HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZORYVE safely and effectively. See full prescribing information for ZORYVE.

ZORYVE™ (roflumilast) cream, for topical use
Initial U.S. Approval: 2011

----------INDICATIONS AND USAGE----------
ZORYVE is a phosphodiesterase 4 inhibitor indicated for topical treatment of plaque psoriasis, including intertriginous areas, in patients 12 years of age and older. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- Apply once daily to affected areas. (2)
- For topical use only. (2)
- Not for ophthalmic, oral, or intravaginal use. (2)

---------- DOSAGE FORMS AND STRENGTHS ----------
Cream, 0.3%: 3 mg of roflumilast per gram in 60-gram tubes. (3)

----------CONTRAINDICATIONS----------
- Moderate to severe liver impairment (Child-Pugh B or C). (4)

---------- ADVERSE REACTIONS ----------
The most common adverse reactions (reported in ≥1% of patients) are diarrhea, headache, insomnia, application site pain, upper respiratory tract infections, and urinary tract infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Arcutis Biotherapeutics, Inc. at 1-844-692-6729 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Coadministration of roflumilast with systemic CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and CYP1A2 simultaneously may increase roflumilast systemic exposure and may result in increased adverse reactions. The risk of such concurrent use should be weighed carefully against benefit. (7.1)
- Coadministration of roflumilast with oral contraceptives containing gestodene and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased side effects. The risk of such concurrent use should be weighed carefully against benefit. (7.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 7/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZORYVE™ is indicated for topical treatment of plaque psoriasis, including intertriginous areas, in patients 12 years of age and older.

2 DOSAGE AND ADMINISTRATION

Apply ZORYVE to affected areas once daily and rub in completely. Wash hands after application, unless ZORYVE is for treatment of the hands.

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

3 DOSAGE FORMS AND STRENGTHS

Cream, 0.3%: 3 mg of roflumilast per gram of white to off-white cream in 60-gram tubes.

4 CONTRAINDICATIONS

The use of ZORYVE is contraindicated in the following condition:

- Moderate to severe liver impairment (Child-Pugh B or C) *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

In two multicenter, randomized, double-blind, vehicle-controlled trials (DERMIS-1 and DERMIS-2), 881 subjects 2 years of age or older with plaque psoriasis were treated with ZORYVE or vehicle once daily for 8 weeks.

The median age was 47 years (range 6 to 88). The majority of the subjects were male (64%) and White (82%). The median body surface area (BSA) affected was 5.5% (range 2% to 20%).

The proportion of subjects who discontinued treatment due to adverse reaction was 1.0% for subjects treated with ZORYVE and 1.3% for subjects treated with vehicle. The most common adverse reactions that led to discontinuation of ZORYVE was application site urticaria (0.3%).

Table 1 presents adverse reactions that occurred in at least 1% of subjects treated with ZORYVE, and for which the rate exceeded the rate for vehicle.

Table 1. Adverse Reactions Reported in ≥1% of Subjects Treated with ZORYVE for 8 Weeks

Adverse Reaction	ZORYVE (N=576) n (%)	Vehicle (N=305) n (%)
Diarrhea	18 (3.1)	0 (0.0)
Headache	14 (2.4)	3 (1.0)
Insomnia	8 (1.4)	2 (0.7)
Nausea	7 (1.2)	1 (0.3)
Application site pain	6 (1.0)	1 (0.3)
Upper respiratory tract infection	6 (1.0)	1 (0.3)
Urinary tract infection	6 (1.0)	2 (0.7)

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

7 DRUG INTERACTIONS

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

7.1 Drugs that Inhibit Cytochrome P450 (CYP) Enzymes

The coadministration of roflumilast with systemic CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and CYP1A2 simultaneously (e.g., erythromycin, ketoconazole, fluvoxamine, 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 *[see Clinical Pharmacology (12.3)]*.

7.2 Oral Contraceptives Containing Gestodene and Ethinyl Estradiol

The coadministration of roflumilast with oral contraceptives containing gestodene and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased side effects. The risk of such concurrent use should be weighed carefully against benefit *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no randomized clinical trials of oral or topical roflumilast in pregnant women. In animal reproduction studies, roflumilast administered orally to pregnant rats and rabbits during the period of organogenesis produced no fetal structural abnormalities at doses up to 9 and 8 times the maximum recommended human dose (MRHD), respectively. Roflumilast induced post-implantation loss in rats at oral doses greater than or equal to 3 times the MRHD. Roflumilast induced stillbirth and decreased pup viability in mice at oral doses 5 and 15 times the MRHD, respectively. Roflumilast has been shown to adversely affect pup post-natal development when dams were treated with an oral dose 15 times the MRHD during pregnancy and lactation periods in mice *(see Data)*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Labor and delivery

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.

Data

Animal data

In an embryo-fetal development study, pregnant rats were dosed orally during the period of organogenesis with up to 1.8 mg/kg/day roflumilast (9 times the MRHD on a mg/m^2 basis). No evidence of structural abnormalities or effects on survival rates were observed. Roflumilast did not affect embryo-fetal development at a maternal oral dose of 0.2 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis).

In a fertility and embryo-fetal development study, male rats were dosed orally with up to 1.8 mg/kg/day roflumilast for 10 weeks and females for 2 weeks prior to pairing and throughout the organogenesis period. Roflumilast induced pre- and post-implantation loss at maternal oral doses greater than or equal to 0.6 mg/kg/day (3 times the MRHD on a mg/m^2 basis). Roflumilast did not cause fetal structural abnormalities at maternal oral doses up to 1.8 mg/kg/day (9 times the MRHD on a mg/m^2 basis).

In an embryo-fetal development study in rabbits, pregnant does were dosed orally with 0.8 mg/kg/day roflumilast during the period of organogenesis. Roflumilast did not cause fetal structural abnormalities at the maternal oral doses of 0.8 mg/kg/day (8 times the MRHD on a mg/m^2 basis).

In pre- and post-natal developmental studies in mice, dams were dosed orally with up to 12 mg/kg/day roflumilast during the period of organogenesis and lactation. Roflumilast induced stillbirth and decreased pup viability at maternal oral doses greater than 2 mg/kg/day and 6 mg/kg/day, respectively (5 and 15 times the MRHD on a mg/m^2 basis, respectively). Roflumilast induced delivery retardation in pregnant mice at maternal oral doses greater than 2 mg/kg/day (5 times the MRHD on a mg/m^2 basis). Roflumilast decreased pup rearing frequencies at a maternal oral dose of 6 mg/kg/day during pregnancy and lactation (15 times the MRHD on a mg/m^2 basis). Roflumilast also decreased survival and forelimb grip reflex and delayed pinna detachment in mouse pups at a maternal oral dose of 12 mg/kg/day (29 times the MRHD on a mg/m^2 basis).

8.2 Lactation

Risk Summary

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

Roflumilast and/or its metabolites are excreted into the milk of lactating rats *(see Data)*. When a drug is present in animal milk, it is likely that the drug will present in human milk. 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.

Clinical Considerations

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.

Data

Animal data

Roflumilast and/or its metabolite concentrations measured 8 hours after an oral dose of 1 mg/kg given to lactating rats were 0.32 and 0.02 mcg/g in the milk and pup liver, respectively.

8.4 Pediatric Use

The safety and effectiveness of ZORYVE have been established in pediatric patients ages 12 years and older for the treatment of plaque psoriasis. Use of ZORYVE in this age group is supported by data from two 8-week vehicle-controlled safety and efficacy trials which included 14 adolescent patients aged 12 to 17 years, of whom 8 received ZORYVE. Eighteen adolescent patients were treated with ZORYVE in open-label trials of 2- and 24-weeks duration. The adverse

reaction profile was similar to that observed in adults *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

The safety and effectiveness of ZORYVE in pediatric patients below the age of 12 years have not been established.

8.5 Geriatric Use

Of the 881 subjects with psoriasis exposed to ZORYVE or vehicle for up to 8 weeks in 2 controlled clinical trials, 106 were 65 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the geriatric and younger patients, but 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 Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

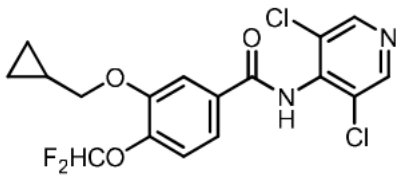
Oral roflumilast 250 mcg once daily for 14 days was studied in subjects with hepatic impairment. The AUC and C_{max} values of roflumilast and roflumilast N-oxide were increased in subjects with moderate (Child-Pugh B) hepatic impairment. ZORYVE is contraindicated in patients with moderate to severe liver impairment (Child-Pugh B or C) *[see Contraindications (4), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

ZORYVE (roflumilast) cream, 0.3% is a white to off-white cream for topical use. The active ingredient, roflumilast, is a phosphodiesterase 4 (PDE4) inhibitor.

Roflumilast is described chemically as 3-cyclopropylmethoxy-*N*-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)benzamide. The empirical formula is $C_{17}H_{14}Cl_2F_2N_2O_3$, and the molecular weight is 403.21.

The structural formula is represented below:



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

Each gram of ZORYVE contains 3 mg of roflumilast in a cream base containing 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Roflumilast and its active metabolite (roflumilast N-oxide) are inhibitors of PDE4. Roflumilast and roflumilast N-oxide inhibition of PDE4 (a major cyclic 3′,5′-adenosine monophosphate (cyclic AMP) metabolizing enzyme) activity leads to accumulation of intracellular cyclic AMP. The specific mechanism(s) by which roflumilast exerts its therapeutic action is not well defined.

12.2 Pharmacodynamics

Pharmacodynamics of ZORYVE in the treatment of plaque psoriasis is unknown.

12.3 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 ± SD body surface area (BSA) involvement of 26.8 ± 6.80% and 13.0 ± 3.58% 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 two subjects 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.

Distribution

Plasma protein binding of roflumilast and its N-oxide metabolite is approximately 99% and 97%, respectively.

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 PDE4 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.

Elimination

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

Hepatic Impairment

No studies were conducted with topical roflumilast in subjects with hepatic impairment; however, oral roflumilast 250 mcg once daily for 14 days was studied in subjects with mild to moderate hepatic impairment classified as Child-Pugh A and B (8 subjects in each group). The AUC of roflumilast and roflumilast N-oxide were increased by 51% and 24%, respectively, in Child-Pugh A subjects and by 92% and 41%, respectively, in Child-Pugh B subjects, as compared to age-, weight-, and gender-matched healthy subjects. The C_{max} of roflumilast and roflumilast N-oxide were increased by 3% and 26%, respectively, in Child-Pugh A subjects and by 26% and 40%, respectively, in Child-Pugh B subjects, as compared to healthy subjects. Oral roflumilast 500 mcg has not been studied in hepatically impaired patients. ZORYVE is contraindicated in patients with moderate or severe liver impairment (Child-Pugh B or C) *[see Contraindications (4)]*.

Renal Impairment

No studies were conducted with topical roflumilast in subjects with renal impairment. In 12 subjects with severe renal impairment no clinically significant differences in the pharmacokinetics of roflumilast and roflumilast N-oxide were observed following oral administration.

Special Populations

Following topical administration, no clinically significant differences in the pharmacokinetics of roflumilast and roflumilast N-oxide were observed based on age (12 to 88 years), sex, race, or ethnicity.

Drug Interactions

Clinical Studies

Since a major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2, drug interaction studies were performed with oral roflumilast and systemic inhibitors of CYP3A4 and CYP1A2.

Erythromycin: In an open-label crossover study in 16 healthy volunteers, the coadministration of CYP3A4 inhibitor erythromycin (500 mg three times daily for 13 days) with a single oral dose of 500 mcg roflumilast resulted in 40% and 70% increase in C_{max} and AUC for roflumilast, respectively, and a 34% decrease and a 4% increase in C_{max} and AUC for roflumilast N-oxide, respectively.

Ketoconazole: In an open-label crossover study in 16 healthy volunteers, the coadministration of a strong CYP3A4 inhibitor ketoconazole (200 mg twice daily for 13 days) with a single oral dose of 500 mcg roflumilast resulted in 23% and 99% increase in C_{max} and AUC for roflumilast, respectively, and a 38% reduction and 3% increase in C_{max} and AUC for roflumilast N-oxide, respectively.

Fluvoxamine: In an open-label crossover study in 16 healthy volunteers, the coadministration of dual CYP 3A4/1A2 inhibitor fluvoxamine (50 mg daily for 14 days) with a single oral dose of 500 mcg roflumilast showed a 12% and 156% increase in roflumilast C_{max} and AUC along with a 210% decrease and 52% increase in roflumilast N-oxide C_{max} and AUC, respectively.

Enoxacin: In an open-label crossover study in 16 healthy volunteers, the coadministration of dual CYP 3A4/1A2 inhibitor enoxacin (400 mg twice daily for 12 days) with a single oral dose of 500 mcg roflumilast resulted in an increased C_{max} and AUC of roflumilast by 20% and 56%, respectively. Roflumilast N-oxide C_{max} was decreased by 14% while roflumilast N-oxide AUC was increased by 23%.

Cimetidine: In an open-label crossover study in 16 healthy volunteers, the coadministration of a dual CYP 3A4/1A2 inhibitor cimetidine (400 mg twice daily for 7 days) with a single dose of 500 mcg oral roflumilast resulted in a 46% and 85% increase in roflumilast C_{max} and AUC; and a 4% decrease in C_{max} and 27% increase in AUC for roflumilast N-oxide, respectively.

Oral contraceptives containing gestodene and ethinyl estradiol: In an open-label crossover study in 20 healthy adult volunteers, coadministration of a single oral dose of roflumilast with repeated doses of a fixed combination oral contraceptive containing 0.075 mg gestodene and 0.03 mg ethinyl estradiol to steady state caused a 38% increase and 12% decrease in C_{max} of roflumilast and roflumilast N-oxide, respectively. Roflumilast and roflumilast N-oxide AUCs were increased by 51% and 14%, respectively.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: In vitro studies suggest that the biotransformation 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies were conducted in hamsters and mice with roflumilast to evaluate its carcinogenic potential. In 2-year oral gavage carcinogenicity studies, roflumilast treatment resulted in dose-related, statistically significant increases in the incidence of undifferentiated carcinomas of nasal epithelium in hamsters at doses greater than or equal to 8 mg/kg/day (6 times the MRHD on an AUC basis). The tumorigenicity of roflumilast appears to be attributed to a reactive metabolite of 4-amino-3,5-dichloropyridine N-oxide (ADCP N-oxide). No evidence of tumorigenicity was observed in mice at roflumilast oral doses up to 12 and 18 mg/kg/day in females and males, respectively (6 and 8 times the MRHD, respectively, on an AUC basis).

In a 2-year dermal mouse carcinogenicity study, no evidence of carcinogenicity was observed at topical doses of roflumilast cream up to 1% applied at 2 mL/kg/day (2 times the MRHD on an AUC basis).

Roflumilast tested positive in an *in vivo* mouse micronucleus test, but negative in the following assays: the Ames test, an *in vitro* chromosome aberration assay in human lymphocytes, an *in vitro* HPRT assay with V79 cells, an *in vitro* micronucleus test with V79 cells, a DNA adduct formation assay in rat nasal mucosa, liver and testes, and an *in vivo* mouse bone marrow chromosome aberration assay. Roflumilast N-oxide was negative in the Ames test and an *in vitro* micronucleus test with V79 cells.

In a human spermatogenesis study, oral roflumilast 500 mcg had no effects on semen parameters or reproductive hormones during the 3-month treatment period and the following 3-month off-treatment period. In a fertility study, oral roflumilast decreased fertility rates in male rats at 1.8 mg/kg/day (9 times the MRHD on a mg/m^2 basis). The male rats also showed increases in the incidence of tubular atrophy, degeneration in the testis, and spermiogenic granuloma in the epididymides. No effect on rat fertility rate or male reproductive organ morphology was observed at 0.6 mg/kg/day (3 times the MRHD on a mg/m^2 basis). In a female fertility study, no effect on fertility was observed up to the highest roflumilast dose of 1.5 mg/kg/day in rats (7 times the MRHD on a mg/m^2 basis).

14 CLINICAL STUDIES

Two multicenter, randomized, double-blind, vehicle-controlled trials (DERMIS-1 [NCT04211363] and DERMIS-2 [NCT04211389]) enrolled a total of 881 subjects with mild to severe plaque psoriasis and an affected BSA of 2% to 20%. The study population ranged in age from 6 to 88 years with 4 subjects younger than 12 years of age at baseline. At baseline, 16% of subjects had an Investigator's Global Assessment (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 or higher (mild) at baseline, and 678 (77%) subjects had a baseline Worst Itch-Numeric Rating Score (WI-NRS) score of 4 or higher on a scale of 0 to 10.

Subjects were randomized 2:1 to receive ZORYVE or vehicle applied once daily for 8 weeks. The primary endpoint was the proportion of subjects who achieved IGA treatment success at Week 8 (Table 2). Success was defined as a score of “Clear” (0) or “Almost Clear” (1), plus a 2-grade improvement from baseline.

Secondary endpoints included the proportion of subjects that achieved I-IGA success at Week 8 and WI-NRS success sequentially at Weeks 8, 4, and 2. WI-NRS success was defined as a reduction of at least 4 points from baseline in subjects with a baseline WI-NRS score of at least 4.

Table 2: 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%)	

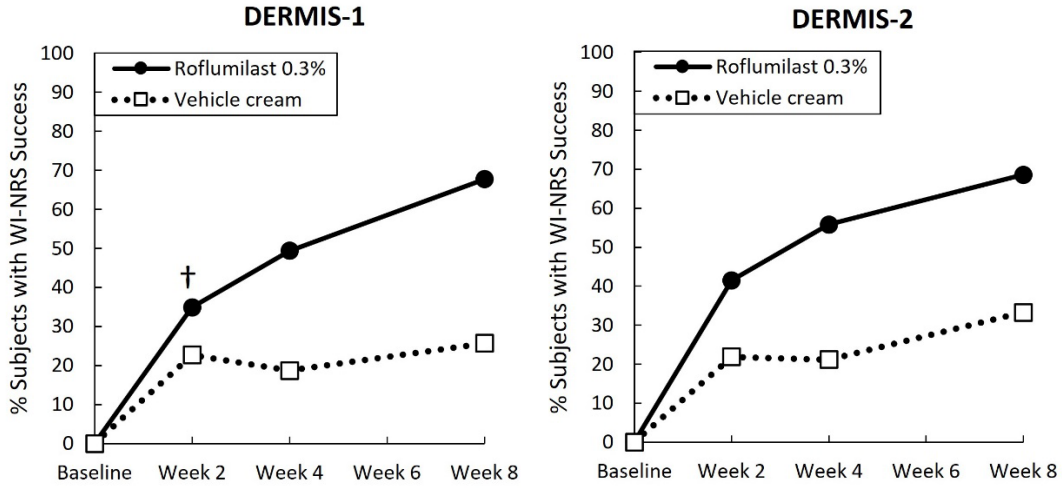
Abbreviations: CI = Confidence Interval

*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 CMH method stratified by site, baseline IGA, and baseline intertriginous involvement.

Among subjects with an I-IGA score of at least 2 (mild) at baseline (approximately 22% of subjects in DERMIS-1 and 19% in DERMIS-2), there was a higher percentage of subjects who achieved I-IGA success at Week 8 in the group who received ZORYVE compared to the group who received vehicle (DERMIS-1: 71.5% vs. 13.8%; DERMIS-2: 67.5% vs. 17.4%).

Figure 1: WI-NRS Success Over Time*



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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ZORYVE (roflumilast) cream is a white to off-white cream containing 3 mg (0.3%) of roflumilast per gram and is supplied in 60-g aluminum tubes (NDC 80610-130-60).

16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F). [See USP Controlled Room Temperature]

17 PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Patient Information).

Patient Information
ZORYVE™ (zor-EEV)
(roflumilast) cream

Important information: ZORYVE is for use on the skin (topical use) only. Do not use ZORYVE in or on your eyes, mouth, or vagina.

What is ZORYVE?
ZORYVE is a prescription medicine used on the skin (topical), including in areas with skin folds, to treat plaque psoriasis in people 12 years of age and older.
It is not known if ZORYVE is safe and effective in children under 12 years of age.

Do not use ZORYVE if you have certain liver problems.

Before using ZORYVE, tell your healthcare provider about all of your medical conditions, including if you:
- have liver problems
- are pregnant or plan to become pregnant. It is not known if ZORYVE will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if ZORYVE passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with ZORYVE.
  Breastfeeding women using ZORYVE should use ZORYVE on the smallest area of the skin and for the shortest time needed. Do not apply ZORYVE directly to the nipple and areola to avoid contact with your baby.

Tell your healthcare provider about the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I use ZORYVE?
- Use ZORYVE exactly as your healthcare provider tells you to use it.
- Apply ZORYVE to the affected areas 1 time a day. Rub the cream in completely until you no longer see it on your skin.
- Wash your hands after applying ZORYVE, unless your hands are being treated. If someone else applies ZORYVE for you, they should wash their hands after applying ZORYVE.

What are the possible side effects of ZORYVE?
The most common side effects of ZORYVE include:
- diarrhea
- headache
- trouble sleeping
- nausea
- application site pain
- upper respiratory tract infections
- urinary tract infections (UTIs)

These are not all of the possible side effects of ZORYVE.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
You may also report side effects to Arcutis Biotherapeutics, Inc. by calling 1-844-692-6729.

How should I store ZORYVE?
- Store ZORYVE at room temperature from 68°F to 77°F (20°C to 25°C).

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

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

What are the ingredients in ZORYVE?
Active ingredient: roflumilast
Inactive 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.

Marketed by: Arcutis Biotherapeutics, Inc.
Westlake Village, CA 91361
For more information, call 1-844-692-6729 or visit http://www.zoryve.com.

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 7/2022