ever had an allergic reaction to any other pain reliever/fever reducer
- unless you have time for a full night's sleep
- in children under 12 years of age
- right before or after heart surgery

- with any other product containing diphenhydramine, even one used on skin
- if you have sleeplessness without pain

**Ask a doctor before use if**

- stomach bleeding warning applies to you
- you have problems or serious side effects from taking pain relievers or fever reducers
- you have a history of stomach problems, such as heartburn
- you have high blood pressure, heart disease, liver cirrhosis, kidney disease, or asthma
- you are taking a diuretic
- you have a breathing problem such as emphysema or chronic bronchitis
- you have glaucoma
- you have trouble urinating due to an enlarged prostate gland

**Ask a doctor or pharmacist before use if you are**

- taking sedatives or tranquilizers, or any other sleep-aid
- under a doctor's care for any serious condition
- taking any other antihistamines
- taking any other drug

**When using this product**

- drowsiness will occur
- avoid alcoholic drinks
- do not drive a motor vehicle or operate machinery
- take with food or milk if stomach upset occurs
- the risk of heart attack or stroke may increase if you use more than directed or for longer than directed

**Stop use and ask a doctor if**

- you experience any of the following signs of stomach bleeding:
    - feel faint
    - vomit blood
    - have bloody or black stools
    - have stomach pain that does not get better
- pain gets worse or lasts more than 10 days
- sleeplessness persists continuously for more than 2 weeks. Insomnia may be a symptom of a serious underlying medical illness.
- redness or swelling is present in the painful area
- any new symptoms appear
- you have difficulty swallowing
- it feels like the pill is stuck in your throat

**If pregnant or breastfeeding,** ask a health professional before use. It is especially important not to use naproxen sodium during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

**Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away.

# 2 DRUG UTILIZATION DATA

Because Aleve PM is available OTC and there is no accurate accounting of OTC product purchases, drug utilization data is not included in this review.

# 3 POSTMARKET ADVERSE EVENT REPORTS

## 3.1 METHODS AND MATERIALS

### 3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategies described in Table 3.1.1.1. See Appendix A for a description of the FAERS database.

***Table 3.1.1.1 FAERS Search Strategy***

| | Search 1 | Search 2 |
|---|---|---|
| Date of Search | 11/15/16 | 11/15/16 |
| Time Period of Search | 01/17/14* - 11/15/16 | 01/17/14* - 11/15/16 |
| Search Type | FBIS Quick Query | Profile – Manufacturer Summary |
| Product Name(s) | Product Name: Aleve PM<br>NDA: 205352<br>Product Active Ingredient: Diphenhydramine sodium/Naproxen sodium | Product Name: Aleve PM<br>Product Active Ingredient: Diphenhydramine sodium/Naproxen sodium |
| Search Parameters | All ages, all outcomes, worldwide | All ages, all outcomes, worldwide |

* *U.S. approval date and approval date of pediatric labeling*

## 3.2 RESULTS

### 3.2.1 Total number of FAERS reports by Age

***Table 3.2.1.1 Total Adult and Pediatric FAERS Reports with Aleve PM, Received by FDA from January 17, 2014 to November 15, 2016***

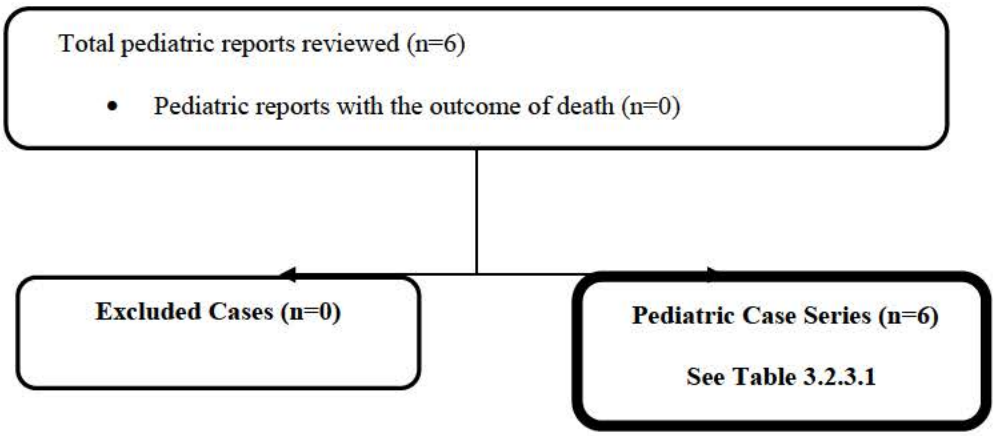
| | All reports (US) | Serious* (US) | Death (US) |
|---|---|---|---|
| **Adults (≥ 17 years)** | 577 (576) | 31 (30) | 0 (0) |
| **Pediatrics (0 - <17 years)** | 6 (6) | 0 (0) | 0 (0) |

***** *For the purposes of this review, the following outcomes qualify as serious:* ***death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.***

### 3.2.2 Selection of Pediatric Cases in FAERS

We identified six pediatric cases (See Table 3.2.1.1), all of which were non-serious. See **Figure 3.2.2.1** below for the specific selection of cases to be summarized in **Sections 3.3 and 3.4.**

***Figure 3.2.2.1 Selection of Pediatric Cases with Aleve PM***




### *3.2.3 Characteristics of Pediatric Case Series*

Appendix B lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the Pediatric Case Series.

***Table 3.2.3.1 Characteristics of Pediatric Cases reported with Aleve PM, received by FDA between January 17, 2014 to November 15, 2016 (N=6)***

| | | |
|---|---|---|
| Age | 0 - < 1 month | 0 |
| | 1 month - <2 years | 2 |
| | 2- < 6 years | 1 |
| | 6- <12 years | 2 |
| | 12- < 17 years | 1 |
| Sex | Male | 3 |
| | Female | 3 |
| Country | United States | 6 |
| Reported Reason for Use | Sleep Disorder Therapy | 1 |
| | Possible Unintentional Exposure | 5 |

## 3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=0)

There were no pediatric deaths identified in the case series.

### 3.4 SUMMARY OF PEDIATRIC UNLABELED ADVERSE EVENT CASES (N=6)

#### 3.4.1 Unintentional Exposure to Product (N=5)

*PT Accidental exposure to product, Accidental exposure to product by child, Product use issue*

Five of the cases[a] describe possible unintentional exposure to Aleve PM by a pediatric patient under the age of 12. All five patients ingested Aleve PM via oral route as the single medication on one occasion. Four patients consumed one pill or a partial pill, and one patient consumed "one or two" pills.

Four of the five cases contain the PT "*Accidental exposure to product*" or "*Accidental exposure to product by child*". The fifth case[b] contained the PT "*Product use issue*". This "product use issue" case has the same reporter as one of the "accidental exposure to product by child" cases[c]. The patient demographics for these two cases are unique so they are not duplicate reports, but they were received by FDA on the same day. In the "product use issue" case the reporter identifies the patient as her child, and in the "accidental exposure to product by child" case the same reporter identifies a second patient as her niece. Therefore, the fifth case labeled as a "product use issue" is a possible case of unintentional exposure as well.

Two of the unintentional exposure cases note that the child opened the bottle independently (ages 22 months and two years).[d] The case of the 22 month old patient also noted the PT "*Medication residue present*" as the reporter noted the child's mouth was the color blue like the caplet, and "*Failure of child resistant mechanism for pharmaceutical product*". The other three cases did not mention how the child accessed the medication. Aleve PM is available in containers with "Easy Open" or "Soft Grip" caps. The "Soft Grip" cap is child resistant whereas the "Easy Open" cap is *not* child resistant.[8] Lot numbers were provided for all five cases (see Appendix B).

Because factors other than type of container closure system can impact unintentional access to medication by children (e.g., incorrect closure of a child resistant cap), it is challenging to draw conclusions from this limited information. None of the five reports contained information on the outcome after the unintentional exposure to Aleve PM. Given the limited information within these five case reports, no safety signal was identified.

#### 3.4.2 Intentional Misuse (N=1)

*PT Incorrect drug administration duration*

One case[e] reported the PTs "*Incorrect drug administration duration*" and "*Medication error*" in a 14 year old male with a past medical history of autism and "sleep issue". Per the reporter (patient's grandmother), the patient was taking two caplets of Aleve PM "every night…as a sleep aid". The start date of Aleve PM is listed in the report as 2014, and the FAERS report was received by FDA on January 30, 2015, but the total duration of therapy by the patient was not

[a] FAERS Cases ID #s for Possible Unintentional Exposure: 10655533, 11366010, 11366010, 11786941, 11865710
[b] FAERS Cases ID # for "Product Use Issue" PT: 11366011
[c] FAERS Case ID # for same reporter as case 11366011: 11366010
[d] FAERS Case ID #s for two cases in which child opened bottle independently: 11865710, 11786941
[e] FAERS Case ID # for "Incorrect Drug Administration Duration": 10751655

expressly stated in the narrative. No other information on outcomes or total duration of therapy was provided. The Aleve PM labeling directs patients to stop use if sleeplessness persists continuously more than two weeks. Given the limited information within this case report, no safety signal was identified.

## 4 DISCUSSION

Of the six pediatric cases reviewed, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with Aleve PM in the pediatric population. All six cases described non-serious adverse events. Five of the six cases were possible unintentional exposures in patients under the age of 12. One case described possible intentional misuse involving a 14 year old patient using Aleve PM every night, possibly for a longer duration than directed. FDA is currently working with Bayer Healthcare to collect additional data about the use of this product for sleeplessness to evaluate if regulatory action would be useful to prevent intentional misuse.

## 5 CONCLUSION

There is no evidence from these data indicating pediatric safety concerns with Aleve PM at this time.

## 6 RECOMMENDATIONS

Continue routine pharmacovigilance monitoring for Aleve PM.

## 7 REFERENCES


1. Aleve PM (naproxen sodium/diphenhydramine hydrochloride) [package insert]. Morristown, NJ: Bayer Heathcare LLC; 2014. Available at http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process. Accessed on December 16, 2016.
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# 8 APPENDICES

## 8.1 APPENDIX A FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

**FDA Adverse Event Reporting System (FAERS)**

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

## 8.2 APPENDIX B. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH DRUG (N=6)

| Case | FAERS Case Number | FAERS Version Number | Manufacturer Control Number | Lot Number | Expiration Date | Bottle Quantity Count |
|---|---|---|---|---|---|---|
| 1 | 10655533 | 1 | US-BAYER-2014-184910 | NAA2T9T | June 2016 | 20 |
| 2 | 10751655 | 1 | US-BAYER-2015-014094 | Not reported | Not reported | Not reported |
| 3 | 11366010 | 1 | US-BAYER-2015-397998 | NAA2ET8* | October 2015 | 20 |
| 4 | 11366011 | 1 | US-BAYER-2015-398134 | NAA2ET8* | October 2015 | 20 |
| 5 | 11786941 | 1 | US-BAYER-2015-471036 | NAA3666 | October 2016 | 80 |
| 6 | 11865710 | 2 | US-BAYER-2015-495176 | NAA38D6 | December 2016 | 80 |
| *same reporter for both reports | | | | | | |

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