Pediatric Focused Safety Review
Doryx® (doxycycline hyclate)
Pediatric Advisory Committee Meeting
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Amy M. Taylor, MD, MHS
Division of Pediatric and Maternal Health
Office of New Drugs/ ODE IV
Center for Drug Evaluation and Research
Food and Drug Administration

Outline

- **Background Information**
- Drug Use Trends
- Safety
- Summary

Background Drug Information
Doryx® (doxycycline hyclate)

- **Drug:** Doryx® (doxycycline hyclate)
- **Formulation:** delayed-release tablets
- **Sponsor:** Mayne Pharma
- **Original Market Approval:** May 6, 2005
- **Therapeutic Category:** tetracycline antimicrobial

Background Drug Information, continued

Doryx® (doxycycline hyclate)

Indications

- 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 for Acute Intestinal Amebiasis and Severe Acne
- Prophylaxis of Malaria

Background Drug Information, continued

Doryx® (doxycycline hyclate)

Indications (continued)

- Doryx® is approved for use in pediatric patients.
- Doryx® should be used in pediatric patients aged 8 years or less only when the potential benefits are expected to outweigh the risks in severe or life-threatening conditions, particularly where there are no alternative therapies.
- Tetracycline-class of drugs can have an effect on tooth development and growth.

Background Drug Information, continued
Doryx® (doxycycline)

4 Contraindications

- Hypersensitivity to any of the tetracyclines

5 Selected Warnings and Precautions

- Tooth Development – Use during tooth development may cause permanent discoloration of the teeth. Enamel hypoplasia has been reported.
- Clostridium Difficile Associated Diarrhea
- Photosensitivity
- Potential for Microbial Overgrowth
- Skeletal Development – A decrease in fibula growth rate has been observed in premature infants
- Intracranial Hypertension

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Drug Utilization: doxycycline hyclate

Nationally estimated number of patients who received a prescription for oral doxycycline hyclate dispensed from U.S. outpatient retail pharmacies from April 1, 2013 through December 31, 2015

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 patients aging during the study, and may be counted more than once in the individual age 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).

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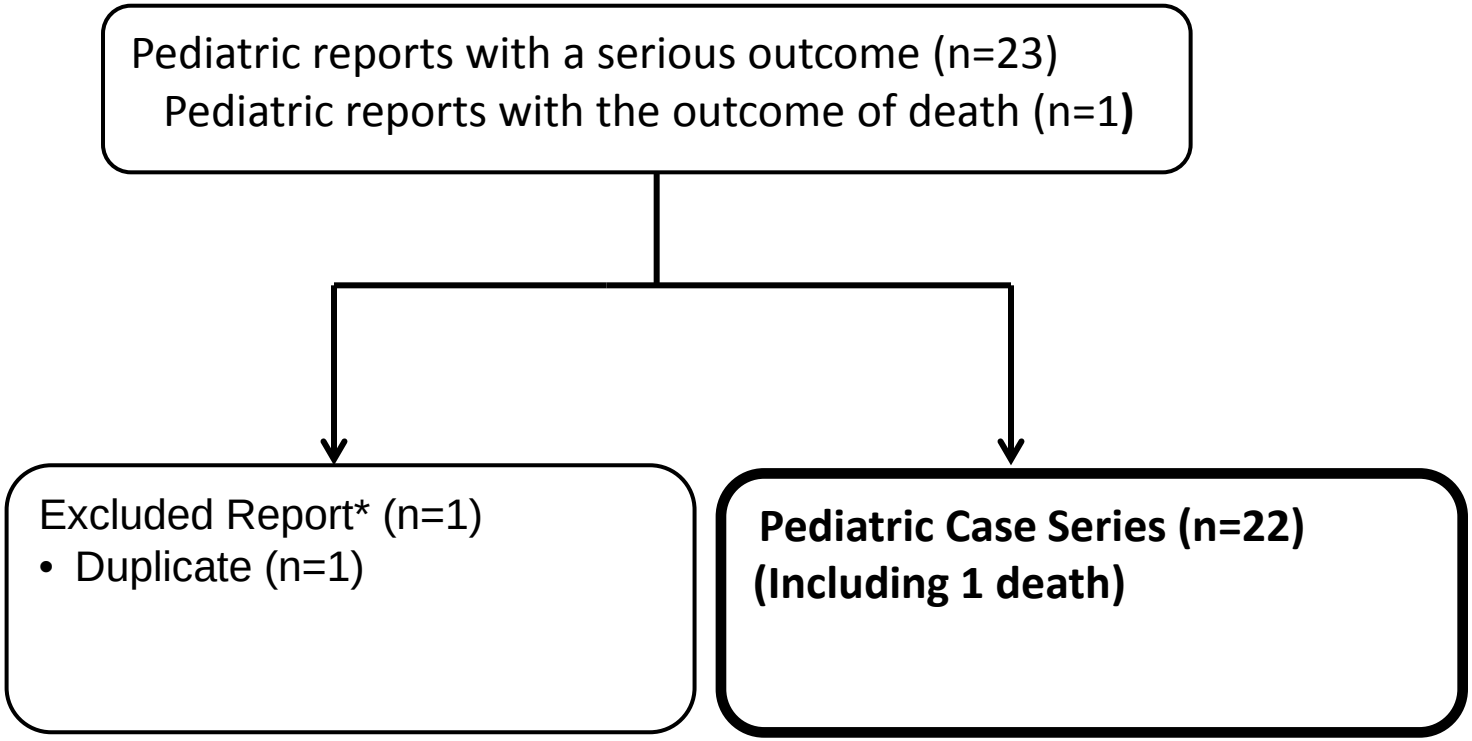
Number* of Adult and Pediatric FDA Adverse Event Reporting System (FAERS) Reports with doxycycline hyclate oral formulations (January 1, 2006 to December 31, 2015)

	All reports (US)	Serious† (US)	Deaths (US)
Adults (≥ 17 yrs.)	514 (270)	430 (187)	14 (6)
Pediatrics (0- <17 yrs.)	**30 (27)**	**23 (20)**	**1(1)**

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

†Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.

Selection of Pediatric FAERS Cases
Doxycycline Hyclate (oral)



* This report was reviewed and excluded from the case series.

Characteristics of Pediatric Case Series
Doxycycline Hyclate (oral)

Characteristics of Pediatric Case Series with doxycycline hyclate (oral) (N=22)

Age	0 - <1 month	0
	1 month - <2 years	0
	2 - <6 years	0
	6 - <12 years	0
	12 - <17 years	22
Indication	Acne	17
	Chlamydial infection	1
	Rocky Mountain Spotted Fever	1
	Headache	1
	Unknown	2

Psychiatric Adverse Events†
Doxycycline Hyclate (oral) (n=5 cases* including 1 death)

Suicide (n=1)

- 13 year old male committed suicide by a gunshot wound to the head. The patient had been on doxycycline for the treatment of acne for 11 months. There was no history of depression or change in behavior prior to the event.

Suicide attempt, Suicidal Ideation, Anxiety, Depression (n=4)

- 14 year old and 15 year old female with suicide attempt
- 13 year old with anxiety
- 12 year old with anxiety and depression

Given the low number of cases relative to time and extent of use, 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.

†Unlabeled events are underlined

*A case may have more than one event

Youth Suicide[§]

- Suicide is the third leading cause of death among youth between the ages of 10 and 24 years.
- Approximately 4,600 pediatric lives are lost each year due to suicide.
- Among youth in grades 9-12, 16% of students reported seriously considering suicide, 13% reported creating a plan and 8% reported trying to take their own life in the 12 months preceding the survey.

[§]CDC website http://www.cdc.gov/ViolencePrevention/suicide/youth_suicide.html

Other Serious Non-Fatal Adverse Events† Doxycycline Hyclate (oral) (n=17 cases*)

Esophageal ulceration (n=5)

Intracranial hypertension (n=3)

Hepatotoxicity (n=2)

Allergic reaction (n=2)

Photosensitivity (n=1)

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)

†Unlabeled events are underlined.

*A case may have more than one event

Summary of Safety Reviews
Doryx® (doxycycline hyclate)

- This concludes the pediatric focused safety review of FAERS reports.
- No new safety signals were identified.
- FDA recommends continuing routine, ongoing post-marketing safety monitoring.
- Does the committee concur?

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Ronald Wassel, PharmD

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Kelly Cao, PharmD

LCDR Justin Mathew, PharmD

CDR S. Christopher Jones, PharmD, MS, MPH

LCDR Grace Chai, PharmD

DPMH

Ethan D. Hausman, MD

Denise Pica-Branco, PhD

Hari Cheryl Sachs, MD

John Alexander, MD, MPH

Lynne Yao, MD

OPT

Judith Cope, MD, MPH

Robert “Skip” Nelson, MD, PhD

Amy Odegaard, MPH

Pam Weinel, MS, MBA, RN

LCDR Kenneth Quinto, MD, MPH