HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OPZELURA cream safely and effectively. See full prescribing information for OPZELURA cream.

OPZELURA® (ruxolitinib) cream, for topical use
Initial U.S. Approval: 2011

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE), AND THROMBOSIS

See full prescribing information for complete boxed warning.

- **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)**
- **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)**
- **Lymphoma and other malignancies have been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. (5.3)**
- **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)**
- **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)**

RECENT MAJOR CHANGES

Indications and Usage (1.1)	09/2025
Dosage and Administration (2.1)	09/2025
Warnings and Precautions (5.6)	09/2025

INDICATIONS AND USAGE

OPZELURA is a Janus kinase (JAK) inhibitor indicated for:

- the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adult and pediatric patients 2 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. (1.1)
- the topical treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older. (1.2)

Limitations of Use

Use of OPZELURA in combination with therapeutic biologics, other JAK inhibitors or potent immunosuppressants such as azathioprine or cyclosporine is not recommended. (1.3)

DOSAGE AND ADMINISTRATION

Atopic Dermatitis

- Apply a thin layer of OPZELURA topically twice daily to affected areas of up to 20% body surface area. (2.1)
- Do not use OPZELURA with occlusive dressings. (2.1)

Adult and Pediatric Patients 12 Years of Age and Older

- Do not use more than one 60 gram tube of OPZELURA per week or one 100 gram tube per 2 weeks. (2.1)

Pediatric Patients 2 to 11 Years of Age

- Do not use more than one 60 gram tube of OPZELURA per 2 weeks. (2.1)

Nonsegmental Vitiligo

- Apply a thin layer of OPZELURA topically twice daily to affected areas of up to 10% body surface area. (2.2)
- Do not use more than one 60 gram tube of OPZELURA per week or one 100 gram tube per 2 weeks. (2.2)

DOSAGE FORMS AND STRENGTHS

Cream: 1.5% ruxolitinib supplied in 60 g and 100 g tubes (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- *Serious Infections:* Serious bacterial, mycobacterial, fungal and viral infections have occurred. Regularly monitor patients for infection and manage it promptly. (5.1)
- *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)
- *Thrombosis.* Thromboembolic events have occurred. (5.5)
- *Cytopenias:* Thrombocytopenia, anemia, neutropenia, lymphopenia, and leukopenia have occurred. Perform CBC monitoring as clinically indicated. (5.6)

ADVERSE REACTIONS

- In atopic dermatitis, the most common adverse reactions (incidence ≥ 1%) are nasopharyngitis, diarrhea, bronchitis, ear infection, eosinophil count increased, urticaria, folliculitis, tonsillitis, rhinorrhea, upper respiratory tract infection, COVID-19, application site reactions, pyrexia, and white blood cell decreased. (6)
- 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)

To report SUSPECTED ADVERSE REACTIONS, contact Incyte Corporation at 1-855-463-3463 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS, AND THROMBOSIS

SERIOUS INFECTIONS

Patients treated with oral Janus kinase inhibitors for inflammatory conditions are at risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease.**
- **Invasive fungal infections, including cryptococcosis, and pneumocystosis.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

Avoid use of OPZELURA in patients with an active, serious infection, including localized infections. If a serious infection develops, interrupt OPZELURA until the infection is controlled.

The risks and benefits of treatment with OPZELURA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with OPZELURA *[see Warnings and Precautions (5.1)]*.

MORTALITY

In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor comparing an oral JAK inhibitor to tumor necrosis factor (TNF) blocker treatment, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with the JAK inhibitor *[see Warnings and Precautions (5.2)]*.

MALIGNANCIES

Malignancies were reported in patients treated with OPZELURA. Lymphoma and other malignancies have been observed in patients receiving JAK inhibitors used to treat inflammatory conditions. In RA patients treated with an oral JAK inhibitor, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC)) was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk *[see Warnings and Precautions (5.3)]*.

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with an oral JAK inhibitor, a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke), was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue OPZELURA in patients who have experienced a myocardial infarction or stroke *[see Warnings and Precautions (5.4)]*.

THROMBOSIS

Thromboembolic events were observed in trials with OPZELURA. Thrombosis, including pulmonary embolism (PE), deep venous thrombosis (DVT), and arterial thrombosis have been reported in patients receiving JAK inhibitors used to treat inflammatory conditions. Many of these adverse reactions were serious and some resulted in death. In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with an oral JAK inhibitor, a higher rate of thrombosis was observed when compared with TNF blockers. Avoid OPZELURA in patients at risk. If symptoms of thrombosis occur, discontinue OPZELURA and treat appropriately *[see Warnings and Precautions (5.5)]*.

1. INDICATIONS AND USAGE

1.1. Atopic Dermatitis

OPZELURA is indicated for the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adult and pediatric patients 2 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

1.2. Nonsegmental Vitiligo

OPZELURA is indicated for the topical treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older.

1.3. Limitations of Use

Use of OPZELURA in combination with therapeutic biologics, other Janus kinase (JAK) inhibitors, or potent immunosuppressants such as azathioprine or cyclosporine is not recommended.

2. DOSAGE AND ADMINISTRATION

2.1. Recommended Dosage and Administration for Atopic Dermatitis

OPZELURA is for topical use only. OPZELURA is not for ophthalmic, oral, or intravaginal use.

Instruct patients to apply a thin layer of OPZELURA twice daily to affected areas of up to 20% body surface area.

Do not use OPZELURA with occlusive dressings.

Stop using when signs and symptoms (e.g., itch, rash, and redness) of atopic dermatitis resolve. If signs and symptoms do not improve within 8 weeks, patients should be re-examined by their healthcare provider *[see Clinical Studies (14.1)]*.

Adult and Pediatric Patients 12 Years of Age and Older

Do not use more than one 60 gram tube of OPZELURA per week or one 100 gram tube per 2 weeks.

Pediatric Patients 2 to 11 Years of Age

Do not use more than one 60 gram tube of OPZELURA per 2 weeks.

2.2. Recommended Dosage and Administration for Nonsegmental Vitiligo

OPZELURA is for topical use only. OPZELURA is not for ophthalmic, oral, or intravaginal use.

Instruct patients to apply a thin layer of OPZELURA twice daily to affected areas of up to 10% body surface area.

Do not use more than one 60 gram tube of OPZELURA per week or one 100 gram tube per 2 weeks.

Satisfactory patient response may require treatment with OPZELURA for more than 24 weeks. If the patient does not find the repigmentation meaningful by 24 weeks, the patient should be re-evaluated by the healthcare provider *[see Clinical Studies (14.2)]*.

3. DOSAGE FORMS AND STRENGTHS

Cream: 15 mg of ruxolitinib per gram (1.5%) of white to off-white cream supplied in 60 g and 100 g tubes

4. CONTRAINDICATIONS

None.

5. WARNINGS AND PRECAUTIONS

5.1. Serious Infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving oral JAK inhibitors.

Serious lower respiratory tract infections were reported in the clinical development program with topical ruxolitinib.

Avoid use of OPZELURA in patients with an active, serious infection, including localized infections. Consider the risks and benefits of treatment prior to initiating OPZELURA in patients:

- with chronic or recurrent infection
- with a history of a serious or an opportunistic infection
- who have been exposed to tuberculosis
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with OPZELURA. Interrupt OPZELURA if a patient develops a serious infection, an opportunistic infection, or sepsis. Do not resume OPZELURA until the infection is controlled.

Tuberculosis

No cases of active tuberculosis (TB) were reported in clinical trials with OPZELURA. Cases of active TB were reported in clinical trials of oral JAK inhibitors used to treat inflammatory conditions. Consider evaluating patients for latent and active TB infection prior to administration of OPZELURA.

During OPZELURA use, monitor patients for the development of signs and symptoms of TB.

Viral Reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical trials with JAK inhibitors used to treat inflammatory conditions including OPZELURA. If a patient develops herpes zoster, consider interrupting OPZELURA treatment until the episode resolves.

Hepatitis B and C

The impact of JAK inhibitors used to treat inflammatory conditions including OPZELURA on chronic viral hepatitis reactivation is unknown. Patients with a history of hepatitis B or C infection were excluded from clinical trials.

Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking oral ruxolitinib.

OPZELURA initiation is not recommended in patients with active hepatitis B or hepatitis C.

5.2. Mortality

In a large, randomized, postmarketing safety study of an oral JAK inhibitor in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed in patients treated with the JAK inhibitor compared with TNF blockers.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA.

5.3. Malignancy and Lymphoproliferative Disorders

Malignancies, including lymphomas, were observed in clinical trials of oral JAK inhibitors used to treat inflammatory conditions. Patients who are current or past smokers are at additional increased risk.

Malignancies, including lymphomas, have occurred in patients receiving JAK inhibitors used to treat inflammatory conditions. In a large, randomized, postmarketing safety study of an oral JAK inhibitor in RA patients, a higher rate of malignancies (excluding non-melanoma skin cancer) was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lymphomas was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lung cancers was observed in current or past smokers treated with the JAK inhibitor compared to those treated with TNF blockers. In this study, current or past smokers had an additional increased risk of overall malignancies.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients with a known malignancy (other than successfully treated non-melanoma skin cancers), patients who develop a malignancy when on treatment, and patients who are current or past smokers.

Non-melanoma Skin Cancers

Non-melanoma skin cancers including basal cell and squamous cell carcinoma have occurred in patients treated with OPZELURA. Perform periodic skin examinations during OPZELURA treatment and following treatment as appropriate. Exposure to sunlight and UV light should be limited by wearing protective clothing and using broad-spectrum sunscreen.

5.4. Major Adverse Cardiovascular Events (MACE)

In a large, randomized, postmarketing safety study of an oral JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of major adverse cardiovascular events (MACE) defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke was observed with the JAK inhibitor compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur. Discontinue OPZELURA in patients that have experienced a myocardial infarction or stroke.

5.5. Thrombosis

Thromboembolic events were observed in clinical trials with OPZELURA.

Thrombosis, including deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis have been reported in patients receiving JAK inhibitors used to treat inflammatory conditions. Many of these adverse reactions were serious and some resulted in death.

In a large, randomized, postmarketing safety study of an oral JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, higher rates of overall thrombosis, DVT, and PE were observed compared to those treated with TNF blockers.

Avoid OPZELURA in patients who may be at increased risk of thrombosis. If symptoms of thrombosis occur, discontinue OPZELURA and evaluate and treat patients appropriately.

5.6. Cytopenias

Thrombocytopenia, anemia, neutropenia, lymphopenia, and leukopenia were reported in the clinical trials with OPZELURA. Consider the benefits and risks for individual patients who have a known history of these events prior to initiating therapy with OPZELURA. Perform CBC monitoring as clinically indicated. Discontinue OPZELURA if signs and/or symptoms associated with clinically significant decreases in laboratory values occur.

5.7. Lipid Elevations

Treatment with oral ruxolitinib has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.

6. ADVERSE REACTIONS

6.1. Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Adult and Pediatric Subjects 2 Years of Age and Older with Atopic Dermatitis

Adult and Pediatric Subjects 12 Years of Age and Older

In two double-blind, vehicle-controlled clinical trials (TRuE-AD1 and TRuE-AD2), 499 adult and pediatric subjects 12 years of age and older with atopic dermatitis were treated topically with OPZELURA twice daily for 8 weeks *[see Clinical Studies (14.1)]*. The adverse reactions reported by ≥ 1% of OPZELURA treated subjects and at a greater incidence than in the vehicle arm are listed in Table 1.

Table 1: Adverse Reactions Occurring in ≥ 1% of Adult and Pediatric Subjects 12 Years of Age and Older Treated with OPZELURA for Atopic Dermatitis through Week 8 in TRuE-AD1 and TRuE-AD2

Adverse Reaction	OPZELURA (N = 499) n (%)	Vehicle (N = 250) n (%)
Nasopharyngitis	13 (3)	2 (1)
Bronchitis	4 (1)	0 (0)
Ear infection	4 (1)	0 (0)

Adverse Reaction	OPZELURA (N = 499) n (%)	Vehicle (N = 250) n (%)
Eosinophil count increased	4 (1)	0 (0)
Urticaria	4 (1)	0 (0)
Diarrhea	3 (1)	1 (< 1)
Folliculitis	3 (1)	0 (0)
Tonsillitis	3 (1)	0 (0)
Rhinorrhea	3 (1)	1 (< 1)

Adverse reactions that occurred in TRuE-AD1 and TRuE-AD2 in < 1% of subjects in the OPZELURA group and none in the vehicle group were: neutropenia, allergic conjunctivitis, pyrexia, seasonal allergy, herpes zoster, otitis externa, Staphylococcal infection, and acneiform dermatitis.

No clinically meaningful differences in safety or effectiveness were observed between adult and pediatric subjects 12 to 17 years of age.

Pediatric Subjects 2 to 11 Years of Age

In a double-blind, vehicle-controlled clinical trial (TRuE-AD3), 130 pediatric subjects 2 to 11 years of age with mild to moderate atopic dermatitis were treated topically with OPZELURA twice daily for 8 weeks *[see Clinical Studies (14.1)]*. The adverse reactions reported by ≥ 1% of subjects treated with OPZELURA and at a greater incidence than in the vehicle arm are listed in Table 2.

Table 2: Adverse Reactions Occurring in ≥ 1% Pediatric Subjects 2 to 11 Years of Age Treated with OPZELURA for Atopic Dermatitis through Week 8 in TRuE-AD3

Adverse Reaction	OPZELURA (N = 130) n (%)	Vehicle (N = 65) n (%)
Upper respiratory tract infection[a]	20 (15)	7 (11)
COVID-19	6 (5)	2 (3)
Application site reaction[b]	6 (5)	1 (2)
Pyrexia	3 (2)	0 (0)
White blood cell decreased[c]	2 (2)	0 (0)

[a] Upper respiratory tract infection includes upper respiratory tract infection, nasopharyngitis, rhinorrhea, oropharyngeal pain, respiratory tract congestion, viral upper respiratory tract infection
[b] Application site reaction includes application site pain, application site irritation, application site discomfort, application site pruritus
[c] White blood cell decreased includes white blood cell decreased, leukopenia

Subjects with cytopenias (defined as hemoglobin < 10 g/dL, absolute neutrophil count (ANC) < 1000/µL, and platelet count < 100,000/µL) at screening were excluded from the trial. The impact of OPZELURA on blood cell counts in this population has not been studied.

Adverse Reactions in Adult and Pediatric Subjects 12 Years of Age and Older with Nonsegmental Vitiligo

In two double-blind, vehicle-controlled clinical trials (TRuE-V1 and TRuE-V2), 449 adult and pediatric subjects 12 years of age and older with nonsegmental vitiligo were treated topically with OPZELURA twice daily for 24 weeks *[see Clinical Studies (14.2)]*. The adverse reactions reported by OPZELURA treated subjects with an incidence of ≥ 1% and at least 1% greater incidence than in the vehicle arm in the 24-week double-blind period are listed in Table 3.

Table 3: Adverse Reactions Occurring in ≥ 1% of Adult and Pediatric Subjects 12 Years of Age and Older Treated with OPZELURA for Nonsegmental Vitiligo through Week 24 in TRuE-V1 and TRuE-V2

Adverse Reaction	OPZELURA (N = 449) n (%)	Vehicle (N = 224) n (%)
Application site acne	26 (6)	2 (1)
Application site pruritus	23 (5)	6 (3)
Nasopharyngitis	19 (4)	5 (2)
Headache	17 (4)	6 (3)
Urinary tract infection	7 (2)	1 (< 1)
Application site erythema	7 (2)	1 (< 1)
Pyrexia	6 (1)	0

Adverse reactions that occurred in TRuE-V1 and TRuE-V2 in ≥ 0.5% to < 1% of subjects in the OPZELURA group and none in the vehicle group were: application site dermatitis, hypertension, anxiety, application site discoloration, application site folliculitis, dermatitis contact, diarrhea, ear infection, gastritis, gastroenteritis, hordeolum, influenza-like illness, insomnia, nasal congestion, and vomiting.

No clinically meaningful differences in safety or effectiveness were observed between adults and pediatric subjects.

7. DRUG INTERACTIONS

Drug interaction studies with OPZELURA have not been conducted.

Ruxolitinib is known to be a substrate for cytochrome P450 3A4 (CYP3A4). Inhibitors of CYP3A4 may increase ruxolitinib systemic concentrations whereas inducers of CYP3A4 may decrease ruxolitinib systemic concentrations *[see Clinical Pharmacology (12.3)]*.

Strong Inhibitors of CYP3A4

Avoid concomitant use of OPZELURA with strong inhibitors of CYP3A4 as there is a potential to increase the systemic exposure of ruxolitinib and could increase the risk of OPZELURA adverse reactions *[see Clinical Pharmacology (12.3)]*.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Pregnancy Exposure Registry

There is a pregnancy registry that monitors pregnancy outcomes in pregnant persons exposed to OPZELURA during pregnancy. Pregnant persons exposed to OPZELURA and healthcare providers should report OPZELURA exposure by calling 1-855-463-3463 or visiting www.opzelura.pregnancy.incyte.com.

Risk Summary

Available data from pregnancies reported in clinical trials with OPZELURA are not sufficient to evaluate a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of ruxolitinib to pregnant rats and rabbits during the period of organogenesis resulted in adverse developmental outcomes at doses associated with maternal toxicity *(see Data)*.

The background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies carry some risk of birth defects, loss, or other adverse outcomes. The background risk in the U.S. general population of major birth defects and miscarriage is 2-4% and 15-20%, respectively.

Data

Animal Data

Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30, or 60 mg/kg/day in rats and 10, 30, or 60 mg/kg/day in rabbits. There were no treatment-related malformations at any dose. A decrease in fetal weight of approximately 9% was noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose resulted in systemic exposure approximately 22 times the clinical systemic exposure at the maximum recommended human dose (MRHD; the clinical systemic exposure from ruxolitinib cream, 1.5% applied twice daily to 25-40% atopic dermatitis-affected body surface area is used for calculation of multiples of human exposure). In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose resulted in systemic exposure approximately 70% the MRHD clinical systemic exposure.

In a pre-and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse effects on embryofetal survival, postnatal growth, development parameters or offspring reproductive function at the highest dose evaluated (3.1 times the MRHD clinical systemic exposure).

8.2. Lactation

Risk Summary

There are no data on the presence of ruxolitinib in human milk, the effects on the breastfed child, or the effects on milk production. Ruxolitinib was present in the milk of lactating rats *(see Data)*.

When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the serious adverse findings in adults, including risks of serious infections, thrombocytopenia, anemia, and neutropenia, advise women not to breastfeed during treatment with OPZELURA and for approximately four weeks after the last dose (approximately 5-6 elimination half-lives).

Data

Lactating rats were administered a single dose of [14C]-labeled ruxolitinib (30 mg/kg) on postnatal Day 10, after which plasma and milk samples were collected for up to 24 hours. The AUC for total radioactivity in milk was approximately 13 times the maternal plasma AUC. Additional analysis showed the presence of ruxolitinib and several of its metabolites in milk, all at levels higher than those in maternal plasma.

8.4. Pediatric Use

Atopic Dermatitis

The safety and effectiveness of OPZELURA for the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis have been established in non-immunocompromised pediatric patients ages 2 years and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Use of OPZELURA in this age group is supported by evidence from adequate and well-controlled trials in adults and pediatric subjects ages 2 years and older with mild to moderate atopic dermatitis *[see Clinical Studies (14.1)]*. Trials included 92 subjects 12 to 17 years of age and 130 subjects 2 to 11 years of age treated with OPZELURA.

Application site reactions, pyrexia, and decreased white blood cell were reported more frequently in pediatric subjects ages 2 to ll years compared to adults and pediatric subjects ages 12 years and older *[see Adverse Reactions (6.1)]*. The safety and effectiveness of OPZELURA have not been established in pediatric patients younger than 2 years of age with atopic dermatitis.

Nonsegmental Vitiligo

The safety and effectiveness of OPZELURA for the topical treatment of nonsegmental vitiligo have been established in pediatric patients ages 12 years and older. Use of OPZELURA in this age group is supported by evidence from TRuE-V1 and TRuE-V2, which included 55 subjects ages 12 to 17 years with nonsegmental vitiligo *[see Clinical Studies (14.2)]*.

The safety and effectiveness of OPZELURA have not been established in pediatric patients younger than 12 years of age with nonsegmental vitiligo.

Juvenile Animal Toxicity Data

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 45% the MRHD in pediatric subjects 2 to 11 years of age (the clinical systemic exposure from ruxolitinib cream, 1.5% applied twice daily to 35-50% atopic dermatitis-affected body surface area in pediatric subjects 2 to 11 years of age is used for the calculation of multiples of human exposure in this subsection).

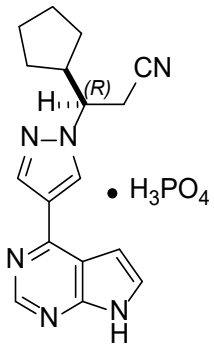
8.5. Geriatric Use

Of the 1249 total subjects with atopic dermatitis in clinical trials with OPZELURA, 115 (9%) were 65 years of age and older *[see Clinical Studies (14.1)]*. No clinically meaningful differences in safety or effectiveness were observed between subjects less than 65 years and subjects 65 years and older.

Of the 831 total subjects enrolled with nonsegmental vitiligo in clinical trials with OPZELURA, 65 (8%) were 65 years of age and older *[see Clinical Studies (14.2)]*. Clinical trials of OPZELURA in subjects with nonsegmental vitiligo did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger adult subjects.

11. DESCRIPTION

Ruxolitinib phosphate is a Janus kinase inhibitor with the chemical name (*R*)-3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate and a molecular weight of 404.36 g/mol. Ruxolitinib phosphate has the following structural formula:



Ruxolitinib phosphate is a white to off-white to light yellow to light pink powder.

OPZELURA (ruxolitinib) cream is a white to off-white oil-in-water, solubilized emulsion cream for topical use.

Each gram of OPZELURA contains 15 mg of ruxolitinib (equivalent to 19.8 mg of ruxolitinib phosphate) in a cream containing cetyl alcohol, dimethicone 350, edetate disodium, glyceryl stearate SE, light mineral oil, medium chain triglycerides, methylparaben, phenoxyethanol, phosphoric acid, polyethylene glycol 200, polysorbate 20, propylene glycol, propylparaben, stearyl alcohol, purified water, white petrolatum, and xanthan gum.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

Ruxolitinib, a Janus kinase (JAK) inhibitor, inhibits JAK1 and JAK2 which mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. JAK signaling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, activation and subsequent localization of STATs to the nucleus leading to modulation of gene expression. The relevance of inhibition of specific JAK enzymes to therapeutic effectiveness is not currently known.

12.2. Pharmacodynamics

The pharmacodynamics of OPZELURA is unknown.

Cardiac Electrophysiology

Under the conditions of clinical use, OPZELURA is not expected to prolong the QT interval.

12.3. Pharmacokinetics

In Trial INCB18424-103, the pharmacokinetics of ruxolitinib were evaluated in 20 adult subjects and 21 pediatric subjects 13 years of age and older with atopic dermatitis with a mean ± SD BSA involvement of 37.5 ± 16.1% (range 25% to 90%). Subjects applied approximately 1.5 mg/cm^2 of OPZELURA (dose range was approximately 1.2 grams to 37.6 grams per application) twice daily for 28 days.

Absorption

Plasma concentrations of ruxolitinib were quantifiable in all subjects. In adult subjects, the mean ± SD maximum plasma concentration (C_{max}) and area under the concentration time curve from 0 to 12 hours post dose ($AUC_{0–12}$) for ruxolitinib on Day 1 were 449 ± 883 nM and 3215 ± 6184 h*nM, respectively.

There is no evidence of ruxolitinib accumulation after daily application of OPZELURA for 28 days in subjects with atopic dermatitis.

Distribution

Plasma protein binding is approximately 97%.

Elimination

The mean terminal half-life of ruxolitinib following topical application of OPZELURA was estimated in 9 subjects and is approximately 116 hours.

Metabolism

Ruxolitinib is primarily metabolized by CYP3A4 and to a lesser extent by CYP2C9 in vitro.

Excretion

Ruxolitinib and its metabolites are primarily excreted by urine (74%) and feces (22%). Less than 1% is excreted as unchanged drug.

Specific Populations

Pediatric Patients

In Trial INCB18424-103, in subjects 13 to 17 years of age with atopic dermatitis, the mean ± SD C_{max} and $AUC_{0–12}$ for ruxolitinib on Day 1 were 110 ± 255 nM and 801 ± 2019 h*nM, respectively.

In Trial INCB18424-109, the pharmacokinetics of ruxolitinib was evaluated in 27 subjects 2 to 11 years of age with atopic dermatitis with a mean ± SD BSA involvement of 58.9 ± 20.6% (range 35% to 92%). The mean ± SD daily dose of the cream was 8.5 ± 6.3 g. Plasma concentrations of ruxolitinib were quantifiable in all subjects. The mean ± SD steady state plasma concentration (C_{ss}) and projected area under the concentration time curve from 0 to 12 hours post dose (AUC_{0-12h}) for ruxolitinib were 84.1 ± 183 nM and 1009.2 ± 2196 h*nM, respectively in subjects 7 to less than 12 years of age (n=12) and 109 ± 122 nM and 1308 ± 1464 h*nM, respectively in subjects 2 to less than 7 years of age (n=15).

There is no evidence of ruxolitinib accumulation after twice daily application of OPZELURA for 28 days in subjects 2 years to 17 years of age with atopic dermatitis.

Drug Interactions

Clinical Studies

Drug interaction studies with OPZELURA have not been conducted.

- *Strong CYP3A4 inhibitors*: The C_{max} and AUC of ruxolitinib increased 33% and 91%, respectively, with administration of 10 mg single dose orally following ketoconazole 200 mg twice daily for four days, compared to receiving the oral ruxolitinib dose alone in healthy subjects.
- *Mild or moderate CYP3A4 inhibitors*: There was an 8% and 27% increase in the C_{max} and AUC of ruxolitinib, respectively, with the administration of 10 mg single dose orally following erythromycin, a moderate CYP3A4 inhibitor, at 500 mg twice daily for 4 days, compared to receiving the oral ruxolitinib dose alone in healthy subjects. There are no clinical studies conducted with mild CYP3A4 inhibitor.
- *CYP3A4 inducers:* The C_{max} and AUC of ruxolitinib decreased 32% and 61%, respectively, with the oral administration of 50 mg single dose of ruxolitinib following rifampin 600 mg once daily for 10 days, compared to receiving the oral ruxolitinib dose alone in healthy subjects.

In Vitro Studies

- *Cytochrome P450 (CYP) Enzymes:* Ruxolitinib is not expected to inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and CYP3A4 or induce CYP1A2, 2B6 and 3A4 following topical application.
- *Transporter Systems:* Ruxolitinib is not expected to inhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, or OAT3 transporter systems following topical application. Ruxolitinib is not a substrate for the P-gp transporter.

13. NONCLINICAL TOXICOLOGY

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Ruxolitinib was not carcinogenic when administered orally in the 6-month Tg.rasH2 transgenic mouse model. In a 2-year oral rat carcinogenicity study, no drug-related tumors were observed at oral doses of ruxolitinib up to 60 mg/kg/day (3.5 times the MRHD clinical systemic exposure). In a 2-year dermal mouse carcinogenicity study, no drug-related tumors were observed at topical doses of ruxolitinib cream up to 1.5% applied at 100 µl/day (2.8 times the MRHD clinical systemic exposure).

Ruxolitinib was not mutagenic in a bacterial mutagenicity assay (Ames test) or clastogenic in an in vitro chromosomal aberration assay (cultured human peripheral blood lymphocytes) or an in vivo rat bone marrow micronucleus assay.

In a fertility study, ruxolitinib was administered orally to male rats prior to and throughout mating and to female rats prior to mating and up to the implantation day (gestation day 7). Ruxolitinib had no effect on fertility or reproductive function in male or female rats at doses up to 60 mg/kg/day (22 times the MRHD clinical systemic exposure). However, in female rats, doses of greater than or equal to 30 mg/kg/day (3.5 times the MRHD clinical systemic exposure) resulted in increased post-implantation loss.

14. CLINICAL STUDIES

14.1. Atopic Dermatitis

Adult and Pediatric Subjects 12 Years of Age and Older

Two double-blind, randomized, vehicle-controlled trials of identical design (TRuE-AD1 and TRuE-AD2, NCT03745638 and NCT03745651, respectively) enrolled a total of 1249 adult and pediatric subjects aged 12 and older, and subjects were treated twice daily (BID) for 8 weeks. A total of 20% of subjects were 12 to 17 years of age and 9% were 65 years or older. Females constituted 62% of subjects, 70% of subjects were White, 23% were Black, 4% were Asian, and 3% were other races. Subjects had affected body surface area (BSA) of 3 to 20%, and an Investigator's Global Assessment (IGA) score of 2 (mild) to 3 (moderate) on a severity scale of 0 to 4. At baseline, subjects had a mean affected BSA of 9.8% and 39% had affected areas on the face, 25% of subjects had an IGA score of 2 and 75% had a score of 3. The baseline Itch Numerical Rating Scale (Itch NRS), defined as the 7-day average of the worst level of itch intensity in the last 24 hours, was 5 on a scale of 0 to 10.

The primary efficacy endpoint was the proportion of subjects at Week 8 achieving IGA treatment success (IGA-TS) defined as a score of 0 (clear) or 1 (almost clear) with ≥ 2 grade improvement from baseline. Efficacy was also assessed using a ≥ 4-point improvement in Itch NRS.

Efficacy results for OPZELURA from the two trials are summarized in Table 4.

Table 4: Efficacy Results at Week 8 in Adult and Pediatric Subjects 12 Years of Age and Older with Atopic Dermatitis (TRuE-AD1 and TRuE-AD2)

	TRuE-AD1			TRuE-AD2		
	OPZELURA (N = 253)	Vehicle (N = 126)	Treatment Difference and 95% Confidence Interval	OPZELURA (N = 228)	Vehicle (N = 118)	Treatment Difference and 95% Confidence Interval
IGA-TS[a]	53.8% (136/253)	15.1% (19/126)	38.9% (30.3%, 47.4%)	51.3% (117/228)	7.6% (9/118)	44.1% (36.2%, 52.0%)
Itch NRS (≥ 4 point reduction) (n/N)[b]	52.2% (84/161)	15.4% (12/78)	36.7% (25.5%, 48.0%)	50.7% (74/146)	16.3% (13/80)	35.8% (24.4%, 47.2%)

[a] Defined as an IGA score of 0 or 1 with a ≥ 2-grade improvement from baseline
[b] N = subjects with a baseline Itch NRS score ≥ 4.

Pediatric Subjects 2 to 11 Years of Age

A double-blind, randomized, vehicle-controlled trial, TRuE-AD3 (NCT04921969), enrolled a total of 330 pediatric subjects, 2 to 11 years of age, and subjects were treated twice daily (BID) for 8 weeks. In the trial, 51% of subjects were 2 to 6 years of age and 49% of subjects were 7 to 11 years of age. Females constituted 54% of subjects, 55% of subjects were White, 32% were Black, 6% were Asian, and 7% were other races. Subjects had affected BSA of 3 to 20%, and an IGA score of 2 (mild) to 3 (moderate) on a severity scale of 0 to 4. At baseline, subjects had a mean affected BSA of 10%, 24% of subjects had an IGA score of 2 and 76% of subjects had a score of 3.

The primary efficacy endpoint was the proportion of subjects at Week 8 achieving IGA treatment success (IGA-TS) defined as a score of 0 (clear) or 1 (almost clear) with ≥ 2 grade improvement from baseline. Efficacy results for OPZELURA from TRuE-AD3 are summarized in Table 5.

Table 5: Efficacy Results at Week 8 in Pediatric Subjects 2 to 11 Years of Age with Atopic Dermatitis (TRuE-AD3)

	OPZELURA (N = 131)	Vehicle (N = 65)	Treatment Difference and 95% Confidence Interval
IGA-TS[a]	56.5%	10.8%	45.7% (34.7%, 56.8%)

[a] Defined as an IGA score of 0 or 1 with a ≥ 2-grade improvement from baseline.

14.2. Nonsegmental Vitiligo

Two double-blind, randomized, vehicle-controlled trials of identical design (TRuE-V1 and TRuE-V2, NCT04052425 and NCT04057573, respectively) enrolled a total of 674 adult and pediatric subjects aged 12 years and older (11% of subjects were 12 to 17 years of age and 7% were 65 years or older). Females constituted 53% of subjects, 82% of subjects were White, 5% were Black, 4% were Asian, and 9% were other races. Fitzpatrick skin types included I (2%), II (30%), III (40%), IV (19%), V (7%), or VI (2%). Subjects had depigmented areas affecting ≥ 0.5% facial body surface area (F-BSA), ≥ 3% non-facial BSA, and total body vitiligo area

(facial and non-facial, including hands, feet, upper and lower extremities, and trunk body areas) of up to 10% BSA. At baseline, subjects had a mean affected F-BSA of 1% and a mean affected total BSA of 7.4%. Phototherapy was not permitted during the trial. The mean time since diagnosis of nonsegmental vitiligo was 14.8 years prior to subjects enrolling in the trials.

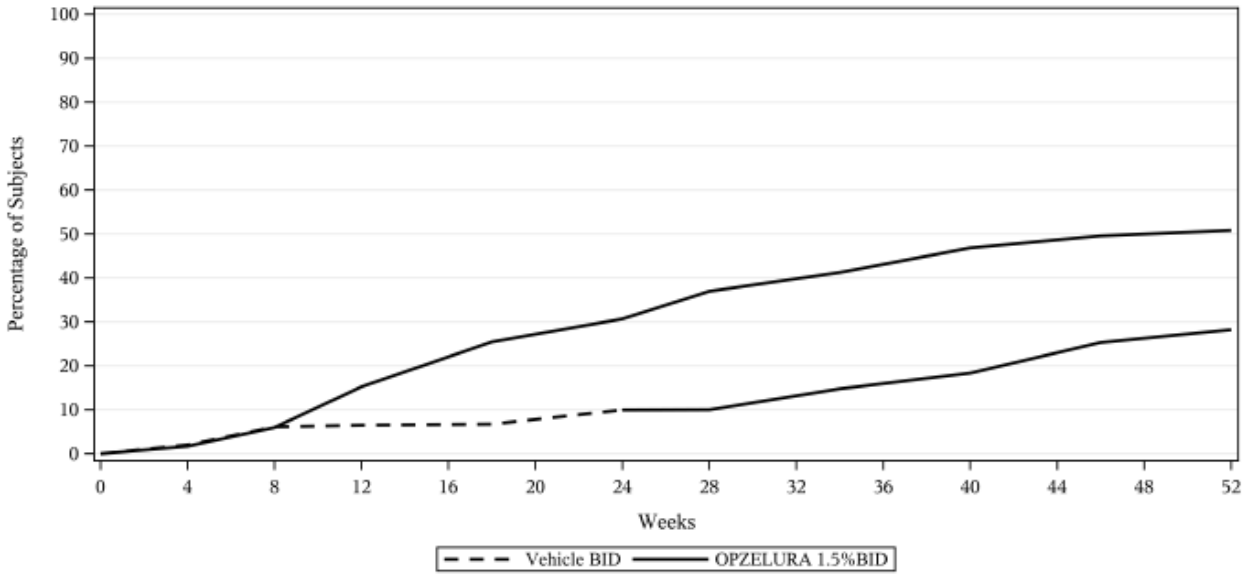
In both trials, subjects were randomized 2:1 to treatment with OPZELURA or vehicle cream twice daily (BID) for 24 weeks followed by an additional 28 weeks of treatment with OPZELURA BID for all subjects. Lesions on the face were assessed with the facial Vitiligo Area Scoring Index (F-VASI) and lesions on the total body (including the face) were assessed with the total body Vitiligo Area Scoring Index (T-VASI). The primary efficacy endpoint was the proportion of subjects achieving at least 75% improvement in F-VASI (F-VASI75) at Week 24. The proportion of participants achieving at least 90% improvement in F-VASI (F-VASI90) was also evaluated.

Efficacy results for OPZELURA at Week 24 from the two trials are summarized in Table 6. The percentage of subjects who achieved F-VASI75 and T-VASI75 (at least 75% improvement in T-VASI) over the 52-week treatment period in both trials are shown in Figure 1 and Figure 2.

Table 6: Efficacy Results at Week 24 in Adult and Pediatric Subjects Aged 12 Years and Older with Nonsegmental Vitiligo (TRuE-V1 and TRuE-V2)

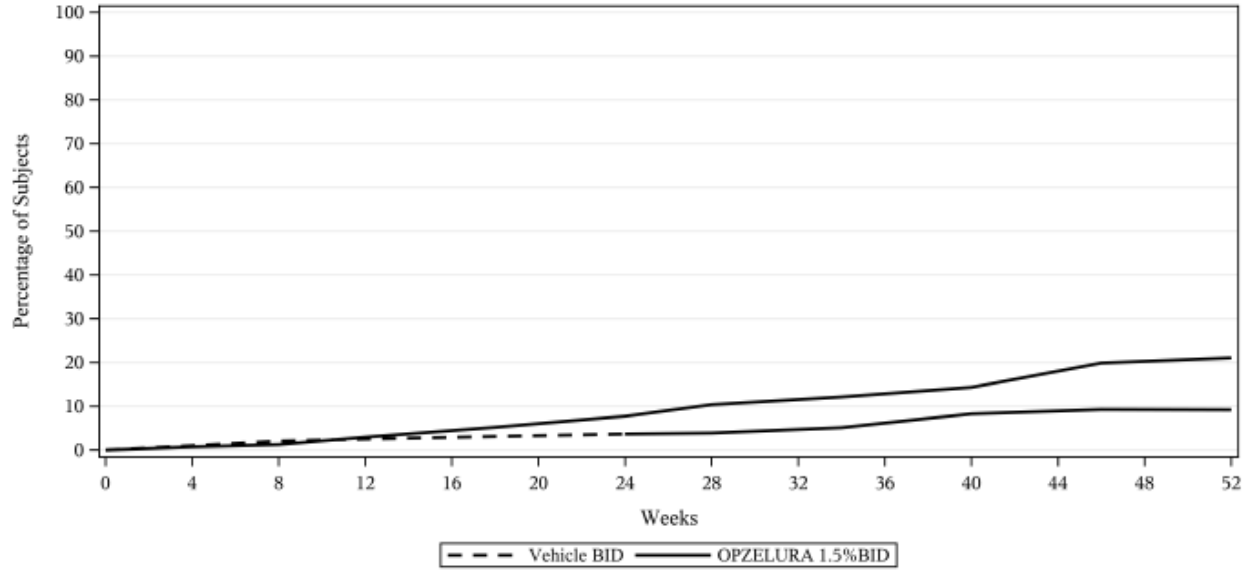
	TRuE-V1			**TRuE-V2**		
	OPZELURA (N = 221)	**Vehicle** (N = 109)	**Treatment Difference and 95% Confidence Interval**	**OPZELURA** (N = 229)	**Vehicle** (N = 115)	**Treatment Difference and 95% Confidence Interval**
F-VASI75	29.9%	7.5%	22.5% (14.2%, 30.8%)	29.9%	12.9%	16.9% (7.8%, 26.0%)
F-VASI90	15.5%	2.2%	13.3% (7.5%, 19.1%)	15.4%	1.9%	13.5% (7.7%, 19.3%)

Figure 1: Percentage of Adult and Pediatric Subjects Aged 12 Years and Older with Nonsegmental Vitiligo Achieving F-VASI75 During the 52-Week Treatment Period (TRuE-V1 and TRuE-V2 Combined)



Note: Subjects on the vehicle arm received vehicle for 24 weeks followed by OPZELURA for 28 weeks.

Figure 2: Percentage of Adult and Pediatric Subjects Aged 12 Years and Older with Nonsegmental Vitiligo Achieving T-VASI75 During the 52-Week Treatment Period (TRuE-V1 and TRuE-V2 Combined)



Note: Subjects on the vehicle arm received vehicle for 24 weeks followed by OPZELURA for 28 weeks.

16. HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

OPZELURA is a white to off-white cream containing 1.5% ruxolitinib and is supplied in 60 g and 100 g tubes.

60 g tube: NDC 50881-007-05

100 g tube: NDC 50881-007-07

Storage and Handling

Store OPZELURA at 20ºC to 25ºC (68ºF to 77ºF); excursions permitted from 15ºC to 30ºC (59ºF to 86ºF) *[see USP Controlled Room Temperature]*.

17. PATIENT COUNSELING INFORMATION

Advise the patient or caregivers to read the FDA-approved patient labeling (Medication Guide).

Infections

Inform patients that they may be at increased risk for developing infections, including serious infections, when taking Janus kinase inhibitors. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of an infection *[see Warnings and Precautions (5.1)]*.

Advise patients that Janus kinase inhibitors increase the risk of herpes zoster, and some cases can be serious *[see Warnings and Precautions (5.1)]*.

Malignancies and Lymphoproliferative Disorders

Inform patients that Janus kinase inhibitors may increase the risk for developing lymphomas and other malignancies including skin cancer *[see Warnings and Precautions (5.3)]*.

Instruct patients to inform their health care provider if they have ever had any type of cancer. Inform patients that periodic skin examinations should be performed while using OPZELURA. Advise patients that exposure to sunlight, and UV light should be limited by wearing protective clothing and using a broad-spectrum sunscreen *[see Warnings and Precautions (5.3)]*.

Major Adverse Cardiovascular Events

Advise patients that events of major adverse cardiovascular events (MACE) including non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, have been reported in clinical studies with Janus kinase inhibitors used to treat inflammatory conditions. Instruct all patients, especially current or past smokers or patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events *[see Warnings and Precautions (5.4)]*.

Thrombosis

Advise patients that events of DVT and PE have been reported in clinical studies with Janus kinase inhibitors used to treat inflammatory conditions. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of a DVT or PE *[see Warnings and Precautions (5.5)]*.

Cytopenias

Advise patients of the risk of thrombocytopenia, anemia, neutropenia, lymphopenia, and leukopenia with OPZELURA. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of thrombocytopenia, anemia, neutropenia, lymphopenia, or leukopenia *[see Warnings and Precautions (5.6)]*.

Administration Instructions

Advise patients or caregivers that OPZELURA is for topical use only *[see Dosage and Administration (2.1,2.2)]*.

Atopic Dermatitis

- *Adult and Pediatric Patients 12 Years of Age and Older*: Advise patients or caregivers to limit treatment to one 60 gram tube of OPZELURA per week or one 100 gram tube per 2 weeks *[see Dosage and Administration (2.1)]*.
- *Pediatric Patients 2 to 11 Years of Age:* Advise patients or caregivers to limit treatment to one 60 gram tube of OPZELURA per 2 weeks *[see Dosage and Administration (2.1)]*.

Nonsegmental Vitiligo

- Advise patients or caregivers to limit treatment to one 60 gram tube of OPZELURA per week or one 100 gram tube per 2 weeks *[see Dosage and Administration (2.2)]*.

Pregnancy Registry

Inform patients to report their pregnancy to Incyte Corporation at 1-855-463-3463 or by visiting www.opzelura.pregnancy.incyte.com *[see Use in Specific Populations (8.1)]*.

Lactation

Advise a patient not to breastfeed during treatment with OPZELURA and for about four weeks after the last dose *[see Use in Specific Populations (8.2)]*.

Manufactured for:
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Wilmington, DE 19803