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:	January 8, 2025
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Product Name:	Tasigna (nilotinib)
Pediatric Labeling Approval Date:	March 22, 2018
Application Type/Number:	NDA 022068
Applicant:	Novartis
TTT Record ID:	2024-10815

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Tasigna (nilotinib) in pediatric patients less than 18 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 nilotinib in pediatric patients.

Tasigna (nilotinib) is a kinase inhibitor and was initially approved in the U.S. on October 29, 2007. Tasigna is currently indicated for the treatment of:

- Adult and pediatric patients greater than or equal to 1 year of age with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP).
- Adult patients with CP and accelerated phase (AP) Ph+ CML resistant to or intolerant to prior therapy that included imatinib.
- Pediatric patients greater than or equal to 1 year of age with Ph+ CML-CP and CML-AP resistant or intolerant to prior tyrosine-kinase inhibitor (TKI) therapy.

This pediatric postmarketing safety review was stimulated by pediatric labeling for Tasigna on March 22, 2018, that expanded the indication of Tasigna to include treatment of pediatric patients greater than or equal to 1 year with newly diagnosed Ph+ CML in CP and the treatment of pediatric patients greater than or equal to 1 year with Ph+ CML-CP resistant or intolerance.

DPV searched FAERS for all U.S. serious reports with nilotinib in pediatric patients less than 18 years of age from October 29, 2007, through September 29, 2024, and identified 17 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 nilotinib in pediatric patients less than 18 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Tasigna (nilotinib) in pediatric patients less than 18 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 nilotinib in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Tasigna (nilotinib) capsule is a kinase inhibitor and was initially approved in the U.S. on October 29, 2007. Tasigna is currently indicated for the treatment of:[1]

- Adult and pediatric patients greater than or equal to 1 year of age with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP).
- Adult patients with CP and accelerated phase (AP) Ph+ CML resistant to or intolerant to prior therapy that included imatinib.
- Pediatric patients greater than or equal to 1 year of age with Ph+ CML-CP and CML-AP resistant or intolerant to prior tyrosine-kinase inhibitor (TKI) therapy.

Danziten (nilotinib) tablet was approved in the U.S. on November 7, 2024. Danziten is indicated for the treatment of:[a,2]

- Adult patients with newly diagnosed Ph+ CML in CP.
- Adult patients with CP and AP Ph+ CML resistant to or intolerant to prior therapy that included imatinib.

This pediatric postmarketing safety review was stimulated by pediatric labeling for Tasigna on March 22, 2018, that expanded the indication of Tasigna to include treatment of pediatric patients greater than or equal to 1 year with newly diagnosed Ph+ CML in CP and the treatment of pediatric patients greater than or equal to 1 year with Ph+ CML-CP resistant or intolerance.[3]

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

1.2 RELEVANT LABELED SAFETY INFORMATION

The Tasigna labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection.[1] For additional Tasigna labeling information, please refer to the full prescribing information.

[a] Additional pediatric use information is approved for Novartis Pharmaceuticals Corporation's Tasigna (nilotinib) capsules. However, due to Novartis Pharmaceuticals Corporation's marketing exclusivity rights, Danziten (nilotinib) tablet is not labeled with that pediatric information.

WARNING: QT PROLONGATION and SUDDEN DEATHS

See full prescribing information for complete boxed warning.

- **Tasigna prolongs the QT interval. Prior to Tasigna administration and periodically, monitor for hypokalemia or hypomagnesemia and correct deficiencies. (5.2) Obtain ECGs to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, and following any dose adjustments. (5.2, 5.3, 5.7, 5.12)**
- **Sudden deaths have been reported in patients receiving Tasigna. (5.3) Do not administer Tasigna to patients with hypokalemia, hypomagnesemia, or long QT syndrome. (4, 5.2)**
- **Avoid use of concomitant drugs known to prolong the QT interval and strong CYP3A4 inhibitors. (7.1, 7.2)**
- **Avoid food 2 hours before and 1 hour after taking the dose. (2.1)**

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

Tasigna is contraindicated in patients with hypokalemia, hypomagnesemia, or long QT syndrome. (4)

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

- Myelosuppression: Monitor complete blood count (CBC) during therapy and manage by treatment interruption or dose reduction. (5.1)
- Cardiac and Arterial Vascular Occlusive Events: Evaluate cardiovascular status, monitor and manage cardiovascular risk factors during Tasigna therapy. (5.4)
- Pancreatitis and Elevated Serum Lipase: Monitor serum lipase; if elevations are accompanied by abdominal symptoms, interrupt doses and consider appropriate diagnostics to exclude pancreatitis. (5.5)
- Hepatotoxicity: Monitor hepatic function tests monthly or as clinically indicated. (5.6)
- Electrolyte Abnormalities: Tasigna can cause hypophosphatemia, hypokalemia, hyperkalemia, hypocalcemia, and hyponatremia. Correct electrolyte abnormalities prior to initiating Tasigna and monitor periodically during therapy. (5.7)
- Tumor Lysis Syndrome: Maintain adequate hydration and correct uric acid levels prior to initiating therapy with Tasigna. (5.8)
- Hemorrhage: Hemorrhage from any site may occur. Advise patients to report signs and symptoms of bleeding and medically manage as needed. (5.9)
- Fluid Retention: Monitor patients for unexpected rapid weight gain, swelling, and shortness of breath. Manage medically. (5.13)
- Effects on Growth and Development in Pediatric Patients: Growth retardation has been reported in pediatric patients treated with Tasigna. Monitor growth and development in pediatric patients. (5.14)
- Embryo-Fetal Toxicity: Advise females of reproductive potential of potential risk to a fetus and to use effective contraception. (5.15, 8.1, 8.3)
- Treatment Discontinuation: Patients must have typical BCR-ABL transcripts. An FDA-authorized test with a detection limit below MR4.5 must be used to determine eligibility for discontinuation. Patients must be frequently monitored by the FDA authorized test to detect possible loss of remission. (5.16)

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

The most commonly reported non-hematologic adverse reactions (≥ 20%) in adult and pediatric patients were nausea, rash, headache, fatigue, pruritus, vomiting, diarrhea, cough, constipation, arthralgia, nasopharyngitis, pyrexia, and night sweats. Hematologic adverse drug reactions include myelosuppression: thrombocytopenia, neutropenia, and anemia. (6.1)

8.4 Pediatric Use

The safety and effectiveness of Tasigna have been established in pediatric patients greater than or equal to 1 year of age with newly diagnosed and resistant or intolerant Ph+ CML in chronic phase [see Clinical Studies (14.5)]. There are no data for pediatric patients under 2 years of age. Use of Tasigna in pediatric

patients 1 year to less than 2 years of age with newly diagnosed or resistant or intolerant Ph+ CML in chronic phase is supported by efficacy in pediatric patients 2 to 6 years of age for these indications. The safety and effectiveness of Tasigna have been established in pediatric patients greater than or equal to 1 year of age with resistant or intolerant Ph+ CML in accelerated phase based on evidence of effectiveness from an adequate and well-controlled single-arm study in adults [see Clinical Studies (14.2)] with safety data from two pediatric studies as described in the next paragraph.

Use of Tasigna in pediatric patients 1 to less than 18 years of age is supported by evidence from two clinical trials [see Clinical Studies (14.5)]. The 25 patients with newly diagnosed Ph+ CML-CP were in the following age groups: 6 children (age 2 to less than 12 years) and 19 adolescents (age 12 to less than 18 years). The 44 patients with resistant or intolerant Ph+ CML-CP included 18 children (age 2 to less than 12 years) and 26 adolescents (age 12 to less than 18 years). All pediatric patients received Tasigna treatment at a dose of 230 mg/m2 twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg). No differences in efficacy or safety were observed between the different age subgroups in the two trials.

The frequency, type, and severity of adverse reactions observed were generally consistent with those observed in adults, with the exception of the laboratory abnormalities of hyperbilirubinemia (Grade 3/4: 16%) and transaminase elevation (AST Grade 3/4: 2.9%, ALT Grade 3/4: 10%), which were reported at a higher frequency in pediatric patients than in adults [see Adverse Reactions (6.1)]. For pediatric growth and development, growth retardation has been reported in pediatric patients with Ph+ CML-CP treated with Tasigna [see Warnings and Precautions (5.14), Adverse Reactions (6.1)].

The safety and effectiveness of Tasigna in pediatric patients below the age of 1 year with newly diagnosed, or resistant or intolerant Ph+ CML in chronic phase and accelerated phase, have not been established.

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	September 30, 2024
Time period of search	October 29, 2007† - September 29, 2024
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product Active Ingredient: Nilotinib, nilotinib hydrochloride monohydrate
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 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

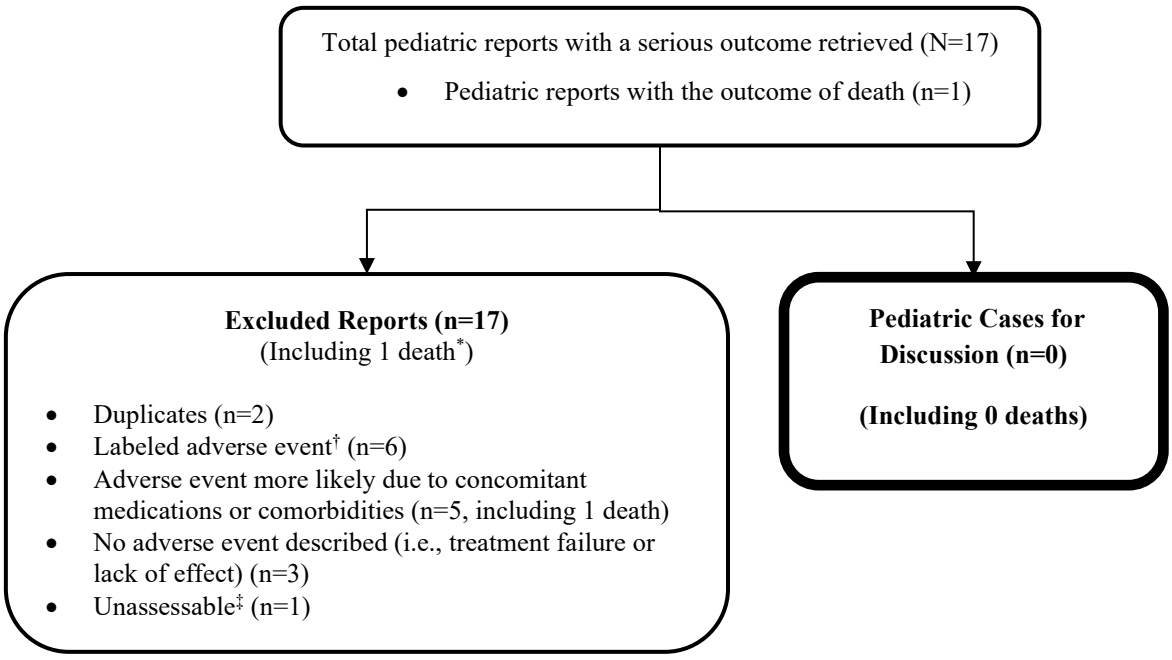
3 RESULTS

3.1 FAERS

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

Our FAERS search retrieved 17 U.S. serious pediatric reports for patients less than 18 years old from October 29, 2007, through September 29, 2024.[b] We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all 17 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 Nilotinib



* One excluded U.S. FAERS report described a fatal outcome. The death was not determined to be attributed to nilotinib. The case described a patient who died from complications of gastrointestinal stromal tumors.
† 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.

[b] Includes one pediatric report that was identified among reports not coded with an age.

4 DISCUSSION

DPV searched FAERS for all U.S. serious reports with nilotinib in pediatric patients less than 18 years of age from October 29, 2007, through September 29, 2024, and identified 17 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 nilotinib in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Tasigna® (nilotinib) capsules, for oral use [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; February 2024.
2. Danziten® (nilotinib) tablets, for oral use [Prescribing Information]. Woburn, MA: Azurity Pharmaceuticals, Inc.; November 2024.
3. Richardson N. Medical Officer Clinical Review of Tasigna (nilotinib) NDA 022068 S-27. September 2017. https://www.fda.gov/media/112713/download.

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.