Department of Health and Human Services
Public Health Service
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:	December 12, 2024
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Product Name:	Sutent (sunitinib malate)
Pediatric Labeling Approval Date:	May 7, 2019
Application Type/Number:	NDA 021938 NDA 021968
Applicant:	C.P. Pharmaceuticals International C.V.
TTT Record ID:	2024-10843

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Sutent (sunitinib malate) in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with sunitinib malate in pediatric patients.

Sutent (sunitinib malate) is a kinase inhibitor and was initially approved in the U.S. on January 26, 2006. Sunitinib malate is currently indicated for:

- treatment of adult patients with gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate.
- treatment of adult patients with advanced renal cell carcinoma (RCC).
- adjuvant treatment of adult patients at high risk of recurrent RCC following nephrectomy.
- treatment of progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) in adult patients with unresectable locally advanced or metastatic disease.

The safety and effectiveness of sunitinib malate in pediatric patients has not been established.

This pediatric postmarketing safety review was stimulated by pediatric labeling on May 7, 2019, that included results from open-label studies that failed to establish the safety and effectiveness for sunitinib malate use in pediatrics.

DPV reviewed all U.S. serious FAERS reports with sunitinib malate in pediatric patients less than 17 years of age from January 26, 2006, through October 17, 2024, and identified 18 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with sunitinib malate in pediatric patients less than 17 years of age.

DPV did not identify any new pediatric safety concerns for sunitinib malate at this time and will continue routine pharmacovigilance monitoring for sunitinib malate.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Sutent (sunitinib malate) in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with sunitinib malate in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Sutent (sunitinib malate) is a kinase inhibitor and was initially approved in the U.S. on January 26, 2006. Sunitinib malate is currently indicated for:

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This pediatric postmarketing safety review was stimulated by pediatric labeling on May 7, 2019, that included results from open-label studies that failed to establish the safety and effectiveness for sunitinib malate use in pediatrics.

A pediatric safety review for sunitinib malate has not previously been presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The sunitinib malate labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional sunitinib malate labeling information, please refer to the full prescribing information.

WARNING: HEPATOTOXICITY
See full prescribing information for complete boxed warning.

Hepatotoxicity may be severe, and in some cases fatal. Monitor hepatic function and interrupt, dose reduce, or discontinue SUTENT as recommended [see Warnings and Precautions (5.1)].

----------**CONTRAINDICATIONS**----------

- None

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

- Hepatotoxicity: Fatal liver failure has been observed. Monitor liver function tests at baseline, during each cycle, and as clinically indicated. Interrupt SUTENT for Grade 3 hepatotoxicity until resolution to Grade ≤1 or baseline and resume SUTENT at a reduced dose; discontinue if no resolution. Discontinue SUTENT in patients with Grade 4 hepatoxicity, in patients who have subsequent severe changes in liver function tests or other signs and symptoms of liver failure.
- Cardiovascular Events: Myocardial ischemia, myocardial infarction, heart failure, cardiomyopathy, and decreased left ventricular ejection fraction (LVEF) to below the lower limit of normal including death have occurred. Monitor for signs and symptoms of congestive heart failure and consider monitoring LVEF at baseline and periodically during treatment. Discontinue SUTENT for clinical manifestations of congestive heart failure. Interrupt and/or dose reduce for decreased LVEF.
- QT Interval Prolongation and Torsade de Pointes: Monitor patients at higher risk for developing QT interval prolongation. Consider monitoring of electrocardiograms and electrolytes.
- Hypertension: Monitor blood pressure at baseline and as clinically indicated. Initiate and/or adjust antihypertensive therapy as appropriate. Interrupt SUTENT for Grade 3 hypertension until resolution to Grade ≤1 or baseline, then resume SUTENT at a reduced dose. Discontinue SUTENT in patients who develop Grade 4 hypertension.
- Hemorrhagic Events: Tumor-related hemorrhage and viscus perforation (both with fatal events) have occurred. Perform serial complete blood counts and physical examinations. Interrupt SUTENT for Grade 3 or 4 hemorrhagic events until resolution to Grade ≤1 or baseline, then resume at a reduced dose; discontinue if no resolution.
- Tumor Lysis Syndrome (TLS): TLS (some fatal) has been reported primarily in patients with RCC and GIST. Monitor these patients and treat as clinically indicated.
- Thrombotic microangiopathy (TMA): TMA, including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, sometimes leading to renal failure or a fatal outcome, has been reported. Discontinue SUTENT for TMA.
- Proteinuria: Renal failure or a fatal outcome has occurred. Monitor urine protein. Interrupt treatment for 24-hour urine protein of 3 or more grams. Discontinue for repeat episodes of 24-hour urine protein of 3 or more grams despite dose reductions or nephrotic syndrome.
- Dermatologic Toxicities: Necrotizing fasciitis, erythema multiforme, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) (some fatal) have occurred. Discontinue SUTENT for these events.
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS (some fatal) has been reported. Monitor for signs and symptoms of RPLS. Withhold SUTENT until resolution.
- Thyroid Dysfunction: Monitor thyroid function at baseline, periodically during treatment, and as clinically indicated. Initiate and/or adjust therapy for thyroid dysfunction as appropriate.
- Hypoglycemia: Check blood glucose levels regularly and assess if antidiabetic drug dose modifications are required.

- Osteonecrosis of the Jaw (ONJ): Withhold SUTENT for at least 3 weeks prior to invasive dental procedure and for development of ONJ until complete resolution.
- Impaired Wound Healing: Withhold SUTENT for at least 3 weeks prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of SUTENT after resolution of wound healing complications has not been established.
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception.

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

- The most common adverse reactions (≥25%) are fatigue/asthenia, diarrhea, mucositis/stomatitis, nausea, decreased appetite/anorexia, vomiting, abdominal pain, hand-foot syndrome, hypertension, bleeding events, dysgeusia/altered taste, dyspepsia, and thrombocytopenia.

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

8.4 Pediatric Use

The safety and effectiveness of SUTENT in pediatric patients have not been established. Safety and pharmacokinetics of sunitinib were assessed in an open-label study (NCT00387920) in pediatric patients 2 years to <17 years of age (n=29) with refractory solid tumors. In addition, efficacy, safety and pharmacokinetics of sunitinib was assessed in another open-label study (NCT01462695) in pediatric patients 2 years to <17 years of age (n=27) with high-grade glioma or ependymoma. The maximum tolerated dose (MTD) normalized for body surface area (BSA) was lower in pediatric patients compared to adults. Sunitinib was poorly tolerated in pediatric patients. The occurrence of dose-limiting cardiotoxicity prompted an amendment of the NCT00387920 study to exclude patients with previous exposure to anthracyclines or cardiac radiation. No responses were reported in patients in either of the trials.

Apparent clearance and volume of distribution normalized for BSA for sunitinib and its active major metabolite were lower in pediatrics as compared to adults.

The effect on open tibial growth plates in pediatric patients who received SUTENT has not been adequately studied. See Juvenile Animal Toxicity Data below.

Juvenile Animal Toxicity Data

Physeal dysplasia was present in cynomolgus monkeys with open growth plates treated with sunitinib for ≥3 months (3 month dosing 2, 6, 12 mg/kg/day; 8 cycles of dosing 0.3, 1.5, 6.0 mg/kg/day) at doses that were >0.4 times the combined AUC (the combined systemic exposure of sunitinib plus its active metabolite) in patients administered the RDD of 50 mg. The no-effect level (NOEL) was 1.5 mg/kg/day in monkeys treated intermittently for 8 cycles, but was not identified in monkeys treated continuously for 3 months. In developing rats treated continuously for 3 months (1.5, 5.0, and 15.0 mg/kg) or 5 cycles (0.3, 1.5, and 6.0 mg/kg/day), bone

abnormalities consisted of thickening of the epiphyseal cartilage of the femur and an increase of fracture of the tibia at doses ≥5 mg/kg (approximately 10 times the combined AUC in patients administered the RDD of 50 mg). Additionally, tooth caries were present in rats at >5 mg/kg. The incidence and severity of physeal dysplasia were dose related and reversible upon cessation of treatment; however, findings in the teeth were not. In rats, the NOEL in bones was ≤2 mg/kg/day.

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 18, 2024
Time period of search	January 26, 2006† - October 17, 2024
Search type	RxLogix Pediatric Focused Review Alert
Product terms	Product Active Ingredient: sunitinib malate Case Application Number: NDA 021938; NDA 021968
MedDRA search terms (Version 27.0)	All Preferred Terms
Other search terms‡	Case Seriousness: Serious
* See Appendix A for a description of the FAERS database. † U.S. approval date for Sutent (sunitinib malate) ‡ 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. Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities	

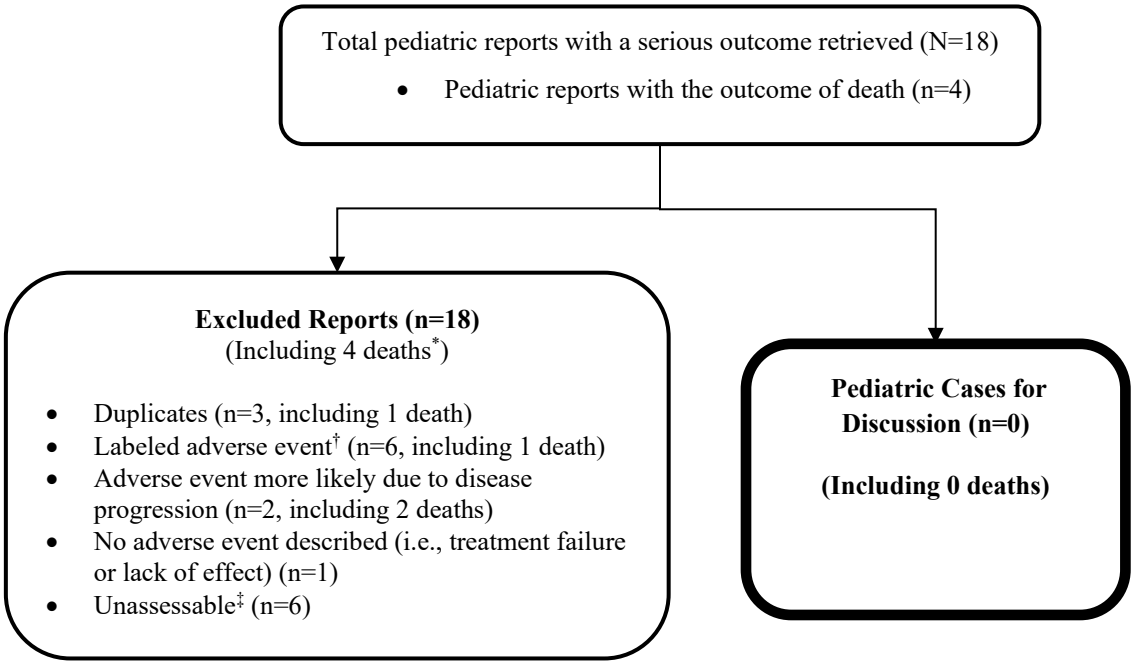
3 RESULTS

3.1 FAERS

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

Our FAERS search retrieved 18 U.S. serious pediatric reports for patients less than 17 years old from January 26, 2006, through October 17, 2024. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all 18 reports from the case series for the reasons listed in Figure 1. Figure 1 presents the selection of cases for the pediatric case series.

Figure 1. Selection of U.S. Serious Pediatric Cases with Sunitinib Malate



* Four excluded U.S. FAERS reports described fatal outcomes. After accounting for duplicate reporting (n=1), we identified three unique cases describing a fatal outcome. Two cases described death due to progression of underlying oncological disease. One case described death due to cardiac arrest.
† Labeled adverse event does not represent increased severity.
‡ Unassessable: The 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.

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

There are no fatal pediatric adverse event cases for discussion.

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

There are no non-fatal pediatric adverse event cases for discussion.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with sunitinib malate in pediatric patients less than 17 years of age from January 26, 2006, through October 17, 2024, and identified 18 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with sunitinib malate in pediatric patients less than 17 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for sunitinib malate at this time and will continue routine pharmacovigilance monitoring for sunitinib malate.

6 REFERENCES

1. Sutent (sunitinib malate) [package insert]. San Diego, CA. CP Pharmaceuticals International CV c/o Pfizer, Inc. Revised August 2021.

7 APPENDICES

7.1 APPENDIX A. 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 terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

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 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.