

Opzelura™ (ruxolitinib) cream 1.5%

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
<i>See full prescribing information for complete boxed warning.</i>
<ul style="list-style-type: none">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)

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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 patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. (1)

Limitation 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)

DOSAGE AND ADMINISTRATION

- Apply a thin layer twice daily to affected areas of up to 20% body surface area. Do not use more than 60 grams per week. (2)
- For topical use only. (2)
- Not for ophthalmic, oral, or intravaginal use. (2)

DOSAGE FORMS AND STRENGTHS

Cream: 1.5% ruxolitinib (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)
- Thrombocytopenia, Anemia and Neutropenia:* Thrombocytopenia, anemia and neutropenia have occurred. Perform CBC monitoring as clinically indicated (5.6).

ADVERSE REACTIONS

- The most common adverse reactions (incidence $\geq 1\%$) are nasopharyngitis, diarrhea, bronchitis, ear infection, eosinophil count increased, urticaria, folliculitis, tonsillitis, and rhinorrhea. (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.

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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: <ul style="list-style-type: none">Active tuberculosis, which may present with pulmonary or extrapulmonary disease.Invasive fungal infections, including candidiasis and pneumocystosis.Bacterial, viral, 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 Higher rate of all-cause mortality, including sudden cardiovascular death have been observed in patients treated with oral Janus kinase inhibitors for inflammatory conditions [see Warnings and Precautions (5.2)].
MALIGNANCIES Lymphoma and other malignancies have been observed in patients treated with Janus kinase inhibitors for inflammatory conditions [see Warnings and Precautions (5.3)].
MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE) Higher rate of MACE (including cardiovascular death, myocardial infarction, and stroke) has been observed in patients treated with Janus kinase inhibitors for inflammatory conditions [see Warnings and Precautions (5.4)].
THROMBOSIS Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis has been observed at an increased incidence in patients treated with oral Janus kinase inhibitors for inflammatory conditions compared to placebo. Many of these adverse reactions were serious and some resulted in death. Patients with symptoms of thrombosis should be promptly evaluated [see Warnings and Precautions (5.5)].

1 INDICATIONS AND USAGE

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

Limitation of Use:

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

2 DOSAGE AND ADMINISTRATION

Instruct patients to apply a thin layer of OPZELURA twice daily to affected areas of up to 20% body surface area. Do not use more than 60 grams per week.

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

3 DOSAGE FORMS AND STRENGTHS

Cream: 15 mg of ruxolitinib per gram (1.5%) of white to off-white cream.

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 Janus kinase 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 Janus kinase 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 Janus kinase 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 Janus kinase 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

A higher rate of all-cause mortality, including sudden cardiovascular death was observed in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. 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 Janus kinase inhibitors used to treat inflammatory conditions. 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 with a known malignancy (other than successfully treated non-melanoma skin cancers), patients who develop a malignancy, 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.

5.4 Major Adverse Cardiovascular Events (MACE)

Major adverse cardiovascular events (MACE) defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke were observed in clinical trials of Janus kinase inhibitors used to treat inflammatory conditions.

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 these symptoms occur.

5.5 Thrombosis

Thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE) and arterial thrombosis, has been observed at an increased incidence in patients treated with oral Janus kinase inhibitors for inflammatory conditions compared to patients treated with placebo. Many of these adverse reactions were serious and some resulted in death.

Thromboembolic events were observed in clinical trials with OPZELURA. There was no clear relationship between platelet count elevations and thrombotic events. OPZELURA should be used with caution in patients who may be at increased risk of thrombosis.

5.6 Thrombocytopenia, Anemia and Neutropenia

Thrombocytopenia, anemia and neutropenia 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. If signs and/or symptoms of clinically significant thrombocytopenia, anemia, and neutropenia occur, patients should discontinue OPZELURA.

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.

In two double-blind, vehicle-controlled clinical trials (Trials 1 and 2), 499 subjects 12 years of age and older with atopic dermatitis were treated with OPZELURA twice daily for 8 weeks. In the OPZELURA group, 62% of subjects were females, and 71% of subjects were White, 23% were Black, and 4% were Asian. The adverse reactions reported by $\geq 1\%$ 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 $\geq 1\%$ of Subjects Treated with OPZELURA for Atopic Dermatitis through Week 8 in Trials 1 and 2

Adverse Reaction	OPZELURA (N=499) n (%)	Vehicle (N=250) n (%)
Subjects with any TEAE*	132 (27)	83 (33)
Nasopharyngitis	13 (3)	2 (1)
Bronchitis	4 (1)	0 (0)
Ear infection	4 (1)	0 (0)
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)

*TEAE – treatment emergent adverse events

Adverse reactions that occurred in Trials 1 and 2 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.

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 will be 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.

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% 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 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

The safety and effectiveness of OPZELURA for the topical treatment of atopic dermatitis have been established in pediatric patients aged 12 to 17 years of age with mild-to-moderate atopic dermatitis. Use of OPZELURA in this age group is supported by evidence from Trials 1 and 2 which included 92 subjects aged 12 to 17 years [see Clinical Pharmacology (12.3) and Clinical Studies (14)]. No clinically meaningful differences in safety or effectiveness were observed between adult and pediatric subjects.

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

Juvenile Animal Toxicity Data

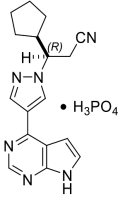
Oral administration of ruxolitinib to juvenile rats resulted in effects on growth and bone measures. When administered starting at postnatal day 7 (the equivalent of a human newborn) at doses of 1.5 to 75 mg/kg/day, evidence of fractures occurred at doses ≥ 30 mg/kg/day, and effects on body weight and 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 40% the MRHD clinical systemic exposure.

8.5 Geriatric Use

Of the 1249 total subjects with atopic dermatitis in clinical trials with OPZELURA, 115 were 65 years of age and older [see Clinical Studies (14)]. No clinically meaningful differences in safety or effectiveness were observed between patients less than 65 years and patients 65 years and older.

11 DESCRIPTION

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



Ruxolitinib phosphate is a white to off-white 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, 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

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

The pharmacokinetics of ruxolitinib were evaluated in a study involving 20 adult subjects and 21 pediatric subjects 13 years and older with atopic dermatitis with a mean \pm SD BSA involvement of 37.5 \pm 16.1% (range 25% to 90%). Subjects applied approximately 1.5 mg/cm² 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 \pm 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 \pm 883 nM and 3215 \pm 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 adolescent subjects with atopic dermatitis (13 – 17 years of age), the mean \pm SD C_{max} and AUC_{0–12} for ruxolitinib on Day 1 were 110 \pm 255 nM and 801 \pm 2019 h*nM, respectively.

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 μ l/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

Two double-blind, randomized, vehicle-controlled trials of identical design (Trial 1 and Trial 2, NCT03745638 and NCT03745651, respectively) enrolled a total of 1249 subjects aged 12 and older. 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, and 4% were Asian. 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.

In both trials, subjects were randomized 2:2:1 to treatment with OPZELURA, ruxolitinib cream, 0.75%, or vehicle cream twice daily (BID) for 8 weeks. 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 \geq 2 grade improvement from baseline. Efficacy was also assessed using a \geq 4-point improvement in Itch NRS.

Efficacy results for OPZELURA from the two trials are summarized in Table 2.

Table 2: Efficacy Results at Week 8 in Subjects with Atopic Dermatitis (Trials 1 and 2)

	Trial 1			Trial 2		
	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 (\geq 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 \geq 2-grade improvement from baseline

^b N = subjects with a baseline Itch NRS score \geq 4.

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 aluminum tubes.

60 g tube: NDC 50881-007-05

Storage and Handling

Store OPZELURA at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [*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 [*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)*].

Thrombocytopenia, Anemia and Neutropenia

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

Administration Instructions

Advise patients or caregivers that OPZELURA is for topical use only [*see Dosage and Administration (2)*].

Advise patients to limit treatment to 60 grams per week.

Pregnancy

Inform patients to report their pregnancy to Incyte Corporation at 1-855-463-3463 [*see Use in Specific Populations (8.1)*].

Lactation

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

Manufactured for:

Incyte Corporation
1801 Augustine Cut-off
Wilmington, DE 19803

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MEDICATION GUIDE OPZELURA™ (OP-zuh-LUR-ah) (ruxolitinib) Cream

Important: OPZELURA cream is for use on the skin only. Do not use OPZELURA cream, in your eyes, mouth or vagina.

What is the most important information I should know about OPZELURA?

OPZELURA may cause serious side effects, including:

- **Serious Infections.** OPZELURA contains ruxolitinib. Ruxolitinib belongs to a class of medicines called Janus kinase (JAK) inhibitors. JAK inhibitors are medicines that affect your immune system. JAK inhibitors can lower the ability of your immune system to fight infections. Some people have had serious infections while taking JAK inhibitors by mouth, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that can spread throughout the body. Some people have been hospitalized or died from these infections. Some people have had serious infections of their lungs while taking OPZELURA.
 - Your healthcare provider should watch you closely for signs and symptoms of TB during treatment with OPZELURA.

OPZELURA should not be used in people with an active, serious infection, including localized infections. You should not start using OPZELURA if you have any kind of infection unless your healthcare provider tells you it is okay. You may be at a higher risk of developing shingles (herpes zoster) while using OPZELURA.

Before starting OPZELURA, tell your healthcare provider if you:

- are being treated for an infection
- have had an infection that does not go away or that keeps coming back
- have diabetes, chronic lung disease, HIV, or a weak immune system
- have TB or have been in close contact with someone with TB
- have had shingles (herpes zoster)
- have had hepatitis B or C
- live in an area, or have lived in an area, or have traveled to certain parts of the country (such as the Ohio and Mississippi River valleys and the Southwest) where there is an increased chance for getting certain kinds of fungal infections. These infections may happen or become more severe if you use OPZELURA. Ask your healthcare provider if you do not know if you have lived in an area where these infections are common.

- think you have an infection or have symptoms of an infection such as:
 - fever, sweating,
 - muscle aches
 - cough or shortness of breath
 - blood in your phlegm
 - weight loss
 - warm, red, or painful skin or sores on your body
 - diarrhea or stomach pain
 - burning when you urinate or urinating more often than usual
 - feeling very tired

After starting OPZELURA, call your healthcare provider right away if you have any symptoms of an infection. OPZELURA can make you more likely to get infections or make worse any infections that you have.

- **Increased risk of death from all causes, including sudden cardiac death, has happened in people taking JAK inhibitors by mouth.**
- **Cancer and immune system problems.** OPZELURA may increase your risk of certain cancers by changing the way your immune system works. Some people have had lymphoma and other cancers while taking JAK inhibitors by mouth, especially if they are a current or past smoker. Some people have had skin cancers while taking OPZELURA. Your healthcare provider will regularly check your skin during your treatment with OPZELURA. Tell your healthcare provider if you have ever had any type of cancer.
- **Increased risk of major cardiovascular events such as heart attack, stroke or death has happened in people with cardiovascular risk factors and who are current or past smokers while using JAK inhibitors to treat inflammatory conditions.** Get emergency help right away if you have any symptoms of a heart attack or stroke while using OPZELURA, including:
 - discomfort in the center of your chest that lasts for more than a few minutes, or that goes away and comes back
 - severe tightness, pain, pressure, or heaviness in your chest, throat, neck, or jaw

- pain or discomfort in your arms, back, neck, jaw, or stomach
- shortness of breath with or without chest discomfort
- breaking out in a cold sweat
- nausea or vomiting
- feeling lightheaded
- weakness in one part or on one side of your body
- slurred speech

- **Blood clots.** Blood clots in the veins of your legs (deep vein thrombosis, DVT) or lungs (pulmonary embolism, PE) can happen in some people taking OPZELURA. This may be life-threatening.
 - Tell your healthcare provider if you have had blood clots in the veins of your legs or lungs in the past.
 - Tell your healthcare provider right away if you have any signs and symptoms of blood clots during treatment with OPZELURA, including:
 - swelling, pain or tenderness in one or both legs
 - sudden, unexplained chest or upper back pain
 - shortness of breath or difficulty breathing

See **“What are the possible side effects of OPZELURA?”** for more information about side effects.

What is OPZELURA?

OPZELURA is a prescription medicine used on the skin (topical) for short-term and non-continuous treatment of mild to moderate eczema (atopic dermatitis) in non-immunocompromised people 12 and older whose disease:

- is not well controlled with topical prescription therapies or
 - when those therapies are not recommended
- The use of OPZELURA along with therapeutic biologics for atopic dermatitis, other JAK inhibitors, or strong immunosuppressants such as azathioprine or cyclosporine is not recommended. It is not known if OPZELURA is safe or effective in children less than 12 years of age.

Before using OPZELURA, tell your healthcare provider about all of your medical conditions, including if you:

- have an infection
- have or had tuberculosis (TB), or have been in close contact with someone who has TB
- have had shingles (herpes zoster)
- have or had hepatitis B or C
- have had skin cancer in the past
- are a current or past smoker
- have or have had low white or red blood cell counts
- have high levels of fat in your blood (high cholesterol or triglycerides)
- are pregnant or plan to become pregnant. It is not known if OPZELURA will harm your unborn baby.
- **Pregnancy Exposure Registry.** There is a pregnancy exposure registry for individuals who use OPZELURA during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. If you become exposed to OPZELURA during pregnancy, you and your healthcare provider should report exposure to Incyte Corporation at 1-855-463-3463.

- are breastfeeding or plan to breastfeed. It is not known if OPZELURA passes into your breast milk. Do not breastfeed during treatment with OPZELURA and for about 4 weeks after the last dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use OPZELURA?

- OPZELURA is for use on the skin only. Do not use OPZELURA in your eyes, mouth, or vagina.
- Use OPZELURA exactly as your healthcare provider tells you.
- Apply a thin layer of OPZELURA 2 times a day to affected areas. **Do not** use more than one 60-gram tube each week. Ask your healthcare provider if you have questions about applying OPZELURA.
- Wash your hands after applying OPZELURA, unless hands are being treated. If someone else applies OPZELURA, they should wash their hands after applying OPZELURA.

What are the possible side effects of OPZELURA? OPZELURA may cause serious side effects, including:

- See **“What is the most important information I should know about OPZELURA?”**
- **Low blood cell counts.** OPZELURA may cause low platelet counts (thrombocytopenia), low red blood cell counts (anemia), and low white blood cell counts (neutropenia). If needed, your healthcare provider will do a blood test to check your blood cell counts during your treatment with OPZELURA and may stop your treatment if signs or symptoms of low blood cell counts happen. Tell your healthcare provider right away if you develop or have worsening of any of these symptoms:
 - unusual bleeding
 - bruising
 - tiredness
 - shortness of breath
 - fever

- **Cholesterol increases.** Cholesterol increase has happened in people when ruxolitinib is taken by mouth. Tell your healthcare provider if you have high levels of fat in your blood (high cholesterol or triglycerides).

The most common side effects of OPZELURA include:

- pain or swelling in your nose or throat (nasopharyngitis)
- diarrhea
- bronchitis
- ear infection
- increase in a type of white blood cell (eosinophil) counts
- hives
- inflamed hair pores (folliculitis)
- swelling of the tonsils (tonsillitis)
- runny nose (rhinorrhea)

These are not all of the possible side effects of OPZELURA. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Incyte Corporation at 1-855-463-3463.

How should I store OPZELURA?

- Store OPZELURA at room temperature from 68°F to 77°F (20°C to 25°C).

Keep OPZELURA and all medicines out of the reach of children.

General information about the safe and effective use of OPZELURA. Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use OPZELURA for a condition for which it is not prescribed. Do not give OPZELURA to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about OPZELURA that is written for healthcare professionals.

What are the ingredients in OPZELURA?

Active ingredient: ruxolitinib phosphate

Inactive ingredients: cetyl alcohol, dimethicone 350, edetate disodium, glyceryl stearate SE, light mineral oil, medium chain triglycerides, methylparaben, phenoxyethanol, polyethylene glycol 200, polysorbate 20, propylene glycol, propylparaben, stearyl alcohol, purified water, white petrolatum, and xanthan gum.

Manufactured for: Incyte Corporation, 1801 Augustine Cut-off, Wilmington, DE 19803
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For more information go to www.Opzelura.com or call 1-855-463-3463

This Medication Guide has been approved by the U.S. Food and Drug Administration.



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