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

Date:	August 3, 2016
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Product Name(s):	Doryx® (doxycycline hyclate delayed–release tablets)
Pediatric Labeling Approval Date:	April 11, 2013
Application Type/Number:	NDA 050795
Applicant/Sponsor:	Mayne Pharma
OSE RCM #:	2016-374

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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 with a serious outcome and drug utilization data for Doryx® in pediatric patients.

Doryx® (NDA 050795) was first approved in 2005 and is indicated for rickettsial infections; sexually transmitted infections; respiratory tract infections; specific bacterial infections; ophthalmic infections; anthrax, including inhalational anthrax (post-exposure); alternative treatment for selected infections when penicillin is contraindicated; adjunctive therapy in acute intestinal amebiasis and severe acne; and prophylaxis of malaria. The approved pediatric labeling is for the same indications in ages 9 to 17, and in pediatric patients 8 years of age or less only when the potential benefits are expected to outweigh the risks in severe or life -threatening conditions (e.g., anthrax, Rocky Mountain spotted fever), particularly when there are no alternative therapies.

Drug utilization data showed there were approximately 1.2 million pediatric patients aged 0-16 years, which accounted for approximately 6% of the total patients who received a prescription for oral doxycycline hyclate from outpatient retail pharmacies from April 2013 through December 2015.

Of the 22 reports reviewed in pediatric patients, there were no new safety signals identified, and no increased severity or frequency of any labeled adverse events. The one report of death (suicide) could not be directly associated with doxycycline hyclate.

In this case series, reports of suicide, suicide attempt, suicidal ideation, anxiety, and depression accounted for five cases. Given the low number of cases and the prevalence of anxiety, depression, and suicide in adolescents, and the potential for acne to contribute to psychiatric conditions such as depression, an association of these events with doxycycline is unlikely.

There is no evidence from these data that there are pediatric safety concerns with this drug at this time. We recommend a return to routine pharmacovigilance monitoring.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Doryx® (doxycycline hyclate delayed–release tablets) is available as 50 mg and 200 mg tablets containing specially coated pellets of doxycycline hyclate equivalent to 50 mg and 200 mg of doxycycline, respectively. It is indicated for rickettsial infections; sexually transmitted infections; respiratory tract infections; specific bacterial infections; ophthalmic infections; anthrax, including inhalational anthrax (post-exposure); alternative treatment for selected infections when penicillin is contraindicated; adjunctive therapy in acute intestinal amebiasis and severe acne; and prophylaxis of malaria.

Pediatric Labeling Date: April 11, 2013

Indications Studied: Uncomplicated urogenital *Chlamydia trachomatis* infection

Label Changes Summary: New 200-mg strength tablet, new alternative dosage regimen for adults and children at least 8 years of age and weighing 45 kg based on studies in adults, new dosage form, new dosage regimen

The Division of Anti-Infective Products requested to waive pediatric studies for Doryx® 200 mg tablets base. The reasons for the waiver depend on the children's age and are as follows:

- Birth to less than 8 years of age - as a tetracycline-class antibacterial, Doryx® should not be used in pediatric patients to the age of 8 years because of the effects of tetracyclines on tooth development and growth.
- Eight years of age to less than 18 years of age – Waiver for some of this age group (up to approximately 11 years of age) is justified based on studies being not feasible. There are too few instances of sexual activity in children 8-11 years of age to be able to conduct a trial of patients in this age group with sexually transmitted infections.
- For patients 8 years and older diagnosed with uncomplicated urogenital *Chlamydia trachomatis* infection and treated with the adult dose of doxycycline, no significant variability as compared to adults is expected in terms of response to doxycycline 200 mg tablet taken once a day versus doxycycline 100 mg tablet taken twice a day. Thus, the Division thinks that no additional studies in the pediatric population are needed. (Pediatric assessment for this age group should be considered completed.)

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

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

Doxycycline is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

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

- The use of drugs of the tetracycline-class during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown).
- *Clostridium difficile*-associated diarrhea. Evaluate patients if diarrhea occurs.
- Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Limit sun exposure.
- Overgrowth of non-susceptible organisms, including fungi, may occur. If such infections occur, discontinue use and institute appropriate therapy.

----------ADVERSE RECTIONS----------

Adverse reactions observed in patients receiving tetracyclines include anorexia, nausea, vomiting, diarrhea, rash, photosensitivity, urticaria, and hemolytic anemia.

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

- Patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage
- Avoid co-administration of tetracyclines with penicillin
- Absorption of tetracyclines, including Doryx MPC is impaired by antacids containing aluminum, calcium, or magnesium, bismuth subsalicylate and iron-containing preparations
- Concurrent use of tetracyclines, including Doryx MPC may render oral contraceptives less effective
- Barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline

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

- Tetracycline-class drugs can cause fetal harm when administered to a pregnant woman, but data for doxycycline are limited.
- Tetracyclines are excreted in human milk; however, the extent of absorption of doxycycline in the breastfed infant is not known. Doryx MPC use during nursing should be avoided if possible.

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

We used proprietary drug utilization databases available to the Agency to conduct this analysis. **Appendix A** includes detailed descriptions of the databases.

2.1.1 Determining Settings of Care

The IMS Health, IMS National Sales Perspectives™ database was used to determine the various settings of care where oral doxycycline hyclate is distributed by the manufacturer. Sales distribution data for 2015 showed that approximately 71% of doxycycline hyclate bottles were sold to U.S. outpatient retail pharmacies, followed by 24% to non-retail settings, and 5% to mail order/specialty pharmacy settings.[1] Based on these results, we examined the drug utilization data for only the U.S. outpatient retail pharmacy settings.

2.1.2 Data Sources Used

The IMS, Total Patient Tracker™ (TPT) database was used to obtain the nationally estimated number of patients who received a prescription for oral forms of doxycycline hyclate from U.S. outpatient retail pharmacies, stratified by patient age groups (0-7, 8-16, and 17 years and older), from April 1, 2013, through December 31, 2015, cumulative.

2.2 RESULTS

2.2.1 Number of Patients

Table 2.2.1 Nationally estimated number of patients who received a prescription for oral doxycycline hyclate, stratified by patient age (0-7, 8-16, and 17+ years), dispensed from U.S. outpatient retail pharmacies from April 1, 2013 through December 31, 2015, cumulative

	Patients (N)	*Share %*
Total Doxycycline Hyclate	**20,783,176**	***100%***
0 – 16 years	1,209,000	*5.8%*
0 – 7 years	103,584	*8.5%*
8 – 16 years	1,110,431	*91.8%*
17+ years	19,588,011	*94.2%*
UNKNOWN AGE	86,391	*0.4%*

Source: IMS Health Total Patient Tracker (TPT), APR2013-DEC2015, Extracted JUN2016; Source Files: 2016-374 TPT oral doxy hyclate 0-7 8-16 APR2013-DEC2015: 2016-374 TPT oral doxy hyclate 0-16 APR 2013- DEC2015

*Unique patient counts may not be added due to the possibility of double counting those patients aging during the study, and may be counted more than once in the individual categories.

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

[1] Source: IMS Health National Sales Perspective (NSP), Y2015, Extracted JUN2016

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	April 7, 2016
Time Period of Search	January 1, 2006* - December 31, 2015
Search Type	Product Manufacturer Reporting Summary
Product Name	Doxycycline hyclate (Product Active Ingredient)
Search Parameters	All ages, all outcomes, worldwide
Filters	Route of administration – oral

* Reflects 10 years of data.

3.2 RESULTS

3.2.1 Total number of FAERS reports by Age

Table 3.2.1: Number of adult and pediatric FAERS reports* from January 1, 2006, to December 31, 2015 with doxycycline hyclate (oral formulations)

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	514 (270)	430 (187)	14 (6)
Pediatrics (0 to <17 years)	30 (27)	23 (20)	1 (1)

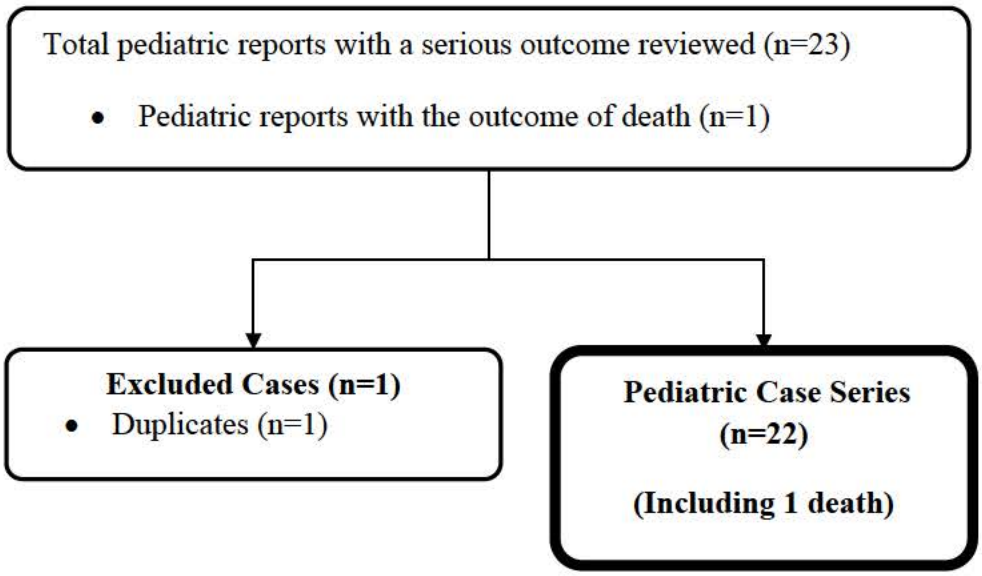
** May include duplicates and transplacental exposures; reports have not been assessed for causality*

† 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 Serious Pediatric Cases in FAERS

We identified 23 pediatric reports with a serious outcome (See Table 3.2.1). See **Figure 3.2.2** below for the specific selection of cases to be summarized in **Sections 3.3 and 3.4.**

Figure 3.2.2 Selection of Serious Pediatric Cases with Doxycycline Hyclate (oral)



Note: The reports involved the product active ingredient doxycycline hyclate. Nine of the 22 cases specifically reported Doryx®.

3.2.3 Characteristics of Pediatric Case Series

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

Table 3.2.3 Characteristics of Pediatric Case Series with Doxycycline Hyclate (oral) (N=22)

Age (n=22)	0 - < 1 month	0
	1 month - <2 years	0
	2- < 6 years	0
	6- <12 years	0
	12- < 17 years	22
Sex	Male	11
	Female	10
	Unknown	1
Country	United States	19
	Foreign	3
Reported Reason for Use	Acne	17
	Chlamydial infection	1
	Rocky Mountain Spotted Fever	1
	Headache	1
	Unknown	2
Serious Outcome*	Death	1
	Life-threatening	0
	Hospitalized	8
	Disability	0
	Congenital anomaly	0
	Required Intervention	0
	Other serious	14

* 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. Reports may have more than one outcome.

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=1)

- A total of 1 case reported death as an outcome.
- The case involved a 13-year-old male who committed suicide by a gunshot wound to the head. The patient began using doxycycline hyclate in (b) (6) for the treatment of acne. The patient committed suicide in (b) (6). The patient's mother stated her son had no change in behavior prior to the event, and no history of depression.

3.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=21)

Note: A case may have had more than one event.

3.4.1 Suicide Attempt, Suicidal Ideation, Anxiety, Depression (Unlabeled events; n=4)

There were two suicide attempts, one in a 14-year-old female who ingested multiple drugs in which doxycycline was included, and a 15-year-old female taking doxycycline for acne and fluoxetine for depression who took an acetaminophen overdose. A 13-year-old female took doxycycline for acne for approximately 1 month and experienced mood swings and anxiety. Nine months after discontinuation, the patient experienced depression with suicidal thoughts and self-injurious behavior. A 12-year-old female took doxycycline for acne and "soon thereafter expressed severe anxiety and depression."

Reviewer's comment: Given the low number of cases and the prevalence of anxiety, depression, and suicide in adolescents, and the potential for acne to contribute to psychiatric conditions such as depression, an association of these events with doxycycline is unlikely.

3.4.2 Other unlabeled events: Immune Thrombocytopenic Purpura (n=1); Severe Neutropenia (n=1); Ulcerative Gingivitis (n=1); Hypokalemia (n=1); multiple complaints including Arthralgia, Mood Swings and Pain (n=1)

These cases had alternative etiologies including medical conditions, other drugs, or did not provide sufficient information for an assessment. See Appendix D for a line listing of cases.

3.4.3 Labeled events

Reported events included esophageal ulceration (n=5), intracranial hypertension (n=3), hepatotoxicity (n=2), allergic reaction (n=2), and photosensitivity (n=1).

The events were consistent with the known risk in the labeling and no increased severity was observed in these reports.

4 DISCUSSION

Drug utilization data showed pediatric patients aged 0-16 years accounted for approximately 6% of the total patients who received a prescription for oral doxycycline hyclate from outpatient retail pharmacies.

Of the 22 reports reviewed in pediatric patients, there were no new safety signals identified, and no increased severity or frequency of any labeled adverse events. The one report of death could not be directly associated with doxycycline hyclate.

5 CONCLUSION

There is no evidence from these data that there are pediatric safety concerns with this drug at this time.

6 RECOMMENDATIONS

Return to routine pharmacovigilance monitoring.

7 APPENDICES

7.1 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.

7.2 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.

7.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH DOXYCYCLINE HYCLATE (ORAL) (N=22)

FAERS Case #	Version #	Manufacturer Control #
6210182	1	05-000640
6322040	1	07-000156
6920532	1	
7034558	1	JP-PFIZER INC-2009219430
7056931	4	09-001053
7329501	1	10-000280
7363204	2	10-000487
7391710	1	10-000588
7423812	2	IT-PFIZER INC-2010070863
7537607	1	10-000135
7810978	1	
7835610	1	
7938593	1	
8069032	1	FR-PFIZER INC-2011172791
8412284	1	2012-000276
8481827	1	
8510664	1	US-JUTA GMBH-2012-05487
8680674	1	US-ENDO PHARMACEUTICALS INC.-DOXY20120004
9324875	1	US-NICOBRDEVP-2013-09313
10389590	1	AUR-APL-2014-08541
10697347	1	
10793478	3	US-PFIZER INC-2015056567

7.4 APPENDIX D. LINE LISTING OF OTHER UNLABELED SERIOUS EVENTS REPORTED WITH DOXYCYCLINE HYCLATE (ORAL) FROM JANUARY 1, 2006, TO DECEMBER 31, 2015

Case ID#	Reported Adverse Event	Age / Sex	Medical History	Concomitant medications	Indication for doxycycline	Comments
10793478	Immune Thrombocytopenic Purpura	13 / M	Grave's disease Type 1 diabetes Immune system disorder Transient ischemic attack Idiopathic thrombocytopenic purpura ADHD	Insulin Adderall Methimazole	Acne	The patient had developed a fever and sinus infection at the time of the thrombocytopenia. Platelets continued to fluctuate after methimazole and doxycycline were stopped.
8069032	Severe neutropenia	15 / F	Traffic accident resulting in pneumothorax, fractures, and contaminated wounds	Bactrim Clindamycin Folinic acid	Infection	Patient recovered after all drugs were stopped and treated with filgrastim.
7363204	Ulcerative gingivitis	15 / M	Not reported	None	Acne	Gingivitis noted after 2 weeks of therapy. Dentist unsure if event was related to doxycycline.
8680674	Hypokalemia	15 / F	Not reported	None	Rocky Mountain Spotted Fever	One week after starting doxycycline, patient experienced unsteadiness, falling, and loss of concentration. She was hospitalized and treatment included IV potassium (no lab values reported). Patient improved and was discharged. Patient's grandmother thought the events were related to doxycycline based on an internet search.

Case ID#	Reported Adverse Event	Age / Sex	Medical History	Concomitant medications	Indication for doxycycline	Comments
8481827	Arthralgia Sweating Mood swings Blood in stool Stomach cramps Diffuse pains	16 / M	Not reported	Not reported	Acne	Work-up could not determine a cause. Patient's parents are convinced the problems are related to the doxycycline.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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