Department of Health and Human Services
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	**November 22, 2022**
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Product Name:	Astagraf XL (tacrolimus extended-release capsules)
Pediatric Labeling Approval Date:	November 29, 2018
Application Type/Number:	NDA 204096
Applicant:	Astellas Pharma US, Inc.
TTT Record ID#:	2022-2576

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Astagraf XL (tacrolimus extended-release capsules) in pediatric patients <17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious unlabeled adverse events associated with tacrolimus in pediatric patients.

Astagraf XL (tacrolimus) was first approved on July 19, 2013 and is currently indicated for the prophylaxis of organ rejection in kidney transplant patients in combination with other immunosuppressants in adult and pediatric patients, 4 years of age and older, who can swallow capsules intact.

This review was prompted by the pediatric labeling change on November 29, 2018 that expanded the use of Astagraf XL to pediatric transplant patients 4 years of age and older, and who are able to swallow capsules intact.

DPV reviewed all U.S. serious FAERS reports with Astagraf XL in the pediatric population (ages 0 - <17 years) from July 19, 2013, through October 24, 2022, and did not identify any cases for inclusion in a case series.

DPV did not identify any new pediatric safety concerns for Astagraf XL at this time and will continue to monitor all adverse events associated with the use of Astagraf XL.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Astagraf XL (tacrolimus extended-release capsules) in pediatric patients <17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious unlabeled adverse events associated with Astagraf XL in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY[1]

Astagraf XL (tacrolimus extended-release capsules) was first approved on July 19, 2013, and is currently indicated for the prophylaxis of organ rejection in kidney transplant patients in combination with other immunosuppressants in adult and pediatric patients who can swallow capsules intact.

This review was prompted by the pediatric labeling change on November 29, 2018, that expanded the use of tacrolimus to pediatric transplant patients 4 years of age and older, and who are able to swallow capsules intact.

The safety and efficacy in pediatric patients were based on evidence from studies of tacrolimus in adult kidney transplant patients with additional pharmacokinetic (PK) studies comparing Astagraf XL to Prograf (tacrolimus).

Forty-four de novo pediatric transplant patients, including 25 pediatric de novo kidney transplant patients, were administered a starting daily dose of 0.3 mg/kg/day of Prograf capsules divided into two daily doses or Astagraf XL once daily. Overall, the tacrolimus PK parameters, AUC_{24}[a] and C_{24}[b] are comparable among Prograf and Astagraf XL on Days 7 and 28.

A PK study was also conducted in 81 stable pediatric transplant patients (5 to 16 years of age), including 48 pediatric kidney transplant patients, comparing Astagraf XL to Prograf capsules. Patients who had been administered Prograf for at least 3 months prior to treatment were converted on a 1:1 (mg:mg) basis from Prograf, given in two divided doses, to Astagraf XL once a day. Overall, the tacrolimus AUC_{24}, C_{max},[c] and C_{24} are comparable upon conversion from Prograf to Astagraf XL on a 1:1 (mg:mg) basis in stable pediatric kidney transplant patients.[2]

DPV has not previously presented an evaluation of postmarketing adverse event reports for Astagraf XL in pediatric patients to the Pediatric Advisory Committee (PAC).

[a] Area under the whole blood concentration-time curve from dosing to 24 hours after dosing
[b] Concentration prior to the morning dose
[c] Maximum concentration

1.2 RELEVANT LABELED SAFETY INFORMATION[1]

The Contraindications, Warnings and Precautions, Adverse Reactions (from the Highlights of Prescribing Information), and the Pediatric Use sections of the Astagraf XL product labeling are reproduced below.

----------BOXED WARNING----------

WARNING: MALIGNANCIES AND SERIOUS INFECTIONS IN TRANSPLANT PATIENTS; and INCREASED MORTALITY IN FEMALE LIVER TRANSPLANT PATIENTS

See full prescribing information for complete boxed warning.

- Increased risk for developing serious infections and malignancies with ASTAGRAF XL or other immunosuppressants that may lead to hospitalization or death.
- Increased mortality in female liver transplant patients with ASTAGRAF XL. Not approved for use in liver transplantation.

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

- Known hypersensitivity to tacrolimus.

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

- Not Interchangeable with Other Tacrolimus Products-Medication Errors: Instruct patients or caregivers to recognize the appearance of ASTAGRAF XL capsules.
- New onset diabetes after transplant: Monitor blood glucose.
- Nephrotoxicity (acute and/or chronic): May occur due to ASTAGRAF XL, drug interactions, concomitant nephrotoxic drugs. Monitor renal function; consider dosage reduction.
- Neurotoxicity: Including risk of posterior reversible encephalopathy syndrome (PRES), monitor for neurologic abnormalities; reduce dosage or discontinue ASTAGRAF XL.
- Hyperkalemia: Risk may be increased with other agents associated with hyperkalemia; monitor serum potassium levels.
- Hypertension: May require antihypertensive therapy; monitor relevant drug interactions.
- QT prolongation: Consider obtaining electrocardiograms and monitoring electrolytes in patients at high risk.
- Immunizations: Avoid live vaccines.
- Pure red cell aplasia: Consider discontinuation of ASTAGRAF XL.

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

- Most common adverse reactions (≥ 30%) are: diarrhea, constipation, nausea, peripheral edema, tremor and anemia.

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

8.4 Pediatric Use

The safety and effectiveness of ASTAGRAF XL in de novo pediatric kidney transplant patients have been established. Use of ASTAGRAF XL in pediatric kidney transplant patients is based on adequate and well-controlled studies of ASTAGRAF XL in adult kidney transplant patients and supported by pharmacokinetic and safety data of ASTAGRAF XL in pediatric transplant patients 4 years of age and older who are able to swallow capsules intact and Prograf (tacrolimus) capsules in adult and pediatric transplant patients.

De Novo Pediatric Kidney Transplant Patients
A pharmacokinetic and safety study included 25 de novo pediatric kidney transplant patients, 4 to 15 years of age, randomized to Prograf (N=12) or ASTAGRAF XL (N=13). Tacrolimus exposures for the two drug products were comparable on Days 7 and 28. Among the 13 pediatric kidney transplant patients who completed 52 weeks on ASTAGRAF XL, there were no graft loss, deaths or episodes of biopsy-proven acute rejection.

Stable Pediatric Kidney Transplant Patients
Another pharmacokinetic and safety study included 48 stable pediatric kidney transplant patients, 5 to 16 years of age, who were converted from a Prograf-based regimen to ASTAGRAF XL. Tacrolimus systemic exposures for the two drug products were comparable. Acute rejections were reported in 2/48 kidney pediatric patients that responded to subsequent treatment. There were no graft failures or deaths following use of ASTAGRAF XL during the 54-week follow up.

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	October 25, 2022
Time period of search	July 19, 2013† - October 24, 2022
Search type	RxLogix PV Reports Quick Query
Product terms	Product Name: Astagraf XL
MedDRA search terms (Version 25.0)	All PTs

* See Appendix A for a description of the FAERS database.
† U.S. approval date for Astagraf XL
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term

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 July 19, 2013, through October 24, 2022, with Astagraf XL.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From July 19, 2013, through October 24, 2022, with Astagraf XL

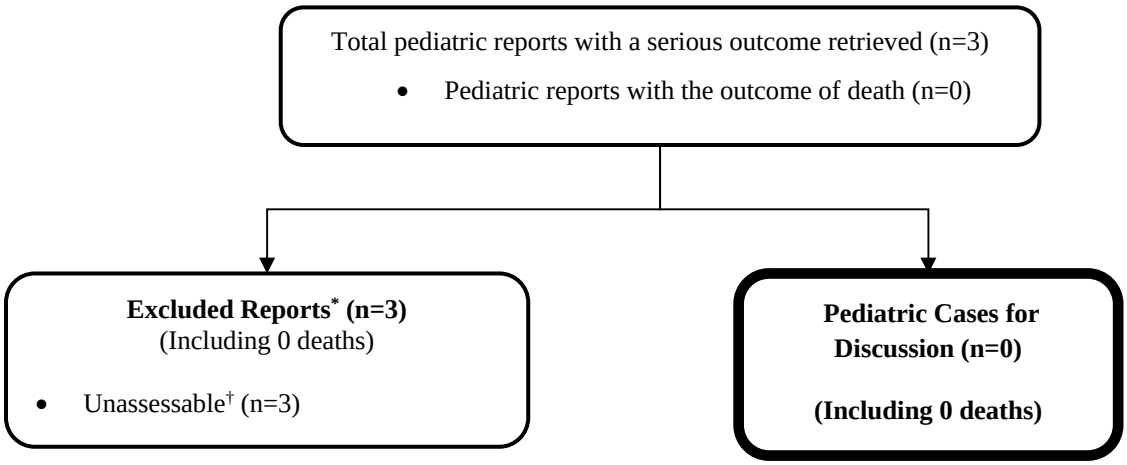
	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	149 (148)	89 (88)	21 (21)
Pediatrics (0 - <17 years)	3 (3)	3 **(3)**	0 **(0)**

* 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 U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved three U.S. serious pediatric reports for Astagraf XL from July 19, 2013, through October 24, 2022. We reviewed the three FAERS reports and excluded all reports from further discussion due to the adverse event being unassessable (n=3). Figure 1 presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious U.S. Pediatric Cases with Astagraf XL



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

† Unassessable: Report 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), the information is contradictory, or information provided in the report cannot be supplemented or verified.

3.1.3 Summary of Fatal Pediatric U.S. Cases (N=0)

We did not identify any FAERS U.S. serious fatal pediatric adverse event cases associated with Astagraf XL in the pediatric population for discussion.

3.1.4 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=0)

We did not identify any FAERS U.S. serious, unlabeled, non-fatal adverse event cases associated with Astagraf XL in the pediatric population.

4 DISCUSSION

DPV reviewed three FAERS U.S. serious reports with Astagraf XL in the pediatric population (ages 0 - <17 years) from July 19, 2013, through October 24, 2022. We identified no new safety signals, no increased severity or frequency of any labeled adverse events, and no deaths associated with Astagraf XL.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for Astagraf XL 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 Astagraf XL.

7 REFERENCES

1. Astagraf XL (tacrolimus extended-release capsules) [package insert]. Northbrook, IL, Astellas Pharms US, Inc. Revised December 2020.

2. Astagraf XL (tacrolimus extended-release capsules) [package insert]. Northbrook, IL, Astellas Pharms US, Inc. Revised November 2018.

8 APPENDICES

8.1 APPENDIX A. 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 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.

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/s/

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