

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)

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 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.

Revised: 04/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

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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:

- 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 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 (%)
<i>Subjects with any TEAE*</i>	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 \geq 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 \geq 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 \geq 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.

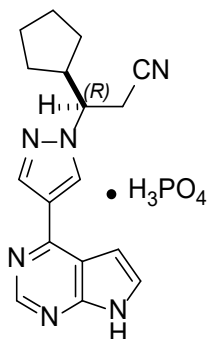
8.5 Geriatric Use

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 ± 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 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 ± 255 nM and 801 ± 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 ≥ 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 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 (≥ 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 .

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 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:
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