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 and Drug Utilization Review

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Product Name(s):	Lysteda (Tranexamic acid)
Pediatric Labeling Approval Date:	August 21, 2013
Application Type/Number:	NDA 022430
Applicant/Sponsor:	Ferring Pharmaceuticals, Inc
OSE RCM #:	2016-375

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EXECUTIVE SUMMARY

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

Lysteda was first approved in 2009 and is indicated for treatment of cyclic heavy menstrual bleeding. Use of this product is for women of reproductive age and is not intended for use in premenarcheal girls.[1] Based on the findings from the pharmacokinetics (PK) study, no dose adjustment is needed in the adolescent population.[1]

The utilization data showed that pediatric patients less than 17 years of age accounted for approximately 3% of the total patients who received prescriptions for Lysteda from outpatient retail pharmacies over the cumulative time period from August 2013 through February 2016. Although the data suggest that there may be some off-label use in patients under 12 years of age, this use cannot be validated due to the lack of access to patient medical records.

With interest in identifying rare, serious, or unlabeled events associated with Lysteda use in the pediatric population, we reviewed pediatric FAERS cases from September 8, 2010, to February 17, 2016.

A total of one FAERS case reported allergic reaction to Lysteda after one month use. It is consistent with the known risk in the labeling and no increased severity was observed. No pediatric deaths were identified.

We did not identify any new pediatric safety issues in this review. DPV recommends returning to routine pharmacovigilance monitoring for Lysteda.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Lysteda is a synthetic lysine amino acid derivative which was approved in 2009 for the treatment of cyclic heavy menstrual bleeding. It diminishes the dissolution of hemostatic fibrin by plasmin and antifibrinolytic effects of tranexamic acid are mediated by reversible interactions at multiple binding sites within plasminogen.[1] Use of this product is for women of reproductive age and is not intended for use in premenarcheal girls.[1]

A pediatric study was required under Pediatric Research Equity Act (PREA) postmarketing requirement for Lysteda. Therefore, the sponsor conducted a pharmacokinetics (PK) study in healthy female adolescents of 12- 16 years of age with heavy menstrual bleeding. Based on the findings from the PK study, no dose adjustment is needed in the adolescent population.[1]

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

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

- Women who are using combination hormonal contraception (4.1)
- Women with active thromboembolic disease or a history or intrinsic risk of thrombosis or thromboembolism, including retinal vein or artery occlusion (4.1)
- Hypersensitivity to tranexamic acid (4.2)

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

- Concomitant use of LYSTEDA with Factor IX complex concentrates, anti-inhibitor coagulant concentrates or all-trans retinoic acid (oral tretinoin) may increase the risk of thrombosis. (5.1)
- Visual or ocular adverse effects may occur with LYSTEDA. Immediately discontinue use if visual or ocular symptoms occur. (5.1)
- In case of severe allergic reaction, discontinue LYSTEDA and seek immediate medical attention. (5.2)
- Cerebral edema and cerebral infarction may be caused by use of LYSTEDA in women with subarachnoid hemorrhage. (5.3)
- Ligneous conjunctivitis has been reported in patients taking tranexamic acid. (5.4)

----------ADVERSE REACTIONS----------

Most common adverse reactions in clinical trials (≥ 5%, and more frequent in LYSTEDA subjects compared to placebo subjects) are headache, sinus and nasal symptoms, back pain, abdominal pain, musculoskeletal pain, joint pain, muscle cramps, migraine, anemia and fatigue. (6.1)

----------DRUG INTERACTIONS----------

Concomitant therapy with tissue plasminogen activators may decrease the efficacy of both LYSTEDA and tissue plasminogen activators. (7.2)

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

- Geriatric Use: Lysteda is not indicated for use in postmenopausal women (8.5)
- Renal impairment: Dosage adjustment is needed. (2.2, 8.6)
- Hepatic impairment: No dosage adjustment is needed. (8.7)

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

Proprietary databases available to the Agency were used to conduct the drug utilization analyses in this review (see Appendix A for full database descriptions and limitations).

2.1.1 Determining Settings of Care

Based on the IMS Health, IMS National Sales Perspectives™ database, approximately 71%, 23%, and 6% of Lysteda bottles were distributed to outpatient retail pharmacies, non-retail settings, and mail-order/specialty settings, respectively, in 2015.[2] As a result, outpatient retail pharmacy utilization patterns of Lysteda were examined. Data from the mail-order/specialty and non-retail pharmacy settings are not included in this review.

2.1.2 Data Sources Used

The IMS Health, Vector One®: Total Patient Tracker (TPT) database was used to provide national estimates of patients who received a Lysteda prescription dispensed from U.S. outpatient retail pharmacies from August 2013 through February 2016, cumulative. These data are stratified by patient age (0-11, 12-16, and 17+ years).

2.2 RESULTS

2.2.1 Number of Patients

Table 2.2.1. National estimates of patients who received a dispensed prescription for Lysteda, stratified by patient age*, from U.S. outpatient retail pharmacies, cumulative August 2013 through February 2016

	Cumulative 8/2013-2/2016	
	N	%
Total Lysteda patients	**10,460**	***100.0%***
0 - 16 years	315	*3.0%*
0 - 11 years	31	*10.0%*
12 - 16 years	285	*90.7%*
17+ years	10,150	*97.0%*
Unknown age	23	*0.2%*

Source: IMS Health, Vector One®: Total Patient Tracker. August 2013 through February 2016. Data extracted April 2016. File: TPT 2016-375 Lysteda BPCA age aggregate 4-11-2016.xls

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years old (16 years and 11 months).

**Patient age subtotals may not sum exactly due to patients aging during the study period, and may be counted more than once in the individual age categories. For this reason, summing across patient age bands is not advisable and will result in overestimates of patient counts.

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 strategy described in Table 3.1.1. See Appendix B for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy

Date of Search	February 18, 2016
Time Period of Search	September 8, 2010* - February 17, 2016
Search Type	Quick Query
Product Name(s)	Lysteda
Search Parameters	All ages, all outcomes, worldwide

* *Date FDA receive the first Lysteda report in FAERS*

3.2 RESULTS

3.2.1 Total number of FAERS reports by Age

Table 3.2.1 Total Adult and pediatric FAERS reports* January 1, 1969 to February 17, 2016 with Lysteda

	All reports (US)	Serious† (US)	Death (US)
Adults (≥ 17 years)	117(92)	106(81)	1(1)
Pediatrics (0 - <17 years)	1(1)	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.

3.2.2 Selection of Pediatric Cases in FAERS

We identified one pediatric report (See Table 3.2.1).

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

No Pediatric deaths were identified.

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

3.4.1 Allergic reaction (n=1)

FAERS Case ID # 8638006, version 1/U.S./Direct Report: A 14-year-old female with Von Willebrand disease and menorrhagia was on Lysteda 650 mg by mouth twice daily for about 1 month. After 1 month on Lysteda, the patient experienced signs and symptoms of respiratory distress including inspiratory stridor and "change in color" approximately 30 minutes after taking a dose of Lysteda. It was reported she wore orthodontic braces and experienced an episode of spitting up blood possibly from the orthodontic braces scraping her gums when she reportedly hit her head. Emergency medical service arrived and gave her supplemental oxygen. The patient demonstrated signs of improvement in color and breathing ability. There were no signs of rash and swelling of the lip, tongue or face. The patient was taken to an emergency department and had normal subsequent examinations including chest x-ray and basic metabolic panel (BMP). Other diagnoses such as asthma were excluded as possible causes for the event. The patient was discharged from the emergency department and advised to follow up with her primary care provider and a hematology specialist. A determination as to whether Lysteda was discontinued or if a diagnosis of allergic reaction was not made.

Reviewer's comments

The recommended dose for Lysteda is 1300 mg taken three times daily for women with normal renal function for a maximum of 5 days during monthly menstruation. This FAERS case noted that the patient took Lysteda 650 mg twice daily for about

one month after which she experienced respiratory distress without signs of rash or swelling. The patient was taking a lower daily dose of Lysteda than the recommended dose in the product labeling and it is not clear if the patient was taking Lysteda for a maximum of 5 days during monthly menstruation or taking Lysteda daily. Based on the limited information available, it is possible that the patient in this FAERS case experienced allergic reaction to Lysteda after one month of use.

Severe allergic reaction is labeled under the Warnings and Precautions section for Lysteda citing one published case report of anaphylactic shock with intravenous tranexamic acid and one case of allergic reaction from the Lysteda clinical trials involving a subject who experienced dyspnea, tightening of her throat, and facial flushing that required emergency medical treatment on her fourth cycle of treatment. [1]

4 DISCUSSION

The utilization data showed that pediatric patients less than 17 years of age accounted for approximately 3% of the total patients who received dispensed prescriptions for Lysteda from outpatient retail pharmacies. Although the data suggest that there may be some off-label use in patients under 12 years of age, this use cannot be validated due to the lack of access to patient medical records.

With interest in identifying rare, serious, or unlabeled events associated with Lysteda use in the pediatric population, we reviewed pediatric FAERS cases from September 8, 2010, to February 17, 2016.

A total of one FAERS case was retrieved and reviewed. There were no new safety signals identified and no increased severity or frequency of any labeled adverse events.

5 CONCLUSION

We identified one pediatric case in the FAERS database; no deaths were reported. Based on this pediatric review, there is no evidence from these data that there are pediatric safety concerns with Lysteda at this time.

6 RECOMMENDATIONS

DPV recommends returning to routine pharmacovigilance monitoring for Lysteda.

7 REFERENCES

[1] Lysteda [Prescribing Information]. Parsippany, NJ:Ferring Pharmaceuticals, Inc.;October 2013.

[2] IMS Health, IMS National Sales Perspectives™. Year 2015. Data extracted March 2016.

8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

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.

IMS Vector One®: Total Patient Tracker (TPT)

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

The patient estimates focus on only outpatient retail pharmacies; therefore, they may not be representative of utilization in other settings of care such as mail-order/specialty and non-retail settings.

8.2 APPENDIX B. 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.

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/s/

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07/05/2016

TRACY M PHAM
07/06/2016

RAJDEEP K GILL
07/06/2016
Drug utilization data are cleared by data vendors.

NEHA GADA
07/08/2016
Presented review to OPT on 7/8. No further issues.

GRACE CHAI
07/08/2016

STEVEN C JONES
07/08/2016