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:	June 14, 2021
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Product Name:	Cialis (tadalafil)
Pediatric Labeling Change Date:	February 15, 2018
Application Type/Number:	NDA 021368
Applicant:	Eli Lilly and Company
OSE RCM #:	2021-362

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Cialis (tadalafil) in pediatric patients through age 17. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA). This review focuses on unlabeled adverse events associated with tadalafil in pediatric patients.

Tadalafil is a phosphodiesterase 5 inhibitor, FDA approved on November 21, 2003 for the treatment of erectile dysfunction and again on October 6, 2011 for the treatment of benign prostatic hyperplasia. Based on one randomized, double-blind, placebo-controlled trial, efficacy of tadalafil could not be established for the treatment of Duchenne muscular dystrophy in pediatric patients. Therefore, the tadalafil labeling states that it is not indicated for use in pediatric patients because the safety and efficacy in patients below 18 years of age have not been established for any indication.

DPV reviewed 26 worldwide pediatric FAERS reports associated with tadalafil, from which no new safety signals were identified. There were no fatal pediatric reports. One serious pediatric U.S. case from 2011 reported adverse events that may be clinically consistent with a hypersensitivity reaction; however, further assessment was limited by the lack of case details and confounding medication (i.e., sildenafil). We did not identify any pediatric safety concerns for tadalafil.

Tadalafil is not indicated for use in pediatric patients. DPV recommends no regulatory action at this time and will continue routine surveillance of all adverse events associated with the use of tadalafil.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Cialis (tadalafil) in pediatric patients through age 17. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA). This review focuses on unlabeled adverse events associated with tadalafil in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Tadalafil is a phosphodiesterase 5 inhibitor, FDA approved on November 21, 2003 for the treatment of erectile dysfunction and again on October 6, 2011 for the treatment of benign prostatic hyperplasia. The safety and efficacy of tadalafil has not been established in pediatric patients below 18 years of age for any indication.

On September 17, 2015, FDA amended a Written Request to the Applicant to include a Phase 3 clinical study in pediatric patients with DMD, pharmacokinetic analyses, and a juvenile rat toxicology study.[a,1] The applicant hypothesized that tadalafil may restore normal skeletal muscle hemodynamic responses to exercise and ameliorate progressive muscle damage in DMD.[1] On November 16, 2017, the applicant was granted pediatric exclusivity for studies conducted on tadalafil.[1]

One pediatric study (H6D-MC-LVJJ or "study LVJJ") evaluated tadalafil for the treatment of 7 to 14-year-old males with DMD. It failed to demonstrate any benefit of treatment with tadalafil on a range of assessments of muscle strength and performance.[1] Study LVJJ[2] was a randomized, double-blind, placebo-controlled, Phase 3 trial in participants between the ages of 7 to 14 years old with DMD. Three hundred thirty-one participants concomitantly taking glucocorticoids were randomized to tadalafil 0.3 mg/kg/d, tadalafil 0.6 mg/kg/d, or placebo. The primary efficacy measure was a 6-minute walk distance (6MWD) after 48 weeks. Secondary efficacy measures included North Star Ambulatory Assessment and time function tests. Tadalafil had no effect on the primary outcome compared to placebo: 48-week declines in 6MWD were 51 ± 9.3 m with placebo, 64.7 ± 9.8 m with low-dose tadalafil ($p = 0.307$ vs. placebo), and 59.1 ± 9.4 m with high-dose tadalafil ($p = 0.538$ vs. placebo). Tadalafil had no effect on secondary outcomes as well.

FDA concluded that there is no evidence from study LVJJ to support the efficacy of tadalafil in the treatment of patients with DMD.[1] On February 15, 2018, FDA approved the pediatric labeling change of tadalafil to update the Pediatric Use Subsection (8.4) with information about the negative study.[3]

[a] On November 16, 2006, FDA issued a Written Request (WR) to study tadalafil in pediatric patients with pulmonary arterial hypertension (PAH). In September 2012, the applicant was approached by the DMD community with an unsolicited request to collaborate on a registration study of tadalafil in boys with DMD. On August 4, 2017, FDA amended the WR to remove sections related to PAH because of the applicant's inability to complete the PAH study due to inadequate enrollment.

Tadalafil has not previously been presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The following provides safety information and information on use in pediatrics adapted from the pertinent sections of the tadalafil labeling.[4]

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

- Administration of CIALIS to patients using any form of organic nitrate is contraindicated. CIALIS was shown to potentiate the hypotensive effect of nitrates.
- History of known serious hypersensitivity reaction to CIALIS or ADCIRCA®.
- Administration with guanylate cyclase stimulators, such as riociguat.

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

- Patients should not use CIALIS if sex is inadvisable due to cardiovascular status.
- Use of CIALIS with alpha-blockers, antihypertensives or substantial amounts of alcohol (≥5 units) may lead to hypotension.
- CIALIS is not recommended in combination with alpha-blockers for the treatment of BPH because efficacy of the combination has not been adequately studied and because of the risk of blood pressure lowering. Caution is advised when CIALIS is used as a treatment for ED in men taking alpha-blockers.
- Patients should seek emergency treatment if an erection lasts >4 hours. Use CIALIS with caution in patients predisposed to priapism.
- Patients should stop CIALIS and seek medical care if a sudden loss of vision occurs in one or both eyes, which could be a sign of non-arteritic anterior ischemic optic neuropathy (NAION). CIALIS should be used with caution, and only when the anticipated benefits outweigh the risks, in patients with a history of NAION. Patients with a "crowded" optic disc may also be at an increased risk of NAION.
- Patients should stop CIALIS and seek prompt medical attention in the event of sudden decrease or loss of hearing.
- Prior to initiating treatment with CIALIS for BPH, consideration should be given to other urological conditions that may cause similar symptoms.

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

- Most common adverse reactions (≥2%) include headache, dyspepsia, back pain, myalgia, nasal congestion, flushing, and pain in limb.

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

8.4 Pediatric Use

CIALIS is not indicated for use in pediatric patients. Safety and efficacy in patients below the age of 18 years have not been established.

A randomized, double-blind, placebo-controlled trial in pediatric patients (7 to 14 years of age) with Duchenne muscular dystrophy, who received CIALIS 0.3 mg/kg, CIALIS

0.6 mg/kg, or placebo daily for 48 weeks failed to demonstrate any benefit of treatment with CIALIS on a range of assessments of muscle strength and performance.

Juvenile Animal Study

No adverse effects were observed in a study in which tadalafil was administered orally at doses of 60, 200, and 1000 mg/kg/day to juvenile rats on postnatal days 14 to 90. The highest plasma tadalafil exposures (AUC) achieved were approximately 10-fold that observed at the MRHD.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

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

Table 1. FAERS Search Strategy*	
Date of search	February 17, 2021
Time period of search	November 21, 2003† - February 16, 2021
Search type	*Quick Query*
Product term	Product name: Cialis
MedDRA search terms (Version 23.1)	All Preferred Terms (PTs)

* See **Appendix A** for a description of the FAERS database.

† We searched starting with the U.S. approval date rather than pediatric labeling change date, as tadalafil is not labeled for use in pediatric patients below 18 years of age.

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 provides the number of adult and pediatric FAERS reports from November 21, 2003 through February 16, 2021 with tadalafil.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From November 21, 2003 through February 16, 2021 With Tadalafil			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	8,397 (6,849)	3,143 (1,941)	232 (121)
Pediatrics (0 - <18 years)	26 (12)	20 (7)	0 (0)

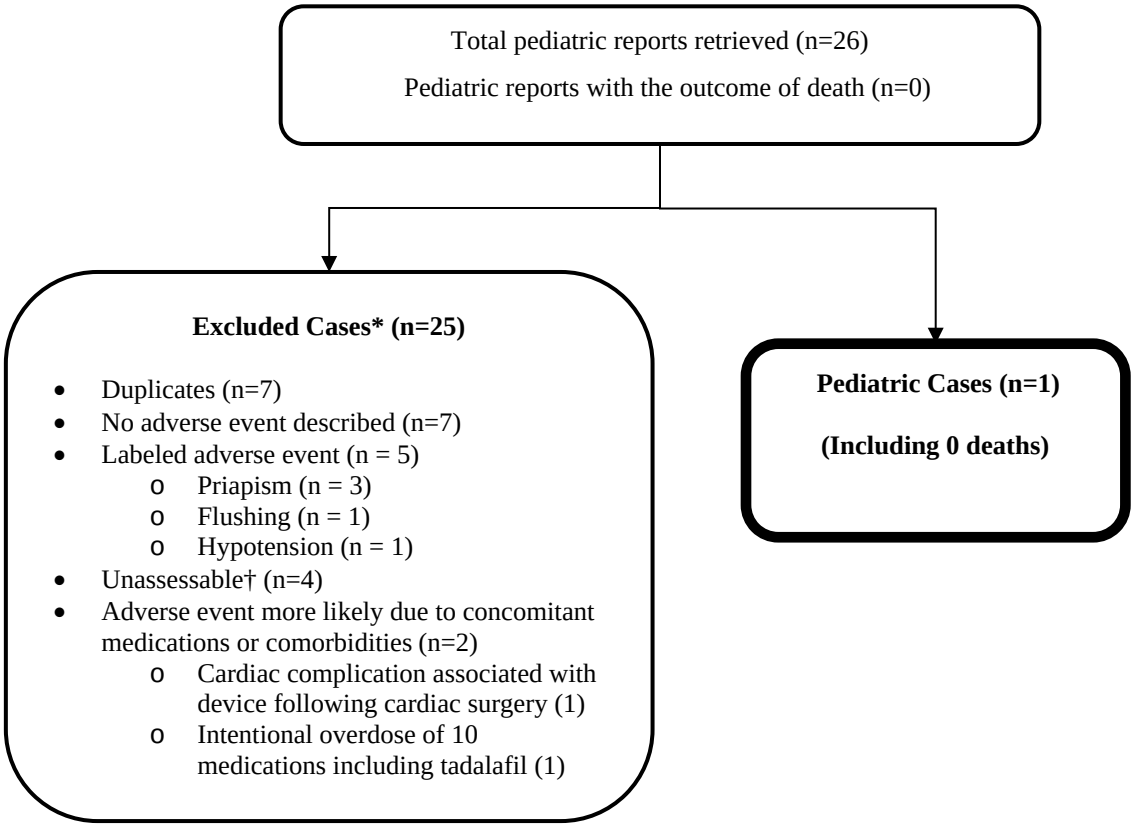
* May include duplicates and transplacental exposures, and have not been assessed for causality.

† For the purposes of this review, the following outcomes qualify as serious: death, life- threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.

3.1.2 Selection of Pediatric Cases in FAERS

We retrieved 26 pediatric FAERS reports involving tadalafil from November 21, 2003 through February 16, 2021. No pediatric fatal reports were identified. We excluded 25 reports for one of the following reasons: duplicate report (n = 7), did not describe an adverse event (n = 7), labeled adverse event (n = 5), unassessable because information was insufficient or contradictory (n = 4), adverse event was unlikely to be related to the use of tadalafil (e.g., confounded by underlying comorbidity or concomitant medications) (n = 2). **Figure 1** outlines the reasons for exclusion and selection of the one pediatric case reporting a non-fatal serious outcome, which is summarized in **subsection 3.1.3**.

Figure 1. Selection of Tadalafil Pediatric Cases



* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above.

† Unassessable: Case cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome) or the information is contradictory or information provided in the case cannot be supplemented or verified.

3.1.3 Summary of Non-Fatal Serious Pediatric U.S. Case (N=1)

Case ID 7953693; Direct; 2011

PTs: *Circumoral oedema:clitoral engorgement:ecchymosis:face oedema:lip disorder:lip swelling:localised oedema:nausea:oedema genital:pain in jaw*

A nurse reported that a 12-year-old female was initiated on sildenafil suspension 15 mg every 8 hours for the treatment of pulmonary arterial hypertension; however, after 2 days, the patient had nausea and bilateral labial and clitoral swelling. Because of these adverse events, the patient was switched to tadalafil 20 mg daily. Later in the day after starting tadalafil, the patient had significant clitoral and labial swelling, ecchymosis, left sided oral and lip swelling, an unspecified lesion inside of her lip, tenderness along the jaw line, and facial and neck edema. No difficulty breathing was reported. She was given diphenhydramine orally and tadalafil was discontinued. It was reported that the adverse events resolved after discontinuation of tadalafil; however, there were no case details included. Other concomitant medications reported were leuprolide intramuscular monthly to delay puberty and prednisone 52.5 mg daily.

Reviewer comments: There is a possible drug-event relationship between tadalafil and the reported adverse events such as swelling (clitoral, labial, oral, lip, face, and neck), ecchymosis, and jaw tenderness. The time to onset of these adverse events occurred less than 24 hours after one dose of tadalafil. The adverse events are clinically consistent with a hypersensitivity reaction, a labeled event. Airway, facial, and genital edema may also be consistent with angioedema which may be secondary to a hypersensitivity reaction; however, it is difficult to ascertain a diagnosis without additional clinical information.[5,6] We also cannot exclude the contribution of sildenafil because of the close temporal relationship between drug exposure and reported adverse events.

4 DISCUSSION

DPV reviewed 26 worldwide pediatric FAERS reports associated with tadalafil, from which no new safety signals were identified. There were no fatal reports. One serious pediatric U.S. case from 2011 reported adverse events that may be clinically consistent with a hypersensitivity reaction; however, further assessment was limited by the lack of case details and confounding medication (i.e., sildenafil).

5 CONCLUSION

Tadalafil is not approved for pediatric use. DPV did not identify any pediatric safety concerns for tadalafil.

6 RECOMMENDATION

DPV recommends no regulatory action at this time and will continue routine surveillance of all adverse events associated with the use of tadalafil.

7 REFERENCES

1. Paine RW. Clinical review NDA Supplement 021368/S-030 Cialis (tadalafil). January 23, 2018. Accessed on February 24, 2021 at https://www.fda.gov/media/112224/download.
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3. FDA. New pediatric labeling information database. Accessed on February 24, 2021 at https://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?filter=Cialis&sortColumn=1d&sd=labelingdatabase&page=1.
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5. Nedelea I and Deleanu D. Isolated angioedema: an overview of clinical features and etiology. *Exp Ther Med*. 2019;17(2):1068-72.
6. Memon RJ, Tiwari V. Angioedema. 2020 Aug 10. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan. PMID: 30860724.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council 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.

8.2 APPENDIX B. FAERS LINE LISTING OF THE INCLUDED PEDIATRIC CASE (N=1)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	5/10/2011	7953693	1	---	Direct	12	Female	USA	HO,OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events.

Abbreviations: HO=hospitalization, OT=other medically significant

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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/

JENNY J KIM
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IVONE E KIM
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LYNDA V MCCULLEY
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IDA-LINA DIAK
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