Product Monograph

Including Patient Medication Information

PrOPZELURA®

Ruxolitinib cream

Cream, 1.5% w/w ruxolitinib (as ruxolitinib phosphate), Topical

Janus Kinase (JAK) Inhibitor

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Wilmington, DE 19803

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Recent Major Label Changes

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Part 1: Healthcare Professional Information

1. Indications

OPZELURA (ruxolitinib (as ruxolitinib phosphate)) cream 1.5% is indicated for:

- topical treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older.
- topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 2 years of age and older whose disease is not adequately controlled with conventional topical prescription therapies (topical corticosteroids, topical calcineurin inhibitors) or when those therapies are not advisable.

Limitations of Use: Use of OPZELURA in combination with other JAK inhibitors, biological immunomodulators or potent immunosuppressants has not been studied and is not recommended.

1.1. Pediatrics

Pediatrics (< 18 years of age):

Nonsegmental vitiligo

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of OPZELURA have been established in pediatric patients aged 12 years and older with nonsegmental vitiligo. Therefore, Health Canada has authorized this indication for pediatric patients ≥ 12 years of age.

The safety and efficacy of OPZELURA in pediatric patients under 12 years of age have not been established for nonsegmental vitiligo. Therefore, Health Canada has not authorized this indication for pediatric patients below the age of 12 years.

Atopic Dermatitis

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of OPZELURA have been established in pediatric patients aged 2 years and older with atopic dermatitis. Therefore, Health Canada has authorized this indication for pediatric patients ≥ 2 years of age.

The safety and efficacy of OPZELURA in pediatric patients under 2 years of age have not been established for atopic dermatitis. Therefore, Health Canada has not authorized this indication for pediatric patients below the age of 2 years.

1.2. Geriatrics

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 subjects.

Based on clinical trials of OPZELURA in subjects with atopic dermatitis, no clinically meaningful differences in safety or efficacy were observed between subjects less than 65 years of age and subjects 65 years of age and older.

2. Contraindications

OPZELURA is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For complete listing, see 6. Dosage Forms, Strengths, Composition, and Packaging.

3. Serious Warnings and Precautions Box

Serious Warnings and Precautions

SERIOUS INFECTIONS

Serious bacterial, mycobacterial, fungal and viral infections including viral reactivation and other opportunistic infections (in some cases life-threatening or fatal) have been reported in patients treated with oral JAK inhibitors, including oral ruxolitinib (for noninflammatory conditions). Reported infections included: Tuberculosis, Herpes Zoster, JC Virus, Hepatitis B and Pneumonia.

Patients with risk factors should be carefully assessed and monitored for the risk of developing serious infections (see 7. Warnings and Precautions).

MALIGNANCIES

In a large, randomized, post-marketing safety study with an oral JAK inhibitor in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased risk of lymphoma and other malignancies, excluding non-melanoma skin cancers (NMSCs), was observed compared to those treated with TNF blockers. OPZELURA is not indicated for rheumatoid arthritis. Based on the safety signal observed with an oral JAK inhibitor, the benefits and risks should be evaluated for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers (see 7. Warnings and Precautions).

THROMBOSIS

Thromboembolic events were observed in clinical trials with OPZELURA in patients with vitiligo and atopic dermatitis (AD). In a large, randomized, post-marketing safety study with an oral JAK inhibitor in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of thrombosis, including pulmonary embolism (PE), deep venous thrombosis (DVT), and arterial thrombosis, was observed compared to those treated with TNF blockers. OPZELURA is not indicated for rheumatoid arthritis. There is no evidence that OPZELURA increases the risk of thromboembolic events. However, based on the safety signal observed with an oral JAK inhibitor, OPZELURA should be avoided in patients with a known risk of thrombosis. If symptoms of thrombosis occur, discontinue OPZELURA and evaluate and treat appropriately (see 7. Warnings and Precautions).

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

MACE were observed in clinical trials with OPZELURA in patients with AD. In a large, randomized, post-marketing safety study with an oral JAK inhibitor in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of MACE, including non-fatal myocardial infarction, was observed compared to those treated with TNF blockers. OPZELURA is not indicated for rheumatoid arthritis. There is no evidence that OPZELURA increases the risk of MACE. However, based on the safety signal observed with an oral JAK inhibitor, the benefits and risks for the individual patient should be evaluated prior to initiating or continuing therapy with OPZELURA in patients who are current or past smokers or patients with cardiovascular risk factors (see 7. Warnings and Precautions).

4. Dosage and Administration

4.1. Dosing Considerations

OPZELURA should not be used in combination with other JAK inhibitors, biological immunomodulators or potent immunosuppressants (see 1. Indications).

4.2. Recommended Dose and Dosage Adjustment

Vitiligo

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

The recommended dose is a thin layer of OPZELURA applied twice daily to affected skin areas up to a maximum of 10% of body surface area (BSA) for each application.

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, consider re-evaluation by the healthcare provider.

Atopic Dermatitis

Adult and Pediatric Patients 12 Years of Age and Older

Do not use more than one 60 gram tube 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 per 2 weeks or one 100 gram tube per 4 weeks.

The recommended dose is a thin layer of OPZELURA applied twice daily to affected skin areas up to a maximum of 20% of body surface area (BSA) for each application. Total BSA calculation excludes the scalp. Discontinue use when signs and symptoms (e.g., itch, rash, and redness) of atopic dermatitis resolve.

If signs and symptoms do not improve within 8 weeks, consider re-evaluation by the healthcare provider.

Hepatic Impairment

No dose adjustment is required in patients with hepatic impairment (see 10.3 Pharmacokinetics).

Renal Impairment

No dose adjustment is required for patients with mild to severe renal impairment. OPZELURA should be used with caution by patients with end stage renal disease (see 10.3 Pharmacokinetics).

4.4. Administration

OPZELURA is for topical use only. OPZELURA is not for ophthalmic, oral, or intravaginal use. In order to avoid ingestion of cream, do not apply to the lips.

OPZELURA should be applied topically twice daily to affected areas of skin with a minimum of 8 hours between applications.

Patients should be instructed to wash their hands after applying OPZELURA, unless their hands are being treated. If someone else applies OPZELURA onto the patient, they should wash their hands after application.

4.5. Missed Dose

If a dose is missed, resume application at the next regularly scheduled time.

5. Overdose

There are no data from clinical trials regarding overdose with OPZELURA. If excess OPZELURA is inadvertently applied, wipe off the excess cream.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Topical	Cream: 1.5% w/w Each gram contains 15 mg of ruxolitinib (equivalent to 19.8 mg of ruxolitinib phosphate).	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, purified water, stearyl alcohol, white petrolatum, and xanthan gum.

OPZELURA is supplied in:

- 5 g (sample) aluminum tube with white high-density polyethylene (HDPE) caps.
- 60 g and 100 g aluminum tubes with polypropylene (PP) caps or laminate polyfoil tubes with PP caps.

Description

Cream: 15 mg of ruxolitinib per gram (1.5% w/w) of white to off-white cream with no visible signs of phase separation.

7. Warnings and Precautions

Please see 3. Serious Warnings and Precautions Box.

General

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

Carcinogenesis and Mutagenesis

Non-melanoma Skin Cancer

NMSCs, including basal cell carcinoma and squamous cell carcinoma, were observed in patients with vitiligo and AD treated with OPZELURA. A skin examination prior to initiation and periodically during treatment with OPZELURA should be considered for patients with a history of skin cancers or who have risk factors for the development of skin cancers.

Malignancies

In a large, randomized, post-marketing safety study with an oral JAK inhibitor in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of lymphoma and other malignancies, excluding NMSCs, was observed compared to those treated with TNF blockers. Patients on an oral JAK inhibitor who were current or past smokers appeared to have an increased risk of lung cancer. OPZELURA is not indicated for rheumatoid arthritis.

Based on the safety signal observed in an oral JAK inhibitor, the benefits and risks should be evaluated for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers.

Cardiovascular

Major Adverse Cardiovascular Events (MACE)

MACE were observed in clinical trials with OPZELURA in patients with AD. In a large, randomized, post-marketing safety study with an oral JAK inhibitor in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of MACE, including cardiovascular death, myocardial infarction, and stroke, was observed compared to those treated with TNF blockers. OPZELURA is not indicated for rheumatoid arthritis. There is no evidence that OPZELURA increases the risk of MACE. However, based on the safety signal observed with an oral JAK inhibitor, the benefits and risks for the individual patient should be evaluated in patients who are current or past smokers or patients with cardiovascular risk factors prior to initiating or continuing therapy with OPZELURA. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur.

Thrombosis

Thromboembolic events were observed in clinical trials with OPZELURA in patients with vitiligo and AD. In a large, randomized, post-marketing safety study with an oral JAK-inhibitor in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis, was observed compared to those treated with TNF blockers. OPZELURA is not indicated for rheumatoid arthritis. There is no evidence that OPZELURA increases the risk of thromboembolic events. However, based on the safety signal observed with an oral JAK inhibitor, OPZELURA should be avoided in patients with a known risk of thrombosis. If symptoms of thrombosis occur, discontinue OPZELURA and evaluate and treat patients appropriately.

Lipid Elevations

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

Hematologic

Decrease in Blood Cell Count

Thrombocytopenia, anemia, and neutropenia were reported in clinical trials with OPZELURA in patients with vitiligo and AD. Consider the benefits and risks for individual patients who have a known history of thrombocytopenia, anemia, or neutropenia prior to initiating therapy with OPZELURA. If clinically indicated, consider monitoring complete blood count in these patients. If signs and/or symptoms of

clinically significant thrombocytopenia, anemia, and neutropenia occur, patients should discontinue OPZELURA.

Immune

Infections

Instances of viral infections, including herpes zoster, and other infections, including respiratory tract infections, were reported in clinical trials with OPZELURA in patients with vitiligo and AD. 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, including oral ruxolitinib (for noninflammatory conditions).

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

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 resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection

Monitor patients for the development of signs and symptoms of serious infection during and after treatment with OPZELURA. If a patient develops a serious infection, an opportunistic infection, or sepsis, interrupt OPZELURA. 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, including oral ruxolitinib and JAK inhibitors used to treat inflammatory conditions.

Consider evaluating patients with risk factors 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.

Herpes Zoster*:* Cases of 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. Physicians should educate patients about early signs and symptoms of herpes zoster, advising that treatment should be sought as early as possible.

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 (for noninflammatory conditions).

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

Reproductive Health: Female and Male Potential

Women of childbearing potential should use effective contraception during treatment with OPZELURA and for 4 weeks after discontinuation of treatment.

- **Fertility:** There are no data on the effect of ruxolitinib on human fertility (see 16. Non-Clinical Toxicology).
- **Teratogenic risk:** There are no adequate and well-controlled studies of OPZELURA in pregnant women. Ruxolitinib was embryotoxic and fetotoxic in rats and rabbits (increases in post-implementation loss and reduced fetal weights (see 7. Warnings and Precautions, 7.1.1 Pregnancy and 16. Non-Clinical Toxicology). The potential risk of teratogenicity for humans is unknown. The use of OPZELURA during pregnancy is not recommended.

7.1. Special Populations

7.1.1. Pregnancy

The use of OPZELURA during pregnancy is not recommended. Women of childbearing potential should use effective contraception during treatment and for 4 weeks after discontinuation of treatment. If pregnancy occurs during treatment, discontinue use and contact your health care provider.

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. Oral administration of ruxolitinib to pregnant rabbits resulted in decreased fetal weight and increased late resorptions at maternal exposure approximately 0.7 times the maximum recommended human dose (MRHD). Oral administration of ruxolitinib to pregnant rats resulted in decreased fetal weight at maternal exposure approximately 22 times the MRHD (see 16. Non-Clinical Toxicology).

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.

7.1.2. Breastfeeding

No data are available regarding the presence of ruxolitinib in human milk, the effects on the breastfed child, or the effects on milk production after topical application of OPZELURA.

Because no data are available on the presence of ruxolitinib in human breast milk, it is recommended that women should not breast-feed during treatment with OPZELURA and for 4 weeks (half-life of 116 hours) after the final dose.

Following oral administration of ruxolitinib to lactating rats, ruxolitinib and/or its metabolites were present in the milk.

7.1.3. Pediatrics

Pediatrics (< 18 years of age):

Nonsegmental Vitiligo

The safety and efficacy of OPZELURA for the topical treatment of nonsegmental vitiligo have been established in pediatric patients aged 12 to < 18 years based on evidence from 2 double-blind, randomized, vehicle-controlled clinical trials (TRuE-V1 and TRuE-V2). A total of 55 pediatric subjects (12.4%) aged 12 to < 18 years were treated with OPZELURA in these clinical trials (see 14. Clinical Trials). No clinically meaningful differences in safety or efficacy were observed between adult and pediatric subjects aged 12 to < 18 years.

The safety and efficacy of OPZELURA in pediatric patients under 12 years of age for the topical treatment of nonsegmental vitiligo have not been established; therefore, Health Canada has not authorized this indication for pediatric patients below the age of 12 years.

Atopic Dermatitis

The safety and efficacy of OPZELURA for the topical treatment of atopic dermatitis have been established in pediatric patients aged 12 to < 18 years based on evidence from 2 double-blind, randomized, vehicle-controlled clinical trials (TRuE-AD1 and TRuE-AD2). A total of 92 pediatric subjects (18.4%) aged 12 to < 18 years were treated with OPZELURA in these clinical trials (see 14. Clinical Trials). No clinically meaningful differences in safety or efficacy were observed between adult and pediatric subjects aged 12 to < 18 years.

The safety and efficacy of OPZELURA for the topical treatment of atopic dermatitis have been established in pediatric patients aged 2 to 11 years based on evidence from a double-blind, randomized, vehicle-controlled clinical trial (TRuE-AD3). A total of 130 pediatric subjects aged 2 to 11 years were treated with OPZELURA in this clinical trial (see 14. Clinical Trials). No clinically meaningful differences in safety or efficacy were observed between pediatric subjects aged 2 to 11 years in this trial and subjects aged 12 years and older in TRuE-AD1 and TRuE AD2.

The safety and efficacy of OPZELURA in pediatric patients under 2 years of age for the topical treatment of atopic dermatitis have not been established; therefore, Health Canada has not authorized this indication for pediatric patients below the age of 2 years.

7.1.4. Geriatrics

Nonsegmental vitiligo

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 subjects.

Atopic dermatitis

Of the 1249 total subjects with atopic dermatitis enrolled in clinical trials (TRuE-AD1 and TRuE-AD2) with OPZELURA, 115 were 65 years of age and older. No clinically meaningful differences in safety or efficacy were observed between subjects with atopic dermatitis less than 65 years old and those 65 years and older.

8. Adverse Reactions

8.1. Adverse Reaction Overview

Application site acne, application site pruritus, nasopharyngitis, headache, upper respiratory tract infection, application site erythema, application site rash, influenza, pyrexia, urinary tract infection, alanine aminotransferase increased, and application site exfoliation were reported as common adverse reactions in ≥ 1% of subjects with nonsegmental vitiligo applying OPZELURA during the double-blind period of the Phase 3 trials in subjects with nonsegmental vitiligo (TRuE-V1 and TRuE-V2). Application site acne, the most common reported adverse reaction, was nonserious and of mild or moderate severity. The majority of application site acne events did not recover/resolve, but subjects continued on treatment without interrupting OPZELURA in all but 1 case.

Nasopharyngitis, upper respiratory tract infection, and headache were reported as common adverse

reactions in ≥ 1% of subjects with atopic dermatitis applying OPZELURA during the double-blind period of the Phase 3 trials in subjects with atopic dermatitis (TRuE-AD1 and TRuE-AD2). All events of nasopharyngitis, upper respiratory tract infection, and headache in subjects on OPZELURA were nonserious, of mild severity, and recovered/resolved without the interruption of treatment.

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

Nonsegmental Vitiligo

In two double-blind, vehicle-controlled, Phase 3, clinical trials (TRuE-V1 and TRuE-V2), 449 subjects 12 years of age and older with nonsegmental vitiligo were treated with OPZELURA twice daily for 24 weeks. The adverse reactions reported by OPZELURA-treated subjects in the 24-week double-blind period is listed in Table 2.

Table 2: Adverse Reactions Occurring in Subjects 12 years of Age and Older Treated with OPZELURA for 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)	3 (1)
Application site pruritus	23 (5)	6 (3)
Nasopharyngitis	19 (4)	5 (2)
Headache	17 (4)	6 (3)
Upper respiratory tract infection	13 (3)	5 (2)
Application site erythema	7 (2)	1 (< 1)
Application site rash	7 (2)	2 (1)
Influenza	6 (1)	1 (< 1)
Pyrexia	6 (1)	0
Urinary tract infection	6 (1)	1 (< 1)
Alanine aminotransferase increased	5 (1)	1 (< 1)
Application site exfoliation	5 (1)	1 (< 1)

The long-term safety of OPZELURA in subjects with nonsegmental vitiligo was assessed in clinical trials TRuE-V1 and TRuE-V2 for up to 52 weeks. The safety profile of OPZELURA in terms of the types of adverse events observed during the 28-week treatment extension period was consistent with the safety profile observed during the 24-week vehicle-controlled period.

Atopic Dermatitis

In two double-blind, vehicle-controlled, Phase 3, clinical trials (TRuE-AD1 and TRuE-AD2), 499 subjects 12 years and older with atopic dermatitis were treated with OPZELURA twice daily for 8 weeks. The adverse reactions reported by OPZELURA treated subjects in the 8-week vehicle-controlled period are

listed in Table 3.

Table 3: Adverse Reactions Occurring in 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)
Upper respiratory tract infection	12 (2)	5 (2)
Headache	11 (2)	5 (2)

The long-term safety of OPZELURA was assessed in clinical trials TRuE-AD1 and TRuE-AD2 for up to 52 weeks. The safety profile in terms of the types of adverse events observed during the 44-week long-term safety period with intermittent use of OPZELURA was consistent with the safety profile observed during the 8-week vehicle-controlled period with continuous use of OPZELURA.

8.2.1. Clinical Trial Adverse Reactions – Pediatrics

Subjects 12 to < 18 years of age:

The Phase 3 trials for vitiligo (TRuE-V1 and TRuE-V2) and atopic dermatitis (TRuE-AD1 and TRuE-AD2) included adolescents, i.e., subjects 12 to < 18 years of age. When compared with subjects ≥ 18 years of age, there were no meaningful differences in the safety profile of OPZELURA in adolescent subjects aged 12 to < 18 years with nonsegmental vitiligo or in adolescent subjects aged 12 to < 18 years with atopic dermatitis.

Subjects 2 to 11 years of age:

The Phase 3 TRuE-AD3 trial for atopic dermatitis included pediatric subjects 2 to 11 years of age; 130 subjects were treated with OPZELURA and 65 subjects applied vehicle cream. During the 8-week vehicle controlled period, application site reaction (including application site pain, application site irritation, application site discomfort; 5% and 0%), COVID-19 (4% and 2%), pyrexia (2% and 0%), and white blood cell decreased (including leukopenia; 2% and 0%) were also reported by subjects treated with OPZELURA and by subjects who applied vehicle cream, respectively. Adverse reactions such as upper respiratory tract infection and nasopharyngitis applicable to 12 years of age and older were also observed in subjects 2 to 11 years of age at higher frequencies (9% vs 3% and 6% vs 2%, OPZELURA vs vehicle cream, respectively). When compared with subjects aged 12 years and older with atopic dermatitis, there were no meaningful differences in the safety profile of OPZELURA.

8.3. Less Common Clinical Trial Adverse Reactions

Nonsegmental Vitiligo

Less common adverse reactions reported in ≥ 0.5% to < 1% of subjects with nonsegmental vitiligo applying OPZELURA include: application site dermatitis, hypertension, acne, anxiety, application site discolouration, application site dryness, application site folliculitis, contusion, dermatitis contact, diarrhoea, ear infection, fatigue, gastritis, gastroenteritis, hordeolum, influenza like illness, insomnia, nasal congestion, oropharyngeal pain, rhinitis, seborrheic dermatitis, toothache, and vomiting.

Atopic Dermatitis

Less common adverse reactions reported in ≥ 0.5% to < 1% of subjects with atopic dermatitis applying OPZELURA include: urticaria, bronchitis, ear infection, eosinophil count increased, diarrhoea, rhinorrhoea, tonsillitis, and folliculitis.

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data

No clinically meaningful trends in hematologic or chemistry parameters or vital signs were observed in clinical trials in subjects with nonsegmental vitiligo or in subjects with atopic dermatitis.

9. Drug Interactions

9.2. Drug Interactions Overview

Drug interaction studies have not been conducted with OPZELURA.

Ruxolitinib is known to be a substrate for cytochrome P450 3A4 (CYP3A4). Based on clinical trials with oral ruxolitinib, inhibitors of CYP3A4 may increase ruxolitinib systemic concentrations whereas inducers of CYP3A4 may decrease ruxolitinib systemic concentrations.

Strong CYP3A4 inhibitors: Co-administration of OPZELURA with strong CYP3A4 inhibitors increases ruxolitinib plasma concentration.

9.3. Drug-Behaviour Interactions

Drug-behavioural interactions have not been evaluated.

9.4. Drug-Drug Interactions

Clinical Studies

CYP3A4 inhibitors

Ruxolitinib is predominantly cleared by CYP3A4 metabolism. Drug-drug interaction potential for oral ruxolitinib was evaluated in dedicated clinical pharmacology studies that included co-administration of strong or moderate CYP3A4 inhibitors. The C_{max} and AUC of ruxolitinib increased 33% and 91%, respectively, with the oral administration of 10 mg single dose of ruxolitinib following ketoconazole 200 mg, a strong CYP3A4 inhibitor, twice daily for 4 days, compared to receiving the oral ruxolitinib dose alone in healthy subjects. The C_{max} and AUC of ruxolitinib increased 8% and 27%, respectively, with the oral administration of 10 mg single dose of ruxolitinib following erythromycin 500 mg, a moderate CYP3A4 inhibitor, twice daily for 4 days, compared to receiving the oral ruxolitinib dose alone in healthy subjects.

CYP3A4 inducers

The C_{max} and AUC of ruxolitinib decreased 52% and 71%, 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, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 or induce CYP1A2, CYP2B6 and CYP3A4 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.

9.5. Drug-Food Interactions

Interactions with food have not been evaluated, as interactions with food are not applicable for topical products.

9.6. Drug-Herb Interactions

Interactions with herbal products have not been evaluated.

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been evaluated.

10. Clinical Pharmacology

10.1. 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.

The JAK/STAT pathway has been shown to mediate the production of IFNγ. IFNγ-producing cytotoxic T lymphocytes have been shown to mediate melanocyte destruction in human vitiligo.

Many inflammatory and pruritic cytokines involved in the pathogenesis of atopic dermatitis, such as IL-4, IL-5, IL-13, IL-22, IL-31, and TSLP (thymic stromal lymphopoietin), require JAK/STAT pathway activation for downstream biological activity. In mouse models of dermatitis, topical administration of ruxolitinib cream significantly decreased expression of inflammatory cytokines in the skin, reduced dermatitis symptoms, and alleviated pruritic behaviors.

10.2. Pharmacodynamics

Cardiac Electrophysiology

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

10.3. Pharmacokinetics

Absorption:

The pharmacokinetics of OPZELURA were investigated in 429 subjects with nonsegmental vitiligo aged

12 years and older (12.6% were 12-17 years of age) with a mean ± SD % BSA involvement of 7.31 ± 2.02 (range: 3.2% to 10.0%). Subjects applied approximately 1.58 mg/cm^2 of ruxolitinib cream (range: 0.18 grams to 8.4 grams of ruxolitinib cream 1.5% per application) twice daily for 24 weeks. The mean ± SD steady-state trough plasma concentration of ruxolitinib (pre-application) was 56.9 ± 62.6 nM with a projected $AUC_{0\text{-}12h}$ at 683 ± 751 h*nM. The mean ± SD bioavailability of topical ruxolitinib was 9.72% ± 8.14% for the ruxolitinib 1.5% cream twice daily.

The pharmacokinetics of OPZELURA were investigated in 479 subjects with atopic dermatitis 12 years and older with a mean ± SD body surface area (BSA) involvement of 9.60 ± 5.30% (range: 3% to 22%). Subjects applied approximately 1.49 mg/cm^2 of ruxolitinib cream (range: 0.048 grams to 6.9 grams per application) twice daily for 8 weeks. The mean ± SD steady-state trough plasma concentration of ruxolitinib (pre-application) was 35.7 ± 55.0 nM.

The pharmacokinetics of OPZELURA were also investigated in 20 adult subjects and 21 pediatric subjects 13 years and older with atopic dermatitis with a mean ± SD BSA involvement of 37.5 ± 16.1% (range: 25% to 90%). Plasma concentrations of ruxolitinib were quantifiable in all subjects. In adult subjects, the mean ± SD peak plasma concentration (C_{max}) and area under the concentration time curve from 0 to 12 hours post dose ($AUC_{0\text{-}12h}$) for ruxolitinib were 449 ± 883 nM and 3220 ± 6190 h*nM on Day 1 and 242 ± 548 nM and 1970 ± 4230 h*nM on Day 28, respectively. There is no evidence of ruxolitinib accumulation after daily application of OPZELURA for 28 days in subjects with atopic dermatitis.

Distribution:

Based on an in vitro study, OPZELURA is 97% bound to human plasma proteins, mostly to albumin.

Metabolism:

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

Elimination:

The mean apparent terminal elimination half-life of orally administered ruxolitinib is approximately 3 hours. The mean apparent terminal half-life of ruxolitinib following topical application of ruxolitinib cream was estimated in 9 adult and adolescent subjects with atopic dermatitis and is 116 hours (range: 10 to 777 hours), reflecting the slow drug absorption rate rather than the drug elimination rate.

Following a single oral dose of [^{14}C]-labeled ruxolitinib in healthy adult subjects, elimination was predominately through metabolism with 74% of radioactivity excreted in urine and 22% excretion via feces. Unchanged drug accounted for less than 1% of the excreted total radioactivity.

Special Populations and Conditions:

- **Pediatrics (2 to < 18 years of age):** In 21 pediatric subjects (13 to 17 years of age) with ≥ 25% BSA involvement with atopic dermatitis, the mean ± SD C_{max} and $AUC_{0\text{-}12h}$ for ruxolitinib were 110 ± 255 nM and 801 ± 2020 h*nM on Day 1 and 52.3 ± 78.2 nM and 435 ± 721 h*nM on Day 28, respectively.

  In 27 pediatric subjects (2 to 11 years of age) with mean ± SD %BSA atopic dermatitis involvement of 58.9% ± 20.6% (range: 35%-92%) who applied OPZELURA twice daily for 28 days, the arithmetic mean ± SD plasma C_{ss} and projected $AUC_{0\text{-}12h}$ of ruxolitinib were 98.2 ± 148 nM and 1178 ± 1776 h*nM, respectively. There was no evidence of ruxolitinib accumulation after daily application of OPZELURA for 28 days in pediatric subjects 2 to 11 years of age with atopic dermatitis.

- **Hepatic Insufficiency:** The AUC was increased by 87%, 28%, and 65% in patients with mild

(Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment following oral administration of ruxolitinib. There was no clear relationship between the severity of hepatic impairment and the increase in AUC.

- **Renal Insufficiency:** Following a single ruxolitinib 25 mg oral dose, the AUC of the parent compound was similar in patients with mild (CrCl 50-80 mL/min), moderate (CrCL 30-49 mL/min), and severe (CrCl < 30 mL/min) renal impairment. However, relative AUC values of ruxolitinib metabolites increased with increasing severity of renal impairment, and most markedly in the patients with end-stage renal disease requiring hemodialysis.

11. Storage, Stability, and Disposal

Store OPZELURA at room temperature, 15°C to 25°C.

Part 2: Scientific Information

13. Pharmaceutical Information

Drug Substance

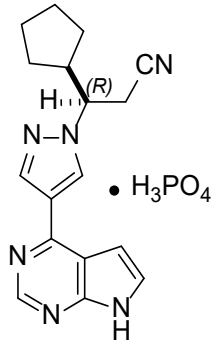
Proper name/Common: ruxolitinib phosphate

Chemical name: (*R*)-3-(4-(7H-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate]

Molecular Formula: $C_{17}H_{21}N_6O_4P$ phosphate salt, $C_{17}H_{18}N_6$ free base;

Relative Molecular Mass: 404.36 g/mole phosphate salt, 306.37 g/mole free base

Structural formula:



Physicochemical properties:

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

Solubility Profile: The solubility of ruxolitinib phosphate in aqueous medium is pH dependent with a range of ≥ 0.54 mg/mL to 0.17 mg/mL in phosphate buffers from pH 1.0 to 8.0, respectively, at 37°C.

Melting Point: The melting point of ruxolitinib phosphate is 197.6°C.

Dissociation Constants: The pKa values are 4.3 and 11.8.

14. Clinical Trials

14.1. Clinical Trials by Indication

Nonsegmental Vitiligo in Subjects 12 Years of Age and Older

Two double-blind, randomized, vehicle-controlled, multicenter, trials of identical design (TRuE-V1 and TRuE-V2, respectively) enrolled a total of 674 subjects aged 12 years and older (673 received treatment; 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, and 4% were Asian. 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% nonfacial BSA, and total body vitiligo area (facial and nonfacial, 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 Phase 3 trials. The mean time since diagnosis of vitiligo was 14.8 years prior to subjects enrolling in the trials.

Table 4: Summary of Patient Demographics for Clinical Trials in Subjects 12 Years of Age and Older with Nonsegmental Vitiligo

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
TRuE-V1	Randomized, double-blind, vehicle-controlled multicenter, Phase 3 study	Vehicle-controlled period: OPZELURA BID, topical, 24 weeks Vehicle cream BID, topical, 24 weeks	330 OPZELURA= 221 Vehicle Cream=109	OPZELURA= 40.5 (12-79) Vehicle Cream=39.7 (12-79)	OPZELURA: Male=85 Female=136 Vehicle Cream: Male=59 Female=50
TRuE-V2	Randomized, double-blind, vehicle-controlled multicenter, Phase 3 study	Vehicle-controlled period: OPZELURA BID, topical, 24 weeks Vehicle cream BID, topical, 24 weeks	344 (343 received treatment) OPZELURA= 228 Vehicle Cream=115	OPZELURA= 38.4 (12-77) Vehicle Cream=39.8 (13-68)	OPZELURA: Male=116 Female=112 Vehicle Cream: Male=55 Female=60

BID = twice daily

Study Results

In both trials, subjects were randomized 2:1 to treatment with OPZELURA or vehicle cream twice daily for 24 weeks followed by an additional 28 weeks of treatment with OPZELURA twice daily 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 a 75% improvement in the F-VASI (F-VASI75) at Week 24. The VASI is based on a composite estimate, the score is a determined by the percentage of vitiligo involvement (% of BSA) and the degree of depigmentation for each body region affected by vitiligo. Other endpoints included the proportions of subjects achieving a 50% improvement in F-VASI (F-VASI50), 90% improvement in F-VASI (F-VASI90), 50% improvement in T-VASI (T-VASI50), and a Vitiligo Noticeability Scale (VNS) score of 4 or 5 (vitiligo "a lot less noticeable" or "no longer noticeable"). The VNS is a patient-reported outcome measure for vitiligo treatment success which records the participant's perceived noticeability of vitiligo on a 5-point scale. The percent change from baseline in facial body surface area (F-BSA) affected by vitiligo was also a key secondary endpoint.

Efficacy results for OPZELURA at Week 24 from the two trials are summarized in Table 5. The proportion of subjects who achieved the primary or key secondary endpoints at Week 24 was significantly higher in subjects who applied OPZELURA compared with subjects who applied vehicle. The treatment effect difference from vehicle emerged as early as Week 12. Furthermore, continued improvement in

repigmentation as assessed by F-VASI (F-VASI50/75/90), T-VASI (T-VASI50/75) and VNS were observed through Week 52 for participants who had continuously applied ruxolitinib 1.5% cream BID from baseline. For participants who crossed over from vehicle cream to ruxolitinib 1.5% cream BID during the 52-week period, improvements in F-VASI, T-VASI, and VNS were similar to the pattern observed during the first 24 weeks of treatment in the ruxolitinib 1.5% cream BID group.

Table 5: Efficacy Results of OPZELURA for Primary and Key Secondary Endpoints at Week 24 in Subjects 12 Years of Age and Older with Nonsegmental Vitiligo (TRuE-V1 and TRuE-V2)

	TRuE-V1			TRuE-V2		
	OPZELURA (N = 221)	**Vehicle (N = 109)**	**Response Rate Difference and 95% Confidence Interval**	**OPZELURA (N = 222)**	**Vehicle (N = 109)**	**Response Rate Difference and 95% Confidence Interval**
F-VASI75	29.8%[a]	7.4%	22.3% (14.2%, 30.5%)	30.9%[b]	11.4%	19.5% (10.5%, 28.4%)
F-VASI50	51.2%[a]	16.9%	34.2% (24.1%, 44.4%)	51.4%[a]	20.9%	30.6% (20.0%, 41.1%)
F-VASI90	15.3%[c]	2.2%	13.2% (7.5%, 18.8%)	16.3%[c]	1.3%	15.0% (9.3%, 20.7%)
T-VASI50	20.6%[c]	5.1%	15.5% (8.3%, 22.6%)	23.9%[b]	6.8%	17.1% (9.5%, 24.7%)
VNS 4 or 5	24.5%[b]	3.3%	21.2% (14.3%, 28.1%)	20.5%[c]	4.9%	15.5% (8.5%, 22.6%)
% Change in F-BSA	-28.9%[a]	-9.5%	-19.3% (-27.1%, -11.6%)	-26.4%[a]	-7.0%	-19.5% (-28.5%, -10.5%)

p-values from Mixed-Model with Repeated Measures: [Response Variable = Treatment + Stratification Factors (Skin Type Fitzpatrick Scale Type I and II vs Type III, IV, V, and VI, Region North America/Europe) + Visit + Treatment*Visit].

[a] p-value < 0.0001

[b] p-value < 0.001

[c] p-value ≤ 0.0065

Atopic Dermatitis in Subjects 12 Years of Age and Older

Two double-blind, randomized, vehicle-controlled, multicenter, Phase 3 trials of identical design (TRuE-AD1 and TRuE-AD2, respectively) enrolled a total of 1249 subjects aged 12 years and older with atopic dermatitis (20% of subjects were 12-17 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. The mean time since diagnosis of atopic dermatitis was 19.97 years prior to subjects enrolling in the trials. Subjects had affected body surface area (BSA) of 3 to 20%, and an Investigator's Global Assessment (IGA) score of 2 to 3. The IGA is an overall eczema severity rating on a 5-point scoring scale (0 = clear, 1 = almost clear, 2 = mild disease, 3 = moderate disease, and 4 = severe disease). At baseline, subjects had a mean affected BSA of 9.8%, 39% of subjects had affected areas on the face, 25% of subjects had an IGA score of 2, and 75% of subjects had a score of 3. The mean Eczema Area & Severity Index (EASI) score of subjects at baseline was 7.95 (moderate). The EASI is a scoring system based on an assessment of the extent and severity of erythema, induration/papulation/edema, excoriations, and lichenification across 4 body regions. The disease severity strata are as follows: 0 = clear, 0.1 to 1.0 = almost clear, 1.1 to 7.0 = mild, 7.1 to 21.0 = moderate, 21.1 to 50.0 = severe, and 50.1 to 72.0 = very severe. The baseline Itch Numerical Rating Scale (Itch NRS), defined as the 7-day average of the daily, worst level of itch intensity with 24-hour recall, was 5.1 on a scale of 0 (no itch) to 10 (worst imaginable itch).

In both trials, subjects were randomized 2:2:1 to treatment with OPZELURA, ruxolitinib 0.75% cream, or vehicle cream twice daily for 8 weeks. Following the 8-week vehicle-controlled period, eligible subjects entered the 44-week long-term safety period in which subjects treated areas of active or recurrent atopic dermatitis lesions as needed. Subjects were instructed to stop treatment 3 days after clearance of lesions and restart treatment at the first signs of recurrence. Subjects applying OPZELURA or ruxolitinib 0.75% cream during the vehicle-controlled period continued on the same treatment in the long-term safety period, but those applying vehicle during the vehicle-controlled period were assigned equally to apply OPZELURA or ruxolitinib 0.75% cream during the long-term safety period.

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. Key secondary endpoints included proportion of subjects who achieved at least 75% improvement over baseline in the EASI score (EASI75), and proportion of subjects at Week 8 with a ≥ 4-point improvement in Itch NRS over baseline.

Table 6: Summary of Patient Demographics for Clinical Trials in Subjects 12 Years of Age and Older with Atopic Dermatitis

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age, years (Range)	Sex
TRuE-AD1	Randomized, double-blind, vehicle-controlled multicenter, Phase 3 study	Vehicle-controlled period: OPZELURA BID, topical, 8 weeks Ruxolitinib 0.75% cream BID, topical, 8 weeks Vehicle cream BID, topical, 8 weeks	631 OPZELURA= 253 Ruxolitinib 0.75% Cream=252 Vehicle Cream= 126	OPZELURA= 33.7 (12-77) Ruxolitinib 0.75% Cream= 36.8 (12-85) Vehicle Cream=35.2 (12-82)	OPZELURA: Male=95 Female=158 Ruxolitinib 0.75% Cream: Male=98 Female=154 Vehicle Cream: Male=47 Female=79

TRuE-AD2	Randomized, double-blind, vehicle-controlled multicenter, Phase 3 study	Vehicle-controlled period: OPZELURA BID, topical, 8 weeks Ruxolitinib 0.75% cream BID, topical, 8 weeks Vehicle cream BID, topical, 8 weeks	618 OPZELURA= 246 Ruxolitinib 0.75% Cream=248 Vehicle Cream= 124	OPZELURA= 35.9 (12-85) Ruxolitinib 0.75% Cream= 35.8 (12-81) Vehicle Cream=38.9 (12-82)	OPZELURA: Male=96 Female=150 Ruxolitinib 0.75% Cream: Male=98 Female=150 Vehicle Cream: Male=44 Female=80

BID = twice daily

Study Results

In both trials, the proportion of subjects who achieved IGA-TS and the proportion of subjects who achieved EASI75 at Week 8 was significantly higher in subjects who applied OPZELURA compared with subjects who applied vehicle cream (Table 7).

The proportion of subjects who achieved ≥ 4-point improvement in Itch NRS at Week 8 was also significantly higher in subjects who applied OPZELURA compared with subjects who applied vehicle (Table 7). A reduction in itch was observed by Day 1 of treatment in some patients.

Table 7: Efficacy Results of OPZELURA at Week 8 in Subjects 12 Years of Age and Older with Atopic Dermatitis

	TRuE-AD1			TRuE-AD2		
	OPZELURA (N = 253)	**Vehicle (N = 126)**	**Response Rate Difference and 95% Confidence Interval**	**OPZELURA (N = 228)**	**Vehicle (N = 118)**	**Response Rate Difference and 95% Confidence Interval**
IGA-TS[a]	53.8%[b]	15.1%	38.7% (29.9%, 47.4%)	51.3%[b]	7.6%	43.7% (35.6%, 51.8%)
EASI75	62.1%[b]	24.6%	37.5% (27.8%, 47.1%)	61.8%[b]	14.4%	47.4% (38.5%, 56.4%)
Itch 4 NRS[c] (≥ 4-point reduction) (n/N*)	52.2%[b] (84/161)	15.4% (12/78)	36.8% (25.7%, 47.9%)	50.7%[b] (74/146)	16.3% (13/80)	34.4% (23.0%, 45.9%)

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

[b] p-value < 0.0001

[c] N* = subjects in the ITT population with a baseline Itch NRS score ≥ 4.

During the long-term safety period, the proportion of subjects with an IGA of 0 (clear) or 1 (almost clear) remained high at study visits during Weeks 8 through 52 for subjects in the OPZELURA treatment group who continued on the study and applied OPZELURA on an intermittent, as needed basis. For subjects who switched from vehicle to OPZELURA, the proportion of subjects with an IGA of 0 (clear) or 1 (almost

clear) increased by Week 12 (4 weeks after switching) and was maintained until the end of the 44-week long-term safety period with intermittent, as needed treatment with OPZELURA.

Atopic Dermatitis in Subjects 2 to 11 Years of Age

A double-blind, randomized, vehicle-controlled trial, TRuE-AD3, enrolled a total of 330 pediatric subjects 2 to 11 years of age (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, and 6% were Asian. 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 10.5%, 23.6% of subjects had an IGA score of 2 and 76.4% of subjects had a score of 3, and subjects had a mean EASI score of 8.6 (moderate). For subjects aged 6 to 11 years, the mean baseline Itch NRS, defined as the 7-day average of the worst level of itch intensity in the last 24 hours, was 6.7 on a scale of 0 (no itch) to 10 (worst imaginable itch).

In TRuE-AD3, subjects were randomized 2:2:1 to treatment with OPZELURA, ruxolitinib 0.75% cream, or vehicle cream BID for 8 weeks. Following the 8-week vehicle-controlled period, eligible subjects entered the 44-week long-term safety period in which subjects treated areas of active or recurrent atopic dermatitis lesions as needed. Subjects were instructed to stop treatment 3 days after clearance of lesions and restart treatment at the first signs of recurrence. Subjects applying OPZELURA or ruxolitinib 0.75% cream during the vehicle controlled period continued on the same treatment in the long-term safety period, but those applying vehicle during the vehicle-controlled period were randomized 1:1 to OPZELURA or ruxolitinib 0.75% cream during the long-term safety period.

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.

Table 8: Summary of Patient Demographics for Clinical Trials in Subjects 2 to 11 Years of Age with Atopic Dermatitis

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age, years (Range)	Sex
TRuE-AD3	Randomized, double-blind, multi-center, vehicle-controlled, Phase 3 study	Vehicle-controlled period: OPZELURA BID, topical, 8 weeks Ruxolitinib 0.75% cream BID, topical, 8 weeks Vehicle cream BID, topical, 8 weeks	330 OPZELURA= 131 Ruxolitinib 0.75% Cream=134 Vehicle Cream= 65	OPZELURA= 6.4 (2-11) Ruxolitinib 0.75% Cream= 6.6 (2-11) Vehicle Cream=6.3 (2-11)	OPZELURA: Male=63 Female=68 Ruxolitinib 0.75% Cream: Male=61 Female=73 Vehicle Cream: Male=27 Female=38

Study Results

The proportion of subjects who achieved IGA-TS at Week 8 in TRuE-AD3 was significantly higher in subjects who applied OPZELURA compared with subjects who applied vehicle cream (Table 9).

Table 9 Efficacy Results of OPZELURA at Week 8 in Subjects 2 to 11 Years of Age with Atopic Dermatitis

	TRuE-AD3		
	OPZELURA (N = 131)	**Vehicle (N = 65)**	**Response Rate 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.

During the long-term safety period, the proportion of subjects with an IGA of 0 (clear) or 1 (almost clear) remained high at study visits during Weeks 8 through 52 for subjects in the OPZELURA treatment group who continued on the study and applied OPZELURA on an intermittent, as needed basis. For subjects who switched from vehicle to OPZELURA, the proportion of subjects with an IGA of 0 (clear) or 1 (almost clear) increased by Week 12 (4 weeks after switching) and was maintained until the end of the 44-week long-term safety period with intermittent, as needed treatment with OPZELURA.

16. Non-Clinical Toxicology

General toxicology: Ruxolitinib has been evaluated in safety pharmacology, repeated dose toxicity, genotoxicity and reproductive toxicity, and carcinogenicity studies following oral administration. Additional studies were conducted following dermal administration in minipigs and mice. Target organs associated with the pharmacological action of ruxolitinib in repeated dose oral studies include bone marrow, peripheral blood and lymphoid tissues. Infections generally associated with immunosuppression were noted in dogs. Exposures (AUC) at non-adverse levels in chronic toxicity studies were approximately 1 times in male rats, 30 times in female rats, and 3 times in dogs relative to systemic clinical exposures in atopic dermatitis subjects administered twice daily MRHD (MRHD; the clinical systemic exposure from 1.5% ruxolitinib cream applied twice daily to 25-40% affected body surface area in atopic dermatitis subjects was used in the calculations for margin of exposure).

A 3-month dermal repeat dose study revealed decreased lymphocyte counts in mice. Margins in mice (based on twice daily MRHD clinical systemic exposure) at non-adverse levels were 8.5 in males and 22 in females. Non-adverse decrease in peripheral lymphocytes were also noted in minipigs in a 9-month dermal toxicity study. Margins (based on twice daily MRHD clinical systemic exposure) at non-adverse levels in minipigs were 0.2-fold in males and 0.3 fold in females. This effect was not observed in a 3-month dermal toxicity study in minipigs. No evidence of systemic toxicity was observed in Gottingen minipigs following topical administration of 1.5% ruxolitinib cream formulation twice daily for up to 9 months.

Genotoxicity: 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.

Carcinogenicity: Ruxolitinib was not carcinogenic when administered orally in the 6-month Tg.rasH2 transgenic mouse model or in a 2-year carcinogenicity study in the rat or when administered topically to mice for two years.

Reproductive and developmental toxicology: Oral administration of ruxolitinib had no effect on fertility or reproductive function in male or female rats. However, in female rats, increased post-implantation loss was observed at exposures greater than 3.5 times the clinical systemic exposure at the MRHD.

Oral administration of ruxolitinib to pregnant rabbits resulted in decreased fetal weight and increased late resorptions at maternal exposure approximately 0.7 times the MRHD. Oral administration of ruxolitinib to pregnant rats resulted in decreased fetal weight at maternal exposure approximately 22 times the MRHD.

There were no adverse effects on postnatal development following administration of ruxolitinib to female rats during gestation and lactation at maternal exposures up to 3.1 times the MRHD clinical exposure.

Juvenile toxicity: Oral administration of ruxolitinib to juvenile rats resulted in effects on growth and bone measures. 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. When dosing was initiated at postpartum Day 7 (comparable to human newborn), the no observed adverse-effect-level (NOAEL) was approximately 3 times greater than the clinical systemic exposure at the MRHD. When dosing was initiated at postpartum Day 21 (equivalent to a 2 year-old human), the NOAEL was approximately 4.5 times the MRHD.

Special toxicology: Topical administration of ruxolitinib up to 10% (w/w) once daily for 3-days did not induce contact sensitization in mice and dermal irritation was minimal to negligible in rabbits when dosed up to 1.5% topically for 24-hours. Ruxolitinib did not show acute phototoxicity or photoallergic potential up to concentrations of 1.5% topical doses in male hairless albino guinea pigs.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrOPZELURA®

Ruxolitinib cream

This Patient Medication Information is written for the person who will be taking **OPZELURA**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **OPZELURA**, talk to a healthcare professional.

Serious warnings and precautions box

Serious infections

- Serious infections have been reported in patients treated with other drugs that belong in the same class of medicines as OPZELURA, called JAK inhibitors, but taken by mouth, including oral ruxolitinib. Ruxolitinib is the medicinal ingredient in OPZELURA. Some cases reported in patients treated with those oral drugs were life-threatening or led to death. Some of the infections reported include: tuberculosis, shingles, a type of a virus infection called JC virus, hepatitis B, and pneumonia.
- Your healthcare professional should carefully assess and monitor you for the risk of developing any serious infections while you are taking OPZELURA.

Lymphoma and other cancers

Lymphoma (cancer of the lymphatic system) and other cancers have been reported with a drug that belongs in the same class of medicines as OPZELURA, called JAK inhibitors, but taken by mouth. This other drug is used to treat a type of arthritis (joint pain, swelling and stiffness) which OPZELURA is not used for. Your healthcare professional should check if you have risk factors for the development of cancer before and during treatment with OPZELURA. Tell your healthcare professional if you:

- are a smoker or were a smoker in the past, or
- had other cancers before.

Blood clots

Blood clots were reported in patients taking OPZELURA. Blood clots in the veins of the legs (deep vein thrombosis), lungs (pulmonary embolism) or arteries (arterial thrombosis) have been reported more often with a drug that belongs in the same class of medicines as OPZELURA, called JAK inhibitors, but taken by mouth. This other drug is used to treat a type of arthritis (joint pain, swelling and stiffness) which OPZELURA is not used for.

- Tell your healthcare professional if you are at risk of getting blood clots or have had blood clots before.
- Tell your healthcare professional right away if you have any signs and symptoms of blood clots while you are taking OPZELURA including:
  - swelling, pain, or tenderness in one or both legs
  - sudden chest or upper back pain

- shortness of breath or difficulty breathing

Heart problems

Major heart and blood vessels problems have been reported with a drug that belongs in the same class of medicines as OPZELURA, called JAK inhibitors, but taken by mouth. This other drug is used to treat a type of arthritis (joint pain, swelling and stiffness) which OPZELURA is not used for. Your healthcare professional should check if you may be at a higher risk of heart and blood vessel problems, including heart failure, heart attack and stroke before and during treatment with OPZELURA. Tell your healthcare professional if you:

- are a smoker or were a smoker in the past, or
- have any heart problems.

Tell your healthcare professional right away if you have any signs and symptoms of serious heart problems (such as a heart attack or a stroke) while you are taking OPZELURA including:

- Heart attack: pressure or pain in the chest, jaw, neck, left arm, back or stomach, shortness of breath, dizziness or feeling light-headed, sweating, irregular heartbeat
- Stroke: sudden numbness or weakness of your arm, leg or face, especially if only on one side of the body; sudden confusion, difficulty speaking or understanding others; sudden difficulty in walking or loss of balance or coordination; suddenly feeling dizzy or sudden severe headache with no known cause.

What OPZELURA is used for:

OPZELURA is used on the skin (topical) to treat:

- patients aged 12 years and older with a skin condition known as nonsegmental vitiligo which causes skin to lose its pigment.
- patients aged 2 years and older with mild to moderate atopic dermatitis, also known as eczema. It is used when treatment with other topical prescription medicines have not worked well or have not been tolerated well, or when those medicines should not be used.

How OPZELURA works:

Nonsegmental vitiligo

Vitiligo is an autoimmune disease causing white or pink (depigmented) patches of skin. OPZELURA reduces the body's attack on pigment-producing cells. This allows the skin to restore pigment and achieve its normal color.

Eczema (atopic dermatitis)

Inflammation causes the signs and symptoms of eczema. OPZELURA works by blocking many of the molecules, called cytokines, that worsen the inflammation and itch. However, the exact way that OPZELURA works to reduce signs and symptoms is not known.

The ingredients in OPZELURA are:

Medicinal ingredient: Ruxolitinib (as ruxolitinib phosphate)

Non-medicinal 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, purified water, stearyl alcohol, white petrolatum, and

xanthan gum.

OPZELURA comes in the following dosage forms:

Cream, 1.5%.

Do not use OPZELURA if:

- you or your child are allergic to ruxolitinib or any of the other ingredients in OPZELURA.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take OPZELURA. Talk about any health conditions or problems you may have, including if you:

- have serious kidney problems.
- are pregnant or plan to become pregnant. It is not known if OPZELURA will harm your unborn baby. If you are able to get pregnant, use an effective method of birth control to avoid becoming pregnant while taking OPZELURA and for 4 weeks after you stop your treatment.
- are breast-feeding or plan to breast-feed. It is not known if OPZELURA passes into breast milk. You should not breastfeed during your treatment with OPZELURA and for 4 weeks after your last dose. Talk with your healthcare professional about the best way to feed your baby if you use OPZELURA.

Other warnings you should know about

Non-melanoma skin cancer

Non-melanoma skin cancers have been reported in patients treated with topical (skin) ruxolitinib medicines. Your healthcare professional may want to check your skin before you begin taking OPZELURA.

Low blood cell count

Low blood cell counts including thrombocytopenia (low platelets), anemia (low hemoglobin) and low white blood cells (neutropenia) were reported in patients taking OPZELURA. Tell your healthcare professional if you have had any of these problems in the past before starting OPZELURA. Your doctor may order blood tests while taking OPZELURA and may stop your treatment based on the results.

Infections

OPZELURA should not be used if you have an active or a serious infection. Before taking OPZELURA, tell your healthcare professional if you have:

- a chronic infection or an infection that keeps coming back
- a history of serious infections
- tuberculosis, had it in the past, or have been in close contact with someone who had tuberculosis
- lived or travelled to areas where you are more likely to contract tuberculosis or if you have underlying conditions that make you more likely to get tuberculosis
- hepatitis C or B

You will be monitored by your healthcare professional for signs and symptoms of an infection during and after treatment with OPZELURA. You will stop your treatment if you get a serious infection. Do not continue your treatment until your infection is under control.

Cases of shingles (herpes zoster) were reported in patients taking OPZELURA and other drugs that belong in the same class of medicines as OPZELURA, called JAK inhibitors, but are taken by mouth. If you develop shingles while you are taking OPZELURA, your healthcare professional may stop your treatment until your shingles goes away.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take OPZELURA:

- OPZELURA is applied twice a day. Use OPZELURA exactly as your healthcare professional tells you.
- Do not use in your eyes, mouth, or vagina. Topical medicine is for use only on the skin.
- Do not use OPZELURA with other medicines known as "JAK inhibitors," or medicines for your immune system. If you are not sure, ask your healthcare professional.
- Do not apply OPZELURA to the lips to avoid swallowing it by accident.
- Wash your hands after applying OPZELURA, unless you are treating your hands. If you are applying the cream to someone you are caring for, wash your hands after you apply OPZELURA.

Nonsegmental vitiligo

- Do not use more than one 60 gram tube per week or one 100 gram tube per 2 weeks.
- If you are using OPZELURA for nonsegmental vitiligo, the cream should not be used on more than 10% of your body surface area for each application. 10% of your body surface area is about 10 times the size of your hand (including the palm and fingers).
- Avoid using OPZELURA on your lips to prevent swallowing it.
- If you are using OPZELURA for nonsegmental vitiligo, tell your healthcare professional if your treated skin does not improve within 24 weeks of treatment.

Eczema (atopic dermatitis)

- *Adult and Pediatric Patients 12 Years of Age and Older*: Do not use more than one 60 gram tube 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 per 2 weeks or one 100 gram tube per 4 weeks.
- If you are using OPZELURA for eczema, the cream should not be used on more than 20% of your body surface area for each application. 20% of your body surface area is about 20 times the size of your hand (including the palm and fingers).
- Avoid using OPZELURA on your lips to prevent swallowing it.
- If you are using OPZELURA for eczema, tell your healthcare professional if your treated skin does not improve within 8 weeks of treatment.

Usual dose:

- Apply a thin layer of OPZELURA twice daily, with at least 8 hours between applications.
- Your healthcare professional will tell you how to use OPZELURA based on you or your child's medical condition and response to the medicine.

Overdose:

If you have applied too much OPZELURA, wipe off any extra cream.

If you think you, or a person you are caring for, have ingested OPZELURA or applied too much on the skin, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If you or your child forget to use OPZELURA as directed, skip the missed application and continue with the next scheduled application.

Possible side effects from using OPZELURA:

These are not all the possible side effects you may have when using OPZELURA. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- common cold
- headache
- influenza
- fever

You may experience the following side effects on the area where you applied OPZELURA:

- acne
- pain, such as burning or stinging sensation
- itching
- redness
- rash
- exfoliation (removal of the dead skin)

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Common			
Urinary tract infection: frequent urination, painful urination, blood in the urine		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store OPZELURA at room temperature, 15-25°C.

Keep out of reach and sight of children.

If you want more information about OPZELURA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.incytebiosciences.ca), or by calling 1-833-309-2759.

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