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:	November 13, 2017
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Product Name(s):	Treximet® (naproxen sodium; sumatriptan succinate)
Pediatric Labeling Approval Date:	May 14, 2015
Application Type/Number:	NDA # 021926
OSE RCM #:	2017-1560

Acknowledgement:

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated all U.S. postmarketing adverse event reports for Treximet in pediatric patients.

FDA first approved Treximet on 4/15/2008 for the acute treatment of migraine with or without aura in adults. FDA approved Treximet on 5/14/2015 for the acute treatment of migraine with or without aura in pediatrics age 12 to 17 years old.

We identified three U.S. pediatric cases with Treximet from a search of the FDA Adverse Event Reporting System (FAERS) database covering the period 2/1/2013 to 7/31/2017. These three cases did not reveal any new safety signals and there were no deaths. One case reported a congenital anomaly, hypospadias, in a male. Hypospadias was unlikely related to Treximet because his epileptic mother was also taking several antiepileptic medications during pregnancy; hypospadias with antiepileptics has been reported in the literature. In addition, hypospadias is a common male genital malformation occurring at a rate of 0.3 – 7 in 1000 live births.

Although the remaining two cases did not report adverse drug reactions, the reported events potentially impact product integrity and patient health outcomes. One case inquired about crushing the Treximet film-coated tablet for easier oral administration. The current product label advises to avoid damaging the tablet's matrix, i.e. crushing, splitting, or chewing. The patient was noted to be 11-years-old; however, Treximet is currently approved for use in pediatrics ages 12 – 17 years. The other case reported Treximet for the treatment of "cluster migraines," and mentioned its use as "off-label." It remains unclear if the reporter meant cluster headaches. Nonetheless, Treximet is approved for acute migraine headaches, but not cluster headaches.

We will continue routine postmarketing pharmacovigilance of Treximet in the adult and pediatric populations.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

FDA approved Treximet on 4/15/2008 under NDA 021926 for the treatment of migraine with or without aura in adults. Treximet is a combination of sumatriptan, a serotonin (5-HT) 1b/1d receptor agonist (triptan), and naproxen sodium, a non-steroidal anti-inflammatory drug (NSAID). The recommended adult dosage is a single tablet of Treximet (85/500 mg) containing 85mg of sumatriptan succinate and 500mg of naproxen sodium in a film coated tablet formulation. The maximum recommended adult dosage is two tablets in a 24-hour period.

FDA approved Treximet on 5/14/2015 for the acute treatment of migraine with or without aura in pediatrics age 12 to 17 years old. The recommended dosage in pediatric patients 12 to 17 years of age is a single tablet of Treximet (10/60 mg) containing 10 mg of sumatriptan succinate and 60 mg of naproxen sodium. The maximum recommended pediatric dosage is one tablet (85/500 mg) of Treximet in a 24-hour period.

As a 505 (b) (2) application, Treximet relies on data from NDA 020132 (Imitrex) and NDA 018164 (Anaprox DS Tablets). This sNDA was submitted to fulfill the requirement for pediatric studies under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c; issued 4/15/2008) and the Written Request (WR) for Pediatric studies (originally issued 6/29/2007 and updated/amended August 2014). At approval on 4/15/2008, pediatric studies in the 0-6 year age group were waived (as it was thought that such studies were highly impossible or impractical to conduct) and studies in the 6 to17 year age group were deferred (until the older 12 to17 years safety and efficacy data was collected). Based on the likelihood that there was general comparability between the adolescent and adult population, the findings in adults that demonstrated sufficient safety served as the basis for studies to be initiated in the adolescent age group without the need for other data.

Therefore, pursuant to PREA and WR, the Sponsor was required to conduct the following studies as a Postmarketing Requirement for the acute treatment of migraine in adolescents 12 to 17 years of age with a history of migraine headaches:

- Study 1: Adolescent Pharmacokinetic Study- was an open-label, randomized, parallel group PK study conducted in *24 adolescents* migraineurs (outside an attack) and in *26 healthy adults* to compare exposure of sumatriptan and naproxen following single-dose administration of Treximet tablets at three doses (10/60 mg, 30/180 mg and 85/500 mg.

- Study 2: (Pivotal) Adolescent Efficacy (and Safety) Study- was a multicenter (US only), outpatient, double-blind, randomized, placebo-controlled, parallel group

study of non-responders to placebo in adolescent migraineurs 12 to 17 years of age.

- Study 3: Adolescent Long-Term Safety Study- This was a Phase IIIB long-term safety study of Treximet for the Treatment of Migraine in Adolescents conducted in the US across 70 centers between 13-Jul-2007 – 20-Aug-2009. This study was a prospective, open-label, single-arm, multicenter, outpatient investigation in which adolescent migraineurs (aged 12 to 17 years) were asked to treat each of their migraine attacks with the Treximet for a period of up to 12 months. A minimum of 200 subjects for at least 6 months, and a minimum of 75 subjects for 12 months were required to be evaluated. Subjects returned to the clinic at 3 month intervals for interim safety evaluations.

The safety and efficacy of Treximet for the acute treatment of migraine in pediatric patients 12 to 17 years of age was established in a double-blind, placebo-controlled trial. No patients who received Treximet experienced adverse reactions leading to withdrawal from the trial. The incidence of adverse reactions in pediatric patients 12 to 17 years of age was comparable across all 3 doses (i.e., 10/60 mg, 30/180 mg, or 85/500 mg) compared with placebo. The most common adverse reactions at a frequency ≥ 2% with Treximet than placebo were hot flush (i.e., hot flash[es]) and muscle tightness.[1]

1.2 HIGHLIGHTS OF TREXIMET[2] LABELED SAFETY ISSUES

----------CONTRAINDICATIONS----------

- None

----------WARNINGS AND PRECAUTIONS----------

- Cardiovascular Thrombotic Events
- Gastrointestinal Bleeding, Ulceration, and Perforation
- Arrhythmias
- Chest, Throat, Neck, and/or Jaw Pain/Tightness/Pressure
- Cerebrovascular Events
- Other Vasospasm Reactions
- Hepatotoxicity
- Hypertension
- Heart Failure and Edema
- Medication Overuse Headache
- Serotonin Syndrome
- Renal Toxicity and Hyperkalemia
- Anaphylactic Reactions

- Serious Skin Reactions
- Premature Closure of the Ductus Arteriosus
- Hematologic Toxicity
- Exacerbation of Asthma Related to Aspirin Sensitivity
- Seizures
- Masking of Inflammation and Fever
- Laboratory Monitoring

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy
- Labor and Delivery
- Nursing Mothers
- Pediatric Use (Safety and effectiveness of Treximet in pediatric patients under 12 years of age have not been established.)
- Geriatric Use
- Renal Impairment
- Hepatic Impairment

1.2.1 Diagnoses Associated with Use

Treximet is indicated for the acute treatment of migraine with or without aura in adults and pediatric patients 12 years of age and older.

Limitations of Use:

- Use only if a clear diagnosis of migraine headache has been established. If a patient has no response to the first migraine attack treated with Treximet, reconsider the diagnosis of migraine before Treximet is administered to treat any subsequent attacks.
- Treximet is not indicated for the prevention of migraine attacks.
- Safety and effectiveness of Treximet have not been established for cluster headache.

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 1. See Appendix A for a description of the FAERS database.

Table 1. FAERS Search Strategy	
Date of Search	7/31/2017
Time Period of Search	2/1/2013* - 7/31/2017
Search Type	FBIS – Profile Report (product manufacturer reporting summary) query
Product Name(s)	Product Name: Treximet Product Active Ingredient: naproxen sodium/sumatriptan succinate
Search Parameters	All ages, all outcomes, worldwide (MedDRA PTs v 20.0)

*One year prior to the data lock date of the medical officer's review, 2/2014.[1]

2.2 RESULTS

2.2.1 Total number of FAERS reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from 2/1/13 to 7/31/2017 with Treximet.

Table 2. Total Adult and Pediatric FAERS Reports* 2/1/2013 to 7/31/2017 with Treximet

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (> 17 years)	81 (80)	13 (13)	2 (2)
Pediatrics (0 - ≤17 years)	4 (4)	1 (1)	0 (0)

* May include duplicates and transplacental exposures, and have not been assessed for causality

† 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.

2.2.2 Selection of Pediatric Cases in FAERS

We identified four U.S. pediatric (ages 12 – 17 years) reports with Treximet from 2/1/2013 to 7/31/2017 (see Table 2). Our pediatric case series included three cases, after excluding a duplicate report (n=1). Appendix B lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the pediatric case series (n=3).

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

We did not identify any pediatric cases reporting a fatal outcome during this period.

2.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=1)

We identified a single litigation case reporting the serious outcome of congenital anomaly. Hypospadias is unlikely related to Treximet. A summary of the case follows:

FAERS# 9145609/US/2013
A newborn male experienced hypospadias variant with ventral curvature-chordee at birth, which was repaired. He had no difficulty urinating and his anomaly was noted on his three-month visit. He received a penoplasty and lateral plication of his penis for the curvature. His mother was epileptic and was treated throughout the pregnancy with topiramate, phenytoin, lamotrigine, and zonisamide. She also received prenatal vitamins, and Treximet for migraines. Family history was positive for short stature/Robinow syndrome. The patient's old brother had proximal shortening of the limbs and hypospadias. The baby was delivered at 40 weeks' gestation by C-section weighing 6 pounds 11 ounces and was 19 inches long.

Reviewer's comment:
Hypospadias is a relatively common genital anomaly occurring in 0.3-7 of 1000 live male births. In addition, hypospadias with antiepileptics, including topiramate and lamotrigine, has been reported in the literature. The case is therefore confounded and causality cannot be established.[3, 4, 5]

2.4.1 Summary of Non-Serious Adverse Event Cases (N=2)

For completeness, we describe two non-serious cases.

The first case described an 11 year-old-male on Treximet (reason for use, dose, and duration of therapy were not provided). The consumer called the manufacturer to determine if the Treximet film-coated tablets could be crushed for easier oral administration.

The second case described a 16 year-old-male who was prescribed Treximet for "cluster migraines," which was reported as "off-label" use of the drug.

The Treximet label[2] reports the following:

> INDICATIONS AND USAGE: Treximet is indicated for the acute treatment of migraine with or without aura in adults and pediatric patients 12 years of age and older.
>
> Limitations of Use:
>
> - Use only if a clear diagnosis of migraine headache has been established.

- If a patient has no response to the first migraine attack treated with Treximet, reconsider the diagnosis of migraine before Treximet is administered to treat any subsequent attacks. Treximet is not indicated for the prevention of migraine attacks.

- Safety and effectiveness of Treximet have not been established for cluster headache.

DOSAGE AND ADMINISTRATION: . . . Treximet tablets should not be split, crushed, or chewed.

3 DISCUSSION

We identified three FAERS pediatric cases describing a single case of hypospadias, and two non-serious cases reporting a potential medication error and an unapproved use of Treximet. Hypospadias was unlikely related to Treximet because his epileptic mother was also taking several antiepileptic medications during pregnancy; hypospadias with antiepileptics has been reported in the literature. In addition, hypospadias is a common male genital malformation occurring at a rate of 0.3 – 7 in 1000 live births.

Although the remaining two cases did not report adverse drug reactions, the reported events potentially impact product integrity and patient health outcomes. One case inquired about crushing the Treximet film-coated tablet for easier oral administration. The current product label advises to avoid damaging the tablet's matrix, i.e. crushing, splitting, or chewing. The patient was noted to be 11-years-old; however, Treximet is currently approved for use in pediatrics ages 12 – 17 years. The other case reported Treximet for the treatment of "cluster migraines," and mentioned its use as "off-label." It remains unclear if the reporter meant cluster headaches. Nonetheless, Treximet is approved for acute migraine headaches, but not cluster headaches.

These three cases did not reveal any newly identified safety signals and there were no deaths associated with Treximet use.

4 CONCLUSION

Our three cases do not suggest any new pediatric safety issues with Treximet at this time.

5 RECOMMENDATIONS

We will continue routine postmarketing pharmacovigilance of Treximet in the adult and pediatric populations.

6 REFERENCES

1. Ramesh, R, Treximet Clinical Review. DARRTS, 4/15/2015
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4. De Jong et al. The risk of specific congenital anomalies in relation to newer antiepileptic drugs: a literature review. Drugs Real World Outcomes. 2016; 6:131-143
5. Källén, B. (2014). Hypospadias. In: Epidemiology of Human Congenital Malformations. Switzerland: Springer, Cham

7 APPENDICES

7.1 APPENDIX A. 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.

7.2 APPENDIX B. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH TREXIMET (N=3)

FAERS Case Number	FAERS Version Number	Manufacturer Control Number
10779805/11190687	1	US-GLAXOSMITHKLINE-A1078780A/ US-PERNIX THERAPEUTICS-2014SO000035
10236339	1	US-GLAXOSMITHKLINE-A1035712A
9145609	2	US-JNJFOC-20130301959

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/s/

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