**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

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| **Product Name** | **Application Type/Number** | **Pediatric Labeling Approval Date** | **Applicant** |
|---|---|---|---|
| Jakafi (ruxolitinib) tablet | NDA 202192 | 12/06/2017<br>12/19/2022 | Incyte Corporation |
| Opzelura (ruxolitinib) cream | NDA 215309 | 09/21/2021<br>07/18/2022 | Incyte Corporation |

**TTT Record ID:** 2024-8993

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## EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for ruxolitinib 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) and the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with ruxolitinib in pediatric patients.

Ruxolitinib, a janus kinase inhibitor, is available as oral tablets and cream for topical use. Jakafi (ruxolitinib) tablet was approved by FDA on November 16, 2011. It is currently indicated for the treatment of (1) intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis in adults, (2) polycythemia vera in adults who have had an inadequate response to or are intolerant of hydroxyurea, (3) steroid-refractory acute graft-versus-host disease (GVHD) in adult and pediatric patients 12 years of age and older, and (4) chronic GVHD after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years of age and older. Opzelura (ruxolitinib) cream was approved on September 21, 2021. It is currently indicated for (1) the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adult and pediatric patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable, and (2) the topical treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older.

This pediatric postmarketing safety review was prompted by the pediatric labeling that included information from the following studies:

- Jakafi
    - December 6, 2017: An open-label, single-arm study failed to establish safety and efficacy of ruxolitinib oral tablets as monotherapy for use in pediatric patients with malignancies. Of note, no new safety signals were observed.
    - December 19, 2022: An open label, single-arm study failed to establish safety and efficacy of ruxolitinib in combination with a standard multi-agent chemotherapy regimen for use in pediatrics with malignancies. Of note, no new safety signals were observed.
- Opzelura
    - September 21, 2021: Two double-blinded, randomized studies established safety and efficacy of ruxolitinib topical cream in pediatric patients aged 12 to 17 years with mild-to-moderate atopic dermatitis
    - July 18, 2022: Two double-blinded, randomized studies established safety and efficacy of ruxolitinib topical cream in pediatric patients aged 12 to 17 years with nonsegmental vitiligo

DPV searched FAERS for all U.S. serious reports with ruxolitinib in pediatric patients less than 18 years of age through April 8, 2024, and identified 872 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 ruxolitinib in pediatric patients less than 18 years of age.

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

# 1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for ruxolitinib 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) and the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with ruxolitinib in pediatric patients.

## 1.1 PEDIATRIC REGULATORY HISTORY

Ruxolitinib, a janus kinase inhibitor, is available as oral tablets and cream for topical use.[1,2]

Jakafi (ruxolitinib phosphate) tablet was approved on November 16, 2011. It is currently indicated for the treatment of:[1]

- intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis in adults.
- polycythemia vera in adults who have had an inadequate response to or are intolerant of hydroxyurea.
- steroid-refractory acute graft-versus-host disease (GVHD) in adult and pediatric patients 12 years of age and older.
- chronic GVHD after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years of age and older.

Opzelura (ruxolitinib) cream was approved on September 21, 2021. It is currently indicated for: [2]

- the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adult and pediatric patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.
- the topical treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older.

This pediatric postmarketing safety review was prompted by the pediatric labeling that included information from the following studies:

- Jakafi
    - December 6, 2017: An open-label, single-arm study failed to establish safety and efficacy of ruxolitinib oral tablets as monotherapy for use in pediatric patients with malignancies.[3-5] Of note, no new safety signals were observed.
    - December 19, 2022: An open label, single-arm study failed to establish safety and efficacy of ruxolitinib in combination with a standard multi-agent chemotherapy regimen for use in pediatrics with malignancies.[6] Of note, no new safety signals were observed.
- Opzelura
    - September 21, 2021: Two double-blinded, randomized studies established safety and efficacy of ruxolitinib topical cream in pediatric patients aged 12 to 17 years with mild-to-moderate atopic dermatitis.[7]

- July 18, 2022: Two double-blinded, randomized studies established safety and efficacy of ruxolitinib topical cream in pediatric patients aged 12 to 17 years with nonsegmental vitiligo.[8]

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

### 1.2 Relevant Labeled Safety Information

The ruxolitinib labeling contains safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection (**Appendix A**). For additional ruxolitinib labeling information, please refer to the full prescribing information.

## 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 | April 9, 2024 |
| Time period of search | All dates through April 8, 2024 |
| Search type | RxLogix Pediatric Focused Review Alert – DPV |
| Product terms | Product active ingredient: ruxolitinib, ruxolitinib phosphate |
| MedDRA search terms (Version 26.1) | All Preferred Terms |
| Other search terms[‡] | Case Seriousness: Serious<br>Country Derived: USA |
| * See Appendix B for a description of the FAERS database.<br>† The Information Visualization Platform (InfoViP) tool was utilized to support de-duplication of FAERS reports. This tool suggests duplicate reports in FAERS query results based on a detection algorithm that incorporates both structured field data and narrative free text. DPV then manually reviewed suggested duplicates to confirm the duplicate reports in this FAERS query.<br>‡ 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.<br>Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; USA=United States of America | |

## 3 RESULTS

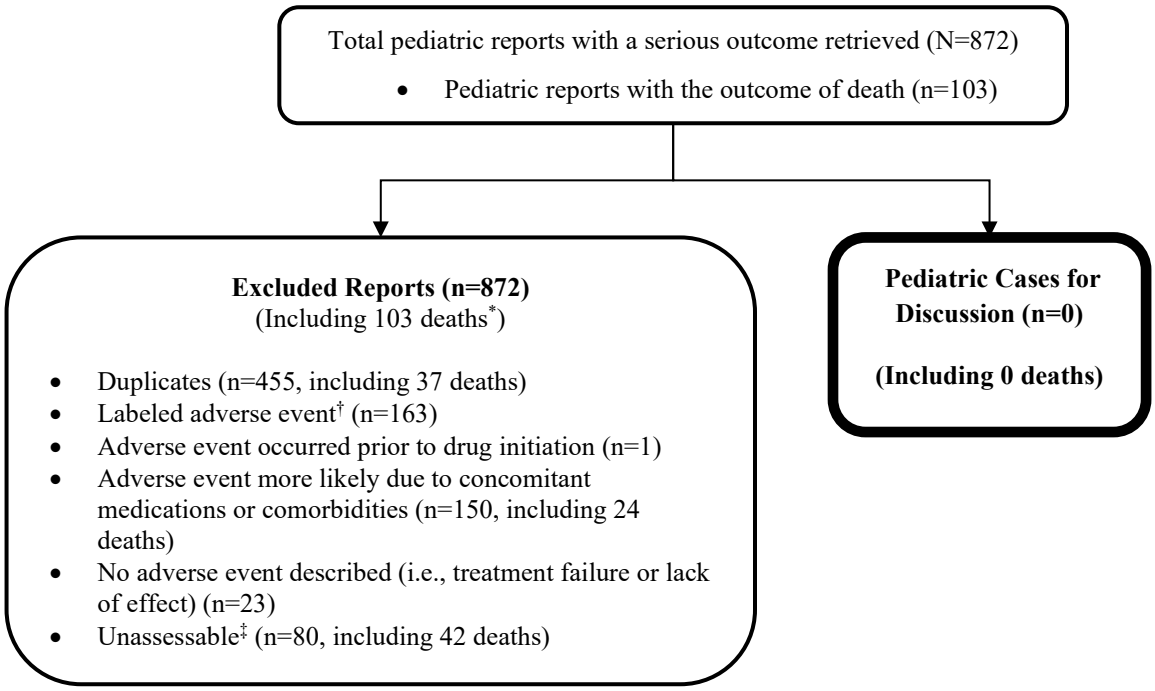
### 3.1 FAERS

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

Our FAERS search retrieved 872 U.S. serious pediatric reports less than 18 years old through April 8, 2024.[a] We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all 872 reports from the case series for the reasons listed in Figure 1. Figure 1 presents the selection of cases for the pediatric case series.

[a] Includes 52 pediatric reports identified among reports not coded with an age.

**Figure 1. Selection of U.S. Serious Pediatric Cases With Ruxolitinib**




*Of the excluded U.S. FAERS reports, 103 described fatal outcomes. After accounting for duplicate reports (n=37), we identified 66 unique cases describing fatal outcomes. Fifty-six cases reported using the oral formulation, while the remaining ten cases did not specify the drug formulation. None of the 66 deaths were determined to be attributed to ruxolitinib. In 24 cases, death was attributable to other causes. Other causes included progression of underlying disease (n=22): GVHD (n=10), hemophagocytic lymphohistiocytosis (n=4), Degos disease (n=2), acute lymphoblastic leukemia (n=2), acute myeloid leukemia (n=2), Wilm's tumor (n=1), mixed type leukemia (n=1)), complications from bone marrow transplant (n=1), and complications from Covid-19 infection (n=1). Forty-two cases were excluded as they contained insufficient clinical information to determine whether ruxolitinib contributed to the fatal outcome.

† 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 searched FAERS for all U.S. serious reports with ruxolitinib in pediatric patients less than 18 years of age through April 8, 2024, and identified 872 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 ruxolitinib in pediatric patients less than 18 years of age.

## 5 CONCLUSION

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

## 6 REFERENCES


1. Jakafi (ruxolitinib) tablets [Prescribing Information]. Wilmington, DE; Incyte Corporation.: January 2023.
2. Opzelura (ruxolitinib) cream [Prescribing Information]. Wilmington, DE; Incyte Corporation.: September 2023.
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8. Ko HS. Division of Dermatology and Dentistry Multi-Disciplinary Review and Evaluation of NDA 215309 S-001. July 18, 2022. Reference ID: 5015000. Available at: https://www.fda.gov/media/160999/download?attachment. Accessed January 8, 2025.

# 7 APPENDICES

## 7.1 APPENDIX A. RUXOLITINIB LABELING

| | JAKAFI (TABLETS) [1] | OPZELURA (TOPICAL CREAM) [2] |
|---|---|---|
| **BOXED WARNING** | | WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE), AND THROMBOSIS<br><br>*See full prescribing information for complete boxed warning.*<br>• Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving Janus kinase inhibitors for inflammatory conditions. (5.1)<br>• Higher rate of all-cause mortality, including sudden cardiovascular death have been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. (5.2)<br>• Lymphoma and other malignancies have been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. (5.3)<br>• Higher rate of MACE (including cardiovascular death, myocardial infarction, and stroke) has been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. (5.4)<br>• Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, some fatal, have occurred in patients treated with Janus kinase inhibitors for inflammatory conditions. (5.5) |
| **WARNINGS AND PRECAUTIONS** | • Thrombocytopenia, Anemia and Neutropenia: Manage by dose reduction, or interruption, or transfusion. (5.1)<br>• Risk of Infection: Assess patients for signs and symptoms of infection and initiate appropriate treatment promptly. Serious infections should have resolved before starting therapy with Jakafi. (5.2)<br>• Symptom Exacerbation Following Interruption or Discontinuation: Manage with supportive care and consider resuming treatment with Jakafi. (5.3)<br>• Risk of Non-Melanoma Skin Cancer: Perform periodic skin examinations. (5.4)<br>• Lipid Elevations: Assess lipid levels 8-12 weeks from start of therapy and treat as needed. (5.5) | • Serious Infections: Serious bacterial, mycobacterial, fungal and viral infections have occurred. Regularly monitor patients for infection and manage it promptly. (5.1)<br>• Non-melanoma Skin Cancers. Basal cell and squamous cell carcinoma have occurred. Perform periodic skin examinations during treatment and following treatment as appropriate. (5.3)<br>• Thrombosis. Thromboembolic events have occurred. (5.5)<br>• Thrombocytopenia, Anemia, and Neutropenia: Thrombocytopenia, anemia, and neutropenia have occurred. Perform CBC monitoring as clinically indicated. (5.6). |

| | JAKAFI (TABLETS) [1] | OPZELURA (TOPICAL CREAM) [2] |
|---|---|---|
| | • Major Adverse Cardiovascular Events (MACE): Monitor for development of MACE. (5.6)<br>• Thrombosis: Evaluate and treat symptoms of thrombosis promptly. (5.7)<br>• Secondary Malignancies: Monitor for development of secondary malignancies, particularly in patients who are current or past smokers. (5.8) | |
| **ADVERSE REACTIONS** | • In myelofibrosis and polycythemia vera, the most common hematologic adverse reactions (incidence > 20%) are thrombocytopenia and anemia. The most common nonhematologic adverse reactions (incidence = 15%) are bruising, dizziness, headache, and diarrhea. (6.1)<br>• In acute graft-versus-host disease, the most common hematologic adverse reactions (incidence > 50%) are anemia, thrombocytopenia, and neutropenia. The most common nonhematologic adverse reactions (incidence > 50%) are infections (pathogen not specified) and edema. (6.1)<br>• In chronic graft-versus-host disease, the most common hematologic adverse reactions (incidence > 35%) are anemia and thrombocytopenia. The most common nonhematologic adverse reactions (incidence = 20%) are infections (pathogen not specified) and viral infections. (6.1) | • In atopic dermatitis, the most common adverse reactions (incidence ≥ 1%) are nasopharyngitis, diarrhea, bronchitis, ear infection, eosinophil count increased, urticaria, folliculitis, tonsillitis, and rhinorrhea. (6)<br>• In nonsegmental vitiligo, the most common adverse reactions (incidence ≥ 1%) are application site acne, application site pruritus, nasopharyngitis, headache, urinary tract infection, application site erythema, and pyrexia. (6) |
| **8.4 Pediatric Use** | Myelofibrosis<br>The safety and effectiveness of Jakafi for treatment of myelofibrosis in pediatric patients have not been established.<br><br>Polycythemia Vera<br>The safety and effectiveness of Jakafi for treatment of polycythemia vera in pediatric patients have not been established.<br><br>Acute Graft-Versus-Host Disease (aGVHD)<br>The safety and effectiveness of Jakafi for treatment of steroid-refractory aGVHD has been established for treatment of pediatric patients 12 years and older. Use of Jakafi in pediatric patients with steroid-refractory aGVHD is supported by evidence from adequate and well-controlled trials of Jakafi in adults [see Clinical Studies (14.3)] and additional pharmacokinetic and safety data in pediatric patients. The safety and effectiveness of Jakafi for treatment of steroid-refractory aGVHD has not been established in pediatric patients younger than 12 years old.<br><br>Chronic Graft-Versus-Host Disease c(GVHD)<br>The safety and effectiveness of Jakafi for treatment of cGVHD after failure of one or two lines of systemic therapy has been established for treatment of pediatric patients 12 years and older. Use of Jakafi in pediatric patients with cGVHD after failure of one or two lines of systemic therapy is supported by evidence from | Atopic Dermatitis<br>The safety and effectiveness of OPZELURA for the topical treatment of mild-to-moderate atopic dermatitis have been established in pediatric patients aged 12 to 17 years of age. Use of OPZELURA in this age group is supported by evidence from TRuEAD1 and TRuE-AD2, which included 92 pediatric subjects aged 12 to 17 years with mild-to-moderate atopic dermatitis [see Clinical Pharmacology (12.3) and Clinical Studies (14.1)]. No clinically meaningful differences in safety or effectiveness were observed between adult and pediatric subjects.<br><br>The safety and effectiveness of OPZELURA in pediatric patients younger than 12 years of age with atopic dermatitis have not been established.<br><br>Nonsegmental Vitiligo<br>The safety and effectiveness of OPZELURA for the topical treatment of nonsegmental vitiligo have been established in pediatric patients aged 12 to 17 years of age. Use of OPZELURA in this age group is supported by evidence from TRuE-V1 and TRuE-V2, which included 55 pediatric subjects aged 12 to 17 years with nonsegmental vitiligo [see Clinical Studies (14.2)]. No clinically |

| | JAKAFI (TABLETS) [1] | OPZELURA (TOPICAL CREAM) [2] |
|---|---|---|
| | adequate and well-controlled trials of Jakafi in adults and adolescents [see Clinical Studies (14.4)] and additional pharmacokinetic and safety data in pediatric patients. The safety and effectiveness of Jakafi for treatment of cGVHD has not been established in pediatric patients younger than 12 years old.<br><br>Other Myeloproliferative Neoplasms, Leukemias, and Solid Tumors<br>The safety and effectiveness of ruxolitinib were assessed but not established in a single arm trial (NCT01164163) in patients with relapsed or refractory solid tumors, leukemias, or myeloproliferative neoplasms. The patients included 18 children (age 2 to < 12 years) and 14 adolescents (age 12 to < 17 years). Overall, 19% of patients received more than one cycle. No new safety signals were observed in pediatric patients in this trial.<br><br>The safety and effectiveness of ruxolitinib in combination with chemotherapy for treatment of high-risk, de novo CRLF2 rearranged or JAK pathway–mutant Ph-like acute lymphoblastic leukemia (ALL) were assessed but not established in a single-arm trial (NCT02723994). The patients included 2 infants (age < 2 years), 42 children (age 2 to < 12 years) and 62 adolescents (age 12 to < 17 years). No new safety signals were observed in pediatric patients in this trial.<br><br>Juvenile Animal Toxicity Data<br>Administration of ruxolitinib to juvenile rats resulted in effects on growth and bone measures. When administered starting at postnatal day 7 (the equivalent of a human newborn) at doses of 1.5 to 75 mg/kg/day, evidence of fractures occurred at doses = 30 mg/kg/day, and effects on body weight and other bone measures [e.g., bone mineral content, peripheral quantitative computed tomography, and x-ray analysis] occurred at doses = 5 mg/kg/day. When administered starting at postnatal day 21 (the equivalent of a human 2-3 years of age) at doses of 5 to 60 mg/kg/day, effects on body weight and bone occurred at doses = 15 mg/kg/day, which were considered adverse at 60 mg/kg/day. Males were more severely affected than females in all age groups, and effects were generally more severe when administration was initiated earlier in the postnatal period. These findings were observed at exposures that are at least 27% the clinical exposure at the maximum recommended dose of 25 mg twice daily. | meaningful differences in safety or effectiveness were observed between adult and pediatric subjects.<br><br>The safety and effectiveness of OPZELURA in pediatric patients younger than 12 years of age with nonsegmental vitiligo have not been established.<br><br>Juvenile Animal Toxicity Data<br>Oral administration of ruxolitinib to juvenile rats resulted in effects on growth and bone measures. When administered starting at postnatal day 7 (the equivalent of a human newborn) at doses of 1.5 to 75 mg/kg/day, evidence of fractures occurred at doses ≥ 30 mg/kg/day, and effects on body weight and other bone measures [e.g., bone mineral content, peripheral quantitative computed tomography, and x-ray analysis] occurred at doses ≥ 5 mg/kg/day. When administered starting at postnatal day 21 (the equivalent of a human 2-3 years of age) at doses of 5 to 60 mg/kg/day, effects on body weight and bone occurred at doses ≥ 15 mg/kg/day, which were considered adverse at 60 mg/kg/day. Males were more severely affected than females in all age groups, and effects were generally more severe when administration was initiated earlier in the postnatal period. These findings were observed at systemic exposures that are at least 40% the MRHD clinical systemic exposure. |

## 7.1 APPENDIX B. 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.