

**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

Date: September 7, 2018

Reviewers: Dipti Kalra, RPh, Safety Evaluator
Division of Pharmacovigilance I

Ivone Kim, MD, Medical Officer (Pediatrician)
Division of Pharmacovigilance I

Team Leader: Lisa Harinstein, PharmD, Safety Evaluator Team Leader
Division of Pharmacovigilance I

Deputy Division Director: Monica Muñoz, PharmD, MS, BCPS, Deputy Director,
Division of Pharmacovigilance I

Product Names: Dexilant, Dexilant SoluTab (dexlansoprazole)

**Pediatric Labeling
Approval Date:** July 8, 2016

Application Type/Number: NDA 022287, NDA 208056 (discontinued)

Applicant/Sponsor: Takeda Pharmaceuticals America, Inc.

OSE RCM #: 2018-1283

TABLE OF CONTENTS

Executive Summary.....	1
1 Introduction.....	2
1.1 Pediatric Regulatory History.....	2
1.2 Relevant Labeled Safety Information	3
2 Methods and Materials	4
2.1 FAERS Search Strategy	4
3 Results.....	4
3.1 FAERS	4
3.1.1 Total Number of FAERS Reports by Age.....	4
3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS.....	4
3.1.3 Summary of Fatal Pediatric Cases (N=0).....	4
3.1.4 Summary of Non-Fatal Pediatric Serious Cases (N=1).....	4
4 Discussion.....	5
5 Conclusion	5
6 Recommendation	5
7 References.....	6
8 Appendices	6
8.1 Appendix A. FDA Adverse Event Reporting System.....	6

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Dexilant (dexlansoprazole) in pediatric patients less than 17 years of age. The Division of Pharmacovigilance I (DPV-I) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious adverse events associated with dexlansoprazole use in pediatric patients less than 17 years of age.

Dexlansoprazole is a proton pump inhibitor (PPI) indicated for use in patients 12 years of age and older for: healing of all grades of erosive esophagitis (EE), maintenance of healed EE and relief of heartburn, and treatment of symptomatic non-erosive gastroesophageal reflux disease (GERD). The safety and effectiveness of dexlansoprazole has not been established in pediatric patients less than 12 years of age.

Dexlansoprazole delayed-release capsule (30 mg and 60 mg) was approved by FDA on January 30, 2009. Dexlansoprazole delayed-release orally disintegrating tablet was approved for use by FDA on January 26, 2016, but was never marketed and withdrawn Federal Register effective as of March 26, 2018.

We evaluated all pediatric postmarketing adverse event reports with a serious outcome for dexlansoprazole in the FAERS database from January 30, 2009 (U.S. approval date) to June 25, 2018. We did not identify any fatal pediatric adverse event cases. We identified one foreign FAERS case describing a pediatric patient who developed hemolytic anemia reported with dexlansoprazole use that resulted in hospitalization. The adverse event of autoimmune hemolytic anemia is contained in the Adverse Reactions-Postmarketing Experience section (6.2) of the dexlansoprazole product label. The single case identified in this review contains a potential alternative cause for the event (i.e., concomitant azithromycin, which is labeled for hemolytic anemia), insufficient information to confirm the diagnosis (e.g., results of laboratory tests not reported), and limited data to assess causality (e.g., dates of concomitant medication administration, including drug treatment, were not reported). For completeness, we searched the FAERS database for reports of hemolytic anemia in adult patients and did not identify any new cases.

This singular pediatric case does not represent a new safety signal at this time. There is no evidence from this data that there are any new pediatric safety concerns with this drug and we will continue to monitor all adverse events associated with the use of dexlansoprazole.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Dexilant (dexlansoprazole) in pediatric patients less than 17 years of age. The Division of Pharmacovigilance I (DPV-I) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious adverse events associated with dexlansoprazole use in pediatric patients less than 17 years of age.

1.1 PEDIATRIC REGULATORY HISTORY

Dexlansoprazole, the R-enantiomer of lansoprazole, is a proton pump inhibitor (PPI) indicated for use in patients 12 years of age and older for: healing of all grades of erosive esophagitis (EE), maintenance of healed EE and relief of heartburn, and treatment of symptomatic non-erosive gastroesophageal reflux disease (GERD).¹ The safety and effectiveness of dexlansoprazole has not been established in pediatric patients less than 12 years of age.

Dexlansoprazole is currently available as a delayed-release capsule (30 mg and 60 mg) in the United States. Dexlansoprazole delayed-release orally disintegrating tablet was approved for use by FDA on January 26, 2016, but never marketed and withdrawn Federal Register effective as of March 26, 2018.

The following summarizes the pediatric regulatory history regarding dexlansoprazole delayed-release capsule and delayed-release orally disintegrating tablet.^{2,3}

January 30, 2009: FDA approved dexlansoprazole delayed-release capsule 30 mg (NDA 22287) for maintenance of healed EE and treatment of heartburn associated with non-erosive GERD in adult patients, and dexlansoprazole delayed-release capsule 60 mg for healing of all grades of EE.

June 17, 2011: An efficacy supplement for dexlansoprazole delayed-release capsule was approved that expanded the indication for maintenance of healed EE to also include the relief of heartburn in adult patients.

September 30, 2015: Supplemental NDA 22287/S021, S022, and S023 were submitted to support approval of expanding the dexlansoprazole indications to include pediatric patients 12 years of age and older and to fulfill two PREA postmarketing requirements (PMRs) 1788-1 and 1356-5.

January 26, 2016: Dexlansoprazole delayed-release orally disintegrating tablet 30 mg (NDA 208056) was approved for adults to maintain healing of EE and relief of heartburn, and for the treatment of heartburn associated with symptomatic non-erosive GERD.⁴

July 8, 2016: NDA 22287/S021-S023 and NDA 208056/S01 were approved by FDA, expanding the indications for both dexlansoprazole delayed-release capsule and delayed-release orally disintegrating tablet to patients 12 years of age and older. The pediatric trials conducted to support labeling in pediatric patients 12 to 17 years of age utilized dexlansoprazole delayed-release capsules, but the labeling for patients 12 years and older applied to both the capsule and orally disintegrating tablet formulations based on the

establishment of bioequivalence. The clinical trials to support approval fulfilled the PREA PMRs below:

NDA 22287 (capsule)

1356-5: Deferred pediatric study under PREA for treating heartburn associated with non-erosive GERD in pediatric patients aged 12 years to 17 years (NCT01642602).⁵

1788-1: Deferred study under PREA to evaluate the pharmacokinetics, healing, maintenance of healing, and symptoms of endoscopy-proven EE in patients 12 years to 17 years of age (NCT01642615).⁶

NDA 208056 (orally disintegrating tablet)³

3019-4: Deferred pediatric study under PREA for treating heartburn associated with non-erosive GERD in pediatric patients aged 12 years to 17 years (NCT01642602).⁵

3019-2: Deferred study under PREA to evaluate the pharmacokinetics of dexlansoprazole, maintenance of healing, and symptoms of endoscopy-proven EE in patients 12 years to 17 years of age (NCT01642615).⁶

March 26, 2018: FDA withdrew approval of dexlansoprazole orally disintegrating tablet because the sponsor had informed FDA that the product was no longer marketed and had requested that FDA withdrawal approval of the application.

1.2 RELEVANT LABELED SAFETY INFORMATION

The dexlansoprazole product labeling dated June 2018 contains the following select safety highlights:¹

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

Gastric Malignancy: In adults, symptomatic response with DEXILANT does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing.

Acute Interstitial Nephritis: Observed in patients taking PPIs.

Clostridium difficile-Associated Diarrhea: PPI therapy may be associated with increased risk.

Bone Fracture: Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine.

Cutaneous and Systemic Lupus Erythematosus: Mostly cutaneous; new onset or exacerbation of existing disease; discontinue DEXILANT and refer to specialist for evaluation.

Cyanocobalamin (Vitamin B12) Deficiency: Daily long-term use (e.g., longer than 3 years) may lead to malabsorption or a deficiency of cyanocobalamin.

Hypomagnesemia: Reported rarely with prolonged treatment with PPIs.

Interactions with Investigations for Neuroendocrine Tumors: Increases in intragastric pH may result in hypergastrinemia and enterochromaffin-like cell hyperplasia and increased chromogranin A levels which may interfere with diagnostic investigations for neuroendocrine tumors.

Interaction with Methotrexate: Concomitant use with PPIs may elevate and/or prolong serum concentrations of methotrexate and/or its metabolite, possibly leading to toxicity. With high-dose methotrexate administration, consider a temporary withdrawal of DEXILANT.

Fundic Gland Polyps: Risk increases with long-term use, especially beyond 1 year. Use the shortest duration of therapy.

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

The most common adverse reactions are:

Adults (≥2%): diarrhea, abdominal pain, nausea, upper respiratory tract infection, vomiting, and flatulence.

Patients 12 to 17 years of age ($\geq 5\%$): headache, abdominal pain, diarrhea, nasopharyngitis, and oropharyngeal pain.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV-I searched the FAERS database with the strategy described in Table 1.

Date of Search	June 26, 2018
Time Period of Search	January 30, 2009 [†] – June 25, 2018
Search Type	Quick Query
Product Terms	Product Active Ingredient: dexlansoprazole
Search Parameters	All ages, all outcomes, worldwide
* See Appendix A for a description of the FAERS database.	
[†] U.S. approval date for dexlansoprazole capsules	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from January 30, 2009 to June 25, 2018 with dexlansoprazole.

	All reports (U.S.)	Serious [†] (U.S.)	Death (U.S.)
Adults (≥ 17 years)	1264(1110)	827 (677)	60 (58)
Pediatrics (0 - <17 years)	6 (5)	1 (0)	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.			

3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

We reviewed all FAERS pediatric reports (n=1) with a serious outcome from January 30, 2009 to June 25, 2018.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

We did not identify any fatal pediatric adverse event cases.

3.1.4 Summary of Non-Fatal Pediatric Serious Cases (N=1)

We identified one foreign FAERS case describing a pediatric patient who developed hemolytic anemia associated with dexlansoprazole use that resulted in hospitalization (see FAERS case #10361266 below). Hemolytic anemia is labeled in the Adverse Reactions-Postmarketing Experience section of the dexlansoprazole product label.

FAERS Case #10361266, Hospitalization, Other medically significant, Foreign, 2014: A pharmacist reported that a 15-year-old female developed hemolytic anemia requiring hospitalization 15 days and 5 days after starting therapy with oral dexlansoprazole 60 mg and azithromycin, respectively. The patient's hemoglobin level dropped to 6.1 g/dL (when the patient arrived at the hospital). The Coombs direct test, cold agglutinins, and Donath Landsteiner tests were done (results not provided). The patient was switched from dexlansoprazole to lansoprazole with no major modification of her hemoglobin levels. The patient was then switched to ranitidine and her hemoglobin level increased to 10.3 g/dL and normalized after about two weeks to one month. "The patient left with prednisone in decreasing doses, ranitidine 75 mg twice daily, folic acid 5 mg daily, and transfusions." She recovered from the event on an unknown date. The patient's medical history included neutrocytosis, constipation, obesity, cyst retention in sphenoid sinus, and GERD. Other concomitant medications included levonorgestrel/ethinyl estradiol-28 and Vitamin D.

Reviewer Comment: The adverse event of autoimmune hemolytic anemia is contained in the Adverse Reactions-Postmarketing Experience section (6.2) of the dexlansoprazole product label; the adverse event was added to the label after identification of two postmarketing cases of hemolytic anemia in adults.⁷

The single case identified in this review contains a potential alternative cause for the event (i.e., concomitant azithromycin, which is labeled for hemolytic anemia), insufficient information to confirm the diagnosis (e.g., results of laboratory tests not reported), and limited data to assess causality (e.g., dates of concomitant medication administration, including drug treatment, were not reported). For completeness, we searched the FAERS database for reports of hemolytic anemia in adult patients and did not identify any new cases. The single pediatric case identified does not warrant any change to the current labeling of hemolytic anemia in association with dexlansoprazole use.

4 DISCUSSION

Of the one serious report, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and there were no deaths directly associated with dexlansoprazole.

5 CONCLUSION

DPV did not identify any pediatric safety concerns for dexlansoprazole at this time.

6 RECOMMENDATION

DPV recommends no regulatory action at this time, and will continue to monitor all adverse events associated with the use of dexlansoprazole.

7 REFERENCES

1. Dexilant Prescribing Information. Takeda Pharmaceuticals. Deerfield, IL. Revised June 2018.
2. Altepeter, T, MD. Clinical review of dexlansoprazole in pediatric patients 12-17 years of age. June 23, 2016.
3. Tomaino J, MD, Cross-Discipline Team Leader Review for Dexilant. July 1, 2016.
4. Mulberg A, MD, Division Deputy Director Summary Review for Dexilant SoluTab. January 25, 2016.
5. Safety and Efficacy of Dexlansoprazole Delayed-Release Capsules in Treating Symptomatic Non-Erosive Gastroesophageal Reflux Disease in Adolescents. (2012). Available at <https://clinicaltrials.gov/ct2/show/NCT01642602?term=dexlansoprazole+206&rank=1>. Accessed on July 11, 2018. (Identification number: NCT01642602).
6. Safety and Efficacy of Dexlansoprazole Delayed-Release Capsules for Healing of Erosive Esophagitis and Maintenance of Healed Erosive Esophagitis and Relief of Heartburn in Adolescents. (2012). Available at <https://clinicaltrials.gov/ct2/show/NCT01642615?term=dexlansoprazole+207&rank=1>. Accessed on July 11, 2018. (Identification number: NCT01642615).
7. Mackey AK, Johnson T, MD. Postmarketing evaluation background document for non-new molecular entities. January 10, 2011.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

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.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DIPTI KALRA
09/07/2018

IVONE E KIM
09/07/2018

LISA M HARINSTEIN
09/07/2018

MONICA MUNOZ
09/10/2018