PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrZORYVE™

Roflumilast cream

0.3% w/w, topical

Professed

Phosphodiesterase-4 (PDE-4) Inhibitor

Arcutis Biotherapeutics, Inc.
3027 Townsgate Road, Suite 300
Westlake Village, CA 91361

Imported by:
C.R.I.
3544 North Service Road, Unit #400
Burlington, Ontario L7N 3G2

Date of Initial Authorization:
April 27, 2023

Submission Control Number: 264296

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ZORYVE™ (roflumilast cream, 0.3%) is indicated for topical treatment of plaque psoriasis, including treatment of psoriasis in the intertriginous areas, in patients 12 years of age and older.

1.1 Pediatrics

Pediatrics (12 to <18 years): The safety and efficacy data submitted in patients 12 to 17 are very limited. Health Canada has authorized an indication for pediatric use primarily from extrapolation of data generated from adult patients (see 7.1.3 Pediatrics, 8.2 Clinical Trial Adverse Reactions, 10.3 Pharmacokinetics).

Pediatrics (<12 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric patients below the age of 12 years.

1.2 Geriatrics

In pivotal trials, efficacy and safety in subjects 65 years of age and older were found to be comparable to that in adults less than 65 years of age (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

ZORYVE is contraindicated in patients:

- with moderate to severe liver impairment (Child-Pugh B or C) (see 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency).
- who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Not applicable

4.2 Recommended Dose and Dosage Adjustment

Apply ZORYVE to affected areas once daily.

No dosage adjustment is required in geriatric patients, patients with renal impairment, or in patients with mild hepatic impairment (Child-Pugh A) (see 10.3 Pharmacokinetics, Special Populations and Conditions).

4.3 Reconstitution

Not applicable

4.4 Administration

Apply ZORYVE topically once a day to affected areas of skin and rub in completely. Wash hands after

application unless hands are being treated.

If deemed medically necessary to use during breast-feeding, use ZORYVE on the smallest area of skin for the shortest duration possible. Do not apply ZORYVE directly to the nipple and areola to avoid direct infant exposure (see 7.1.2 Breast-Feeding).

ZORYVE is for topical use only and not for ophthalmic, oral, or intravaginal use (see 7 WARNINGS AND PRECAUTIONS, General).

4.5 Missed Dose

Advise patients if they forget to use ZORYVE as directed that they may skip the missed application and go back to their regular schedule the following day.

5 OVERDOSAGE

There are no data from clinical trials regarding signs and symptoms of overdose of ZORYVE. If surplus ZORYVE has been applied, the excess should be wiped off.

For management of a suspected drug overdose, contact your regional poison control centre.

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: 3 mg of roflumilast per gram (0.3%) of white to off-white cream	ceteareth-10 phosphate, cetearyl phosphate, cetostearyl alcohol, diethylene glycol monoethyl ether, hexylene glycol, isopropyl palmitate, methylparaben, propylparaben, purified water, sodium hydroxide, and white petrolatum. Hydrochloric acid may have been added to adjust pH.

ZORYVE contains 0.3% roflumilast (w/w) in a white to off-white cream and is supplied in 5-g (physician sample) and 60-g aluminum tubes.

7 WARNINGS AND PRECAUTIONS

General

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

Hepatic/Biliary/Pancreatic

ZORYVE is contraindicated in patients with moderate to severe liver impairment (Child-Pugh B or C) (see 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency).

Reproductive Health: Female and Male Potential

Fertility

Slight reduction in male fertility was seen in conjunction with epididymal toxicity in rats dosed orally with 1.8 mg/kg/day (about 2.2 and 8.8 times human exposure to unbound roflumilast and roflumilast N-oxide, respectively, when roflumilast was administered orally). However, a human spermatogenesis study investigated reproductive safety of 500-mcg oral roflumilast in healthy male volunteers. No adverse treatment effects were found on parameters of the male reproductive system including reproductive hormones (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

7.1 Special Populations

7.1.1 Pregnant Women

ZORYVE should not be used during labor and delivery. There are no human studies that have investigated effects of ZORYVE on preterm labor or labor at term; however, animal studies showed that oral roflumilast disrupted the labor and delivery process in mice.

There are no adequate and well controlled studies of oral or topical roflumilast in pregnant women. The potential risk for humans is unknown.

Studies of oral roflumilast in animals have shown reproductive toxicity at doses above the human recommended dose (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

7.1.2 Breast-feeding

ZORYVE should only be used by a breast-feeding mother if deemed medically necessary, considering a potential risk to the baby. To minimize potential exposure to the breastfed infant via breast milk, use ZORYVE on the smallest area of skin and for the shortest duration possible while breastfeeding. Advise breastfeeding women not to apply ZORYVE directly to the nipple and areola to avoid direct infant exposure.

There is no information regarding the presence of topically administered roflumilast in human milk, the effects on the breastfed infant, or the effects on milk production.

Oral roflumilast and/or its metabolites are excreted into the milk of lactating rats. Excretion of roflumilast and/or its metabolites into human milk is probable. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZORYVE and any potential adverse effects on the breastfed infant from ZORYVE or from the underlying maternal condition.

7.1.3 Pediatrics

Pediatrics (12 to <18 years): Because of limited data available in this age group, Health Canada has authorized an indication for pediatric use primarily from extrapolation of data generated from adult patients. There was no evidence of a meaningfully different adverse reaction profile in patients aged 12 to 17, relative to adults (see 8.2 Clinical Trial Adverse Reactions and 10.3 Pharmacokinetics).

Pediatrics (<12 years): The safety and effectiveness of ZORYVE in pediatric patients below the age of

12 years have not been established (see 1.1 Pediatrics).

7.1.4 Geriatrics

A total of 70 subjects 65 years of age or older with psoriasis were exposed to ZORYVE in the two 8-week vehicle-controlled clinical trials. No overall differences in safety or effectiveness were observed between these subjects and those <65 years of age. Nevertheless, greater sensitivity of some older individuals cannot be ruled out. Based on available data for roflumilast, no adjustment of dosage in geriatric patients is warranted (see 1.2 Geriatrics and 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse drug reactions reported in clinical trials among patients with plaque psoriasis 12 years of age and older are diarrhea and headache.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

In 2 multicenter, randomized, double-blind, vehicle-controlled trials (DERMIS-1 and DERMIS-2), 877 subjects (of which 14 were aged 12 to 17 years of age and 106 were 65 years of age or older) with plaque psoriasis were treated with ZORYVE or vehicle once daily for 8 weeks. The adverse reactions reported by ≥1% of patients treated with ZORYVE in clinical trials is listed in Table 2.

Table 2 - Adverse Reactions Reported in ≥1% of Patients Treated with ZORYVE for 8 Weeks

	ZORYVE N=576 (%)	Vehicle N=305 (%)
Gastrointestinal		
Diarrhea	18 (3.1)	0
Nausea	7 (1.2)	2 (0.7)
Infections and infestations		
Upper respiratory tract infection	6 (1.0)	1 (0.3)
Urinary tract infection	6 (1.0)	2 (0.7)
Nervous system disorders		
Headache	14 (2.4)	3 (1.0)
Psychiatric disorders		
Insomnia	8 (1.4)	2 (0.7)
Skin and subcutaneous tissue disorders		
Application site pain	6 (1.0)	1 (0.3)

In 594 patients who continued treatment with ZORYVE for up to 64 weeks in open-label extension studies, the adverse reaction profile was similar to that observed in vehicle-controlled studies.

Pediatrics (12 to <18 years): Use of ZORYVE in this age group was limited to two 8-week vehicle-controlled safety and efficacy trials which included 8 patients aged 12 to 17 years who received ZORYVE (1.4% of patients treated with ZORYVE). Eighteen adolescent patients were treated with ZORYVE in open-label studies of 2- and 24-weeks duration. There was no evidence of a meaningfully different adverse reaction profile in patients aged 12 to 17, relative to adults (see 8 ADVERSE REACTIONS, 10.3 Pharmacokinetics, Special Populations and Conditions, Pediatrics and 14.1 Clinical Trials by Indication).

Description of Selected Clinical Trial Findings

Diarrhea

Seventeen of the eighteen cases of diarrhea reported in patients treated with ZORYVE during DERMIS-1 and DERMIS-2 were mild, and the eighteenth was moderate. The majority of the cases occurred within the first 2 weeks of treatment and resolved over time with continued dosing. No cases led to discontinuation or interruption of treatment.

Weight Loss

When body weight was measured in clinical trials, the proportion of patients losing 5% or more of body weight at Week 8 across DERMIS-1 and DERMIS-2 was 4% in the roflumilast group, compared to 2.3% in the vehicle group. In patients who continued to apply roflumilast in open-label extension studies, this number increased to 9.5% by Week 28 and 13.4% at Week 52 of treatment.

Oral Roflumilast in the Treatment of Chronic Obstructive Pulmonary Disease

Cardiovascular

In clinical trials of oral roflumilast, supraventricular arrhythmia including atrial fibrillation was reported as a common event (>1%).

Neurologic

In clinical trials of oral roflumilast, an increased number of neurologic events such as dizziness, headache, and tremor have been reported in patients treated with roflumilast compared to those treated with placebo.

Psychiatric

In clinical trials of oral roflumilast, an increased number of psychiatric events such as anxiety, depression, and insomnia/sleep disorders have been reported in patients treated with roflumilast compared to those treated with placebo.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No formal drug-drug interaction studies were conducted with ZORYVE.

In vitro studies and clinical drug-drug interaction studies suggest that the metabolism of roflumilast to its N-oxide metabolite is mediated by CYP1A2 and 3A4. Both roflumilast and roflumilast N-oxide have intrinsic PDE-4 inhibitory activity. The coadministration of roflumilast with systemic CYP1A2 and/or 3A4 inhibitors may therefore increase roflumilast systemic exposure and may result in increased adverse reactions (see 10 CLINICAL PHARMACOLOGY).

9.4 Drug-Drug Interactions

Drugs that Inhibit Cytochrome P450 (CYP) Enzymes

The coadministration of roflumilast with systemic CYP3A4 inhibitors (e.g., erythromycin, ketoconazole, oral contraceptives containing gestodene and ethinyl estradiol), CYP1A2 inhibitors (e.g., fluvoxamine), or dual inhibitors that inhibit both CYP3A4 and CYP1A2 simultaneously (e.g., enoxacin, cimetidine) may increase roflumilast systemic exposure and may result in increased adverse reactions.

The risk of such concurrent use should be weighed carefully against benefit.

The drugs listed in Table 3 are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

Table 3 – Established or Potential Drug-Drug Interactions

Proper Name	Source of Evidence	Effect	Clinical Comment
Erythromycin	P/CT	↑ tPDE-4i by 9%	Exercise caution when coadministering ZORYVE with potent CYP3A4 inhibitors.
Ketoconazole	P/CT	↑ tPDE-4i by 9%	
Oral contraceptives containing gestodene and ethinyl estradiol	P/CT	↑ tPDE-4i by 17%	
Fluvoxamine	P/CT	↑ tPDE-4i by 59%	Exercise caution when coadministering ZORYVE with potent CYP1A2 inhibitors.
Enoxacin	P/CT	↑ tPDE-4i by 25%	Exercise caution when coadministering ZORYVE with potent CYP3A4/CYP1A2 inhibitors.
Cimetidine	P/CT	↑ tPDE-4i by 47%	

Legend: P = Potential; CT = Clinical Trial; tPDE-4i = Total PDE-4 Inhibition

9.5 Drug-Food Interactions

Interactions with food have not been evaluated, as it is not applicable for topical products.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Roflumilast and its active metabolite (roflumilast N-oxide) are selective inhibitors of PDE-4. Roflumilast and roflumilast N-oxide inhibition of PDE-4 (a major cyclic-3',5'-adenosine monophosphate (cyclic AMP)-metabolizing enzyme) activity leads to accumulation of intracellular cyclic AMP. Roflumilast is a non-steroid, anti-inflammatory agent, which when applied topically, is thought to exert its therapeutic

action via inhibition of PDE-4 and subsequent inhibition of inflammatory markers associated with plaque psoriasis.

10.3 Pharmacokinetics

Absorption

The pharmacokinetics of ZORYVE was investigated in 18 adult and 6 adolescent (13 to 16 years of age) subjects with plaque psoriasis and a mean body surface area (BSA) involvement of approximately 27% and approximately 13% in adults and adolescents, respectively. In this study, on average, subjects applied 3 to 6.5 g of ZORYVE once daily for 15 days. Plasma concentrations of roflumilast and roflumilast N-oxide (see Metabolism) were quantifiable in all but 2 subjects (an adult and an adolescent) at Day 15. Following application of ZORYVE, the plasma concentration versus time profile was relatively flat, generally with a peak-to-trough ratio less than 2.

In adults, the mean ± SD systemic exposure (AUC_{0-24}) was 72.7 ± 53.1 and 628 ± 648 h·ng/mL for roflumilast and the N-oxide metabolite, respectively. In adolescents, the mean ± SD AUC_{0-24} was 25.1 ± 24.0 and 140 ± 179 h·ng/mL for roflumilast and the N-oxide metabolite, respectively.

Table 4 - Summary of ZORYVE Pharmacokinetic Parameters in Adolescents and Adults Following Multiple Topical Administrations Under Maximal Use Conditions

Age (Years)	Analyte	N	BSA (%)	C_{max} (ng/mL)	AUC_{0-24} (h·ng/mL)
18 and older	Roflumilast	18	26.8±6.80 (25.3%)	3.72±2.49 (67.1%)	72.7±53.1 (73.0%)
	N-Oxide	18	26.8±6.80 (25.3%)	30.6±29.4 (96.2%)	628±648 (103%)
12 to <18	Roflumilast	5	13.6±3.65 (26.8%)	1.27±1.23 (96.7%)	25.1±24.0 (95.4%)
	N-Oxide	6	13.0±3.80 (27.5%)	7.17±9.39 (131%)	140±179 (128%)

Data are presented as Mean ± SD (coefficient of variation [%]).

Distribution

Plasma protein binding of roflumilast and its N-oxide metabolite is approximately 99% and 97%, respectively. Studies in rats with radiolabeled oral roflumilast indicate low penetration across the blood-brain barrier. Roflumilast has been demonstrated to cross the placenta in pregnant rats. In addition, it is secreted into milk of breeding dams.

Metabolism

Roflumilast is extensively metabolized via Phase I (cytochrome P450) and Phase II (conjugation) reactions. The N-oxide metabolite is the only major metabolite observed in the plasma of humans. Following oral administration, roflumilast and roflumilast N-oxide account for the majority (87.5%) of total dose administered in plasma. Roflumilast was not detectable in urine, while roflumilast N-oxide was only a trace metabolite (less than 1%). Other conjugated metabolites such as roflumilast N-oxide glucuronide and 4-amino-3,5-dichloropyridine N-oxide were detected in urine.

While roflumilast is three times more potent than roflumilast N-oxide at inhibition of the PDE-4 enzyme *in vitro*, the plasma AUC of roflumilast N-oxide on average is approximately 8-fold greater than the

plasma AUC of roflumilast following topical administration. A similar ratio was observed following intravenous administration, whereas following oral administration the N-oxide metabolite circulated on average about 10-fold higher than the parent.

In vitro studies and clinical drug-drug interaction studies suggest that the metabolism of roflumilast to its N-oxide metabolite is mediated by CYP1A2 and 3A4. Based on further *in vitro* results in human liver microsomes, therapeutic plasma concentrations of roflumilast and roflumilast N-oxide do not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5, or 4A9/11; therefore, there is a low probability of relevant interactions with substances metabolized by these P450 enzymes. In addition, *in vitro* studies demonstrated no induction of the CYP1A2, 2A6, 2C9, 2C19, or 3A4/5 and only a weak induction of CYP2B6 by roflumilast.

Elimination

The plasma clearance after short-term intravenous infusion of roflumilast is on average about 9.6 L/h. Following multiple topical administrations, the half-lives of roflumilast and the N-oxide metabolite were 4.0 and 4.6 days, respectively.

Special Populations and Conditions

- **Pediatrics**

  Adolescents (12 to 17 years): Following topical administration, no clinically significant differences in the exposure of roflumilast and roflumilast N-oxide were observed based on age (see 7.1.3 Pediatrics).

- **Geriatrics**

  Following topical administration, no clinically significant differences in the exposure of roflumilast and roflumilast N-oxide were observed based on age (see 7.1.4 Geriatrics).

- **Sex**

  Following topical administration, no clinically significant differences in the exposure of roflumilast and roflumilast N-oxide were observed based on sex.

- **Ethnic Origin**

  Following topical administration, no clinically significant differences in the exposure of roflumilast and roflumilast N-oxide were observed based on ethnicity.

- **Hepatic Insufficiency**

  No studies were conducted with topical roflumilast in subjects with hepatic impairment. The pharmacokinetics of oral roflumilast 250 mcg once daily were tested in patients with mild to moderate hepatic impairment classified as Child-Pugh A and B. In these patients, the tPDE-4i was increased by about 20% in patients with Child-Pugh A and about 90% in patients with Child-Pugh B. ZORYVE is contraindicated in patients with moderate or severe hepatic impairment classified as Child-Pugh B or C (see 2 CONTRAINDICATIONS).

- **Renal Insufficiency**

  No studies were conducted with topical roflumilast in subjects with renal impairment. Following oral administration, no clinically significant differences in the pharmacokinetics of roflumilast and roflumilast N-oxide were observed in subjects with severe renal impairment (creatinine clearance 10-30 mL/min) (see 4.2 Recommended Dose and Dosage Adjustment).

11 STORAGE, STABILITY AND DISPOSAL

Store at 15°C to 30°C.

12 SPECIAL HANDLING INSTRUCTIONS

Advise the patient or caregivers to read the Patient Medication Information.

Advise patients or caregivers that ZORYVE is for external use only and is not for ophthalmic, oral, or intravaginal use. Wash hands after application unless hands are being treated. (see 4.4 Administration).

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

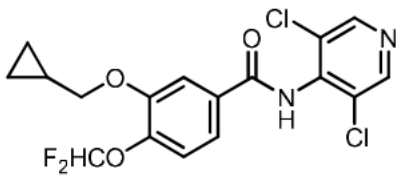
Proper name: Roflumilast

Chemical name: N-(3,5-Dichloropyridin-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxy-benzamide

Molecular formula: $C_{17}H_{14}Cl_2F_2N_2O_3$

Molecular mass: 403.22 g/mol

Structural formula:



Physicochemical properties: Roflumilast is practically insoluble in water and hexane, sparingly soluble in ethanol, and freely soluble in acetone.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Treatment of Plaque Psoriasis

Two Phase 3, multicenter, randomized, double-blind, vehicle-controlled trials (DERMIS-1 and DERMIS-2) enrolled a total of 881 subjects with mild to severe plaque psoriasis [i.e., Investigator's Global Assessment (IGA) of disease severity of 2 to 4 at baseline] and an affected BSA of 2% to 20%, including face, extremities, trunk, genitals, and/or intertriginous areas. The study populations ranged in age from 6 to 88 years with 4 subjects younger than 12 years of age, 14 subjects aged 12 to 17 years, 757 subjects aged 18 to 64 years, and 106 subjects aged 65 years or older. Race was predominantly White (82%). At baseline, 16% of subjects had an IGA score of 2 (mild), 76% had an IGA score of 3 (moderate), and 8% had an IGA score of 4 (severe). One hundred seventy-nine (20%) subjects had an

intertriginous IGA (I-IGA) score of 2 (mild) or higher at baseline, and 678 (77%) subjects had a baseline Worst Itch-Numeric Rating Scale (WI-NRS) score of 4 or higher on a scale of 0 to 10.

Table 5 - Summary of Patient Demographics for Clinical Trials in Plaque Psoriasis

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (years) (range)	Sex
DERMIS-1 [NCT04211363]	Multicenter, randomized, double-blind, vehicle-controlled	Roflumilast cream 0.3%, topical application once daily for 8 weeks	286	47.6 (9 to 86)	Male: 66.1% Female: 33.9%
		Vehicle cream, topical application once daily for 8 weeks	153	48.7 (13 to 88)	Male: 62.7% Female: 37.3%
DERMIS-2 [NCT04211389]	Multicenter, randomized, double-blind, vehicle-controlled	Roflumilast cream 0.3%, topical application once daily for 8 weeks	290	46.9 (6 to 82)	Male: 60.7% Female: 39.3%
		Vehicle cream, topical application once daily for 8 weeks	152	47.1 (8 to 82)	Male: 65.8% Female: 34.2%

Demographic and baseline disease characteristics were similar across studies and treatment groups in the pivotal Phase 3 studies, including mean baseline values for BSA affected by psoriasis, IGA, Psoriasis Symptom Diary© (PSD), Psoriasis Area and Severity Index (PASI), and WI-NRS. Among subjects with I-IGA greater than or equal to 2 (at least mild) at baseline, mean baseline I-IGA was similar across treatment groups and studies.

Subjects were randomized 2:1 to receive ZORYVE or vehicle applied once daily for 8 weeks to lesions of plaque psoriasis (excluding scalp). The primary endpoint was the proportion of subjects who achieved IGA treatment success, defined as an IGA score of clear (0) or almost clear (1), plus at least a 2-grade IGA score improvement from baseline, at Week 8 (Table 6). Secondary endpoints included the proportion of subjects that achieved I-IGA success at Week 8, IGA success at Week 4, WI-NRS success at Weeks 2, 4, and 8, a 75% reduction in PASI at Week 8.

Primary Endpoint

The results of the primary efficacy endpoint analysis in both pivotal trials demonstrated that patients treated with ZORYVE had a clinically meaningful and statistically significant improvement in IGA success at Week 8 (41.5% and 36.7%) when compared with those treated with vehicle (5.8% and 7.1%). The results of the primary efficacy endpoint from the 2 pivotal trials are summarized in Table 6. ZORYVE showed significant improvement based on IGA success compared to vehicle within 4 weeks of the first dose.

Table 6 - IGA Treatment Success at Week 8 in Subjects with Mild to Severe Plaque Psoriasis

	DERMIS-1		DERMIS-2	
	ZORYVE	**Vehicle**	**ZORYVE**	**Vehicle**
Number of subjects randomized	**N=286**	**N=153**	**N=290**	**N=152**
IGA success*	41.5%	5.8%	36.7%	7.1%
Difference from vehicle (95% CI)†	39.7% (32.4%, 47.0%)		29.5% (21.5%, 37.6%)	

Abbreviations: CI = Confidence Interval

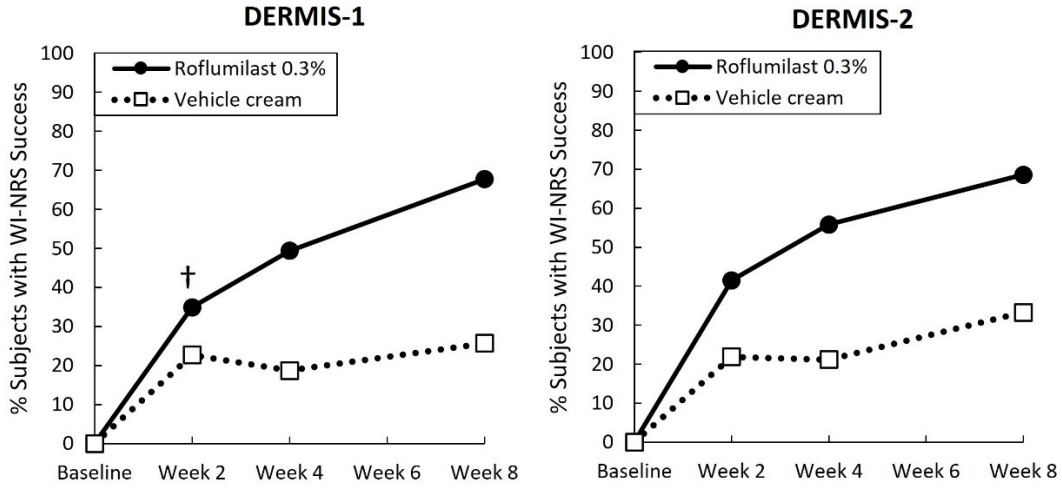
*IGA Treatment Success was defined as an IGA score of "Clear" (0) or "Almost Clear" (1), plus a 2-grade IGA score improvement from baseline at Week 8 (Multiple Imputation).

†Treatment Difference and 95% CI are based on the Cochran-Mantel-Haenszel method stratified by site, baseline IGA, and baseline intertriginous involvement.

Secondary Endpoints

At Week 4 and Week 8, more patients treated with ZORYVE achieved statistical significance in WI-NRS success compared to those receiving vehicle (see Figure 1). For subjects with intertriginous area involvement (baseline I-IGA of at least mild), significantly more achieved I-IGA success at Week 8 in the ZORYVE treatment group compared with the vehicle group. The results of the secondary efficacy endpoints from the 2 pivotal trials are summarized in Table 7.

Figure 1 - WI-NRS Success* Over Time



*WI-NRS success is a reduction of at least 4 points in patients with a WI-NRS score of 4 or higher at baseline.

†The treatment difference at Week 2 in DERMIS-1 was not statistically significant.

Table 7 - Results of the Secondary Efficacy Endpoints in Patients with Plaque Psoriasis at Week 8

Study Endpoint	DERMIS-1		DERMIS-2	
	ZORYVE	Vehicle	ZORYVE	Vehicle
I-IGA success*	N=63	N=32	N=53	N=31
	71.5%	13.8%	67.5%	17.9%
Difference from Vehicle (95% CI)	66.5 (47.1, 85.8) p<0.0001		51.6 (29.3, 73.8) p<0.0004	
PASI-75	N=286	N=153	N=290	N=152
	41.2%	7.0%	37.8%	5.3%
Difference from Vehicle (95% CI)	36.1 (28.5, 43.8) p<0.0001		32.3 (24.9, 39.8) p<0.0001	

*Defined as an I-IGA score of clear (0) or almost clear (1), plus a 2-grade I-IGA score improvement from baseline at Week 8.

Durability of Response

In patients continuing treatment with ZORYVE in open-label extension studies of 6- and 12-months duration, there was no evidence of decreased efficacy beyond 8 weeks of treatment.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Carcinogenicity

In the two 2-year carcinogenicity studies in hamsters, roflumilast was administered by gavage at doses up to 16 mg/kg/day. Nasal neoplasms (undifferentiated carcinomas of the olfactory epithelium and adenocarcinoma of Bowman's gland) were observed at high doses of roflumilast. No other treatment-related neoplastic findings were observed. Overall, the tumor-free level in the animals was 4 mg/kg/day. The significance of this finding to humans is unknown.

Long-term studies were conducted in mice with oral and topical roflumilast to evaluate its carcinogenic potential. In a 2-year oral carcinogenicity study in mice, roflumilast was administered by gavage at doses up to 18 mg/kg/day in males, and 12 mg/kg/day in females. No roflumilast-related tumors occurred. In a 2-year dermal carcinogenicity study in mice, topical doses of 0.15%, 0.5%, or 1% roflumilast cream were administered once daily. No roflumilast-related neoplastic findings were noted at topical doses up to 0.5% roflumilast cream in females and 1% roflumilast cream in males.

Genotoxicity

Roflumilast did not reveal a genotoxic potential in a standard battery of genotoxicity assays *in vitro* and *in vivo* (Ames test, *E. coli* bacterial gene mutation test, gene mutation test in V79 Chinese Hamster cells, unscheduled DNA-synthesis test, cytogenetic study with human lymphocytes micronucleus test) assessing different genetic endpoints.

Reproductive and Developmental Toxicology

No embryo-fetal development studies have been conducted with topical roflumilast. The summed AUCs of roflumilast and its active N-oxide metabolite in humans are comparable when roflumilast is administered at the topical maximum recommended human dose (MRHD) and when roflumilast is

taken orally at the MRHD, suggesting the risk is no greater following topical administration.

Roflumilast was not teratogenic in rats and rabbits following oral administration up to the highest doses of 1.8 mg/kg/day in rats and 0.8 mg/kg/day in rabbits.

Administered at the same doses, roflumilast has been shown to induce mild retardation of embryo-fetal development (incomplete ossification) in the rat, but not in the rabbit. Exposure of pregnant rats to unbound roflumilast and roflumilast N-oxide was 1.7 and 10.8 times higher, respectively, than exposure in women at the 500-mcg oral roflumilast dose. In one of three oral roflumilast rat studies on fertility and embryo-fetal development, post-implantive losses were observed at oral doses of 0.6 mg/kg/day and 1.8 mg/kg/day. Post-implantive losses were not seen in rabbits up to oral doses of 0.8 mg/kg/day. Rat and rabbit fetuses were exposed to roflumilast and the permeability of the placental barrier for drug-related material increased with the progression of pregnancy. Prolongation of gestation was seen in mice due to a potential tocolytic effect.

A fertility study of oral roflumilast in rats showed a slight reduction in male fertility in conjunction with epididymal toxicity in rats dosed orally with 1.8 mg/kg/day (about 2.2 and 8.8 times human exposure to unbound roflumilast and roflumilast N-oxide, respectively, when roflumilast was administered orally) (see 7 Warnings and Precautions, Fertility). There was no effect on female fertility up to the highest oral roflumilast dose of 1.5 mg/kg/day in rats.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrZORYVE™

Roflumilast

Read this carefully before you start using ZORYVE and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about ZORYVE.

What is ZORYVE used for?

ZORYVE is used on the skin to treat plaque psoriasis in patients 12 years of age and older. This includes areas with skin folds such as under the breasts, underarms, and buttocks.

ZORYVE is not approved in children less than 12 years of age.

How does ZORYVE work?

ZORYVE decreases the substances that trigger the skin changes and itchiness of psoriasis.

What are the ingredients in ZORYVE?

Medicinal ingredients: roflumilast

Non-medicinal ingredients: ceteareth-10 phosphate, cetearyl phosphate, cetostearyl alcohol, diethylene glycol monoethyl ether, hexylene glycol, isopropyl palmitate, methylparaben, propylparaben, purified water, sodium hydroxide, and white petrolatum. Hydrochloric acid may have been added to adjust pH.

ZORYVE comes in the following dosage forms:

As a cream containing 3 mg of roflumilast per gram (0.3% w/w).

Do not use ZORYVE if:

- You have certain liver problems. You should not take ZORYVE if you have moderate to severe liver problems. Talk to your healthcare professional about any liver problems you may have.
- You are allergic to roflumilast or to any of the other ingredients in ZORYVE.

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

- Are pregnant or plan to become pregnant. It is not known if ZORYVE will harm your unborn baby.

Other warnings you should know about:

Breastfeeding:

Tell your healthcare professional before you use ZORYVE if you are breastfeeding or plan to breastfeed. You should not breastfeed your baby unless your healthcare professional has said that you can. ZORYVE may pass into your breastmilk and harm your baby. Talk to your healthcare professional about the best way to feed your baby during treatment with ZORYVE. If your healthcare professional says that you can breastfeed your baby, use ZORYVE on the smallest area of the skin and for the shortest time needed. Do not apply ZORYVE directly to the nipple and surrounding area. This is so that your baby does not ingest or is exposed to ZORYVE.

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

The following may interact with ZORYVE:

- Erythromycin, used to treat bacterial infections.
- Oral ketoconazole, used to treat fungal infections.
- Oral contraceptives containing gestodene and ethinyl estradiol, used to prevent pregnancy.
- Fluvoxamine, used to treat certain mental disorders.
- Enoxacin, used to treat bacterial infections.
- Cimetidine, used to treat heartburn and stomach ulcers.

How to take ZORYVE:

- Always use ZORYVE exactly as your healthcare professional has told you to.
- ZORYVE is for use on the skin only. Do not use it in your eyes, mouth, or vagina.
- Rub ZORYVE in completely until you no longer see it on your skin.
- Wash your hands after applying ZORYVE, unless you are treating your hands.
- If someone else applies ZORYVE for you, they should wash their hands after applying it.

Usual dose:

Apply ZORYVE to affected areas once a day.

Overdose:

If you apply too much ZORYVE, wipe off the excess amount.

If you think you, or a person you are caring for, have used too much ZORYVE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to apply ZORYVE, skip the missed dose and go back to your regular dosing schedule the following day.

What are possible side effects from using ZORYVE?

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

Side effects may include:

- headache
- diarrhea
- trouble sleeping
- pain at the cream application site
- weight loss

Side effects reported in clinical trials with roflumilast taken as a pill to treat a condition called chronic obstructive pulmonary disease included:

- fast or irregular heartbeat
- dizziness
- tremor
- anxiety
- depression

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Diarrhea (frequent watery or loose stools)	x		
Upper respiratory tract infection (infection of your nose, sinuses, and throat): cough, runny or stuffy nose, sore throat	x		
Urinary tract infection (infection in urinary system including kidneys, ureters, bladder, and urethra): pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong-smelling urine, cloudy urine		x	
Nausea (feeling sick to your stomach)	x		

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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

Store at 15°C to 30°C.

Keep out of reach and sight of children.

If you want more information about ZORYVE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.arcutis.ca, or by calling 1-844-692-6729.

This leaflet was prepared by Arcutis Biotherapeutics, Inc.

Last Revised: April 27, 2023