HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZORYVE foam, 0.3%, safely and effectively. See full prescribing information for ZORYVE foam, 0.3%.

ZORYVE® (roflumilast) topical foam, 0.3%
Initial U.S. Approval: 2011

----------RECENT MAJOR CHANGES----------
Indications and Usage, Plaque Psoriasis (1.2) 5/2025

----------INDICATIONS AND USAGE----------
ZORYVE topical foam, 0.3%, is a phosphodiesterase 4 inhibitor indicated for the treatment of
- seborrheic dermatitis in adult and pediatric patients 9 years of age and older. (1.1)
- plaque psoriasis of the scalp and body in adult and pediatric patients 12 years of age and older. (1.2)

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

---------- DOSAGE FORMS AND STRENGTHS ----------
Topical foam, 0.3%: 3 mg of roflumilast per gram in 60-gram pressurized cans. (3)

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

---------- WARNINGS AND PRECAUTIONS----------
Flammability: The propellants in ZORYVE foam, 0.3%, are flammable. Avoid fire, flame, and smoking during and immediately following application. (5.1)

---------- ADVERSE REACTIONS ----------
The most common adverse reactions (reported in ≥ 1% of patients) are:
- Seborrheic dermatitis: nasopharyngitis, nausea, and headache. (6.1)
- Plaque psoriasis of the scalp and body: headache, diarrhea, nausea, and nasopharyngitis. (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----------
- Co-administration 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. If these products are co-administered with ZORYVE foam, 0.3%, weigh the potential for increased adverse reactions against benefit. (7.1)
- Co-administration of roflumilast with oral contraceptives containing gestodene and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased adverse reactions. If these products are co-administered with ZORYVE foam, 0.3%, weigh the potential for increased adverse reactions against benefit. (7.1)

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

Revised: 5/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Seborrheic Dermatitis

ZORYVE® topical foam, 0.3%, is indicated for the treatment of seborrheic dermatitis in adult and pediatric patients 9 years of age and older.

1.2 Plaque Psoriasis

ZORYVE topical foam, 0.3%, is indicated for the treatment of plaque psoriasis of the scalp and body in adult and pediatric patients 12 years of age and older.

2 DOSAGE AND ADMINISTRATION

Shake can prior to each use. Apply a thin layer of ZORYVE foam, 0.3%, once daily to affected areas of body and/or scalp when they are not wet. Rub in completely.

Wash hands after application.

Avoid fire, flame, and smoking during and immediately following application *[see Warnings and Precautions (5.1)]*.

ZORYVE foam, 0.3%, is for topical use only and not for ophthalmic, oral, or intravaginal use.

3 DOSAGE FORMS AND STRENGTHS

Topical foam, 0.3%: 3 mg of roflumilast per gram of white to off-white foam in 60-gram pressurized cans.

4 CONTRAINDICATIONS

ZORYVE foam, 0.3%, is contraindicated in patients with moderate to severe liver impairment (Child-Pugh B or C) *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Flammability

The propellants in ZORYVE foam, 0.3%, are flammable. Avoid fire, flame, and smoking during and immediately following application.

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.

Seborrheic Dermatitis

In two multicenter, randomized, double-blind, vehicle-controlled trials (Trial 203 and STRATUM), 683 adult and pediatric subjects 9 years of age or older with seborrheic dermatitis were treated with ZORYVE foam, 0.3%, or vehicle foam once daily for 8 weeks *[see Clinical Studies (14.1)]*.

Table 1 presents adverse reactions that occurred in at least 1% of subjects treated with ZORYVE foam, 0.3%.

Table 1: Adverse Reactions Reported in ≥1% of Adult and Pediatric Subjects 9 Years of Age and Older with Seborrheic Dermatitis Treated with ZORYVE Foam, 0.3%, for 8 Weeks in Trial 203 and Trial STRATUM

Adverse Reaction	ZORYVE foam, 0.3% (N=458) n (%)	Vehicle foam (N=225) n (%)
Nasopharyngitis	7 (1.5)	1 (0.4)
Nausea	6 (1.3)	0 (0)
Headache	5 (1.1)	0 (0)

The following additional adverse reactions were reported in fewer than 1% of subjects treated with ZORYVE foam, 0.3%: diarrhea and insomnia.

The adverse reaction profile in pediatric subjects was consistent with that observed in adults *[see Use in Specific Populations (8.4), Clinical Pharmacology (12.3)]*.

In 408 subjects who continued treatment with ZORYVE foam, 0.3%, for up to 24 to 52 weeks in an open-label, long-term trial, the adverse reaction profile was consistent with that observed in vehicle-controlled trials.

Plaque Psoriasis

In two multicenter, randomized, double-blind, vehicle-controlled trials (Trial 204 and ARRECTOR), 734 adult and pediatric subjects 12 years of age and older with plaque psoriasis of the scalp and body were treated with ZORYVE foam, 0.3%, or vehicle foam once daily for 8 weeks *[see Clinical Studies (14.2)].*

Table 2 presents adverse reactions that occurred in at least 1% of subjects treated with ZORYVE foam, 0.3%.

Table 2: Adverse Reactions Reported in ≥1% of Adult and Pediatric Subjects 12 Years of Age and Older with Plaque Psoriasis of the Scalp and Body Treated with ZORYVE Foam, 0.3%, for 8 Weeks in Trial 204 and Trial ARRECTOR

Adverse Reaction	ZORYVE foam, 0.3% (N=479) n (%)	Vehicle foam (N=255) n (%)
Headache	15 (3.1)	3 (1.2)
Diarrhea	12 (2.5)	4 (1.6)
Nausea	8 (1.7)	0 (0)
Nasopharyngitis	6 (1.3)	2 (0.8)

The following additional adverse reaction was reported in fewer than 1% of subjects treated with ZORYVE foam, 0.3%: insomnia.

The adverse reaction profile in pediatric subjects was consistent with that observed in adults *[see Use in Specific Populations (8.4), Clinical Pharmacology (12.3)]*.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on ZORYVE Foam, 0.3%

Drugs that Inhibit Cytochrome P450 (CYP) Enzymes

No formal drug-drug interaction studies were conducted with ZORYVE foam, 0.3%; however, the co-administration of oral 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. If these products are co-administered with ZORYVE foam,

0.3%, weigh the potential for increased adverse reactions against benefit *[see Clinical Pharmacology (12.3)]*.

Oral Contraceptives Containing Gestodene and Ethinyl Estradiol

The co-administration of roflumilast with oral contraceptives containing gestodene and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased adverse reactions. If these products are co-administered with ZORYVE foam, 0.3%, weigh the potential for increased adverse reactions against benefit *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are insufficient data available on the use of ZORYVE foam, 0.3%, in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. 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 21 and 18 times the maximum recommended human dose (MRHD), respectively. Roflumilast induced post-implantation loss in rats at oral doses greater than or equal to 7 times the MRHD. Roflumilast induced stillbirth and decreased pup viability in mice at oral doses 11 and 34 times the MRHD, respectively. Roflumilast has been shown to adversely affect pup post-natal development when dams were treated with an oral dose 34 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

Avoid using ZORYVE foam, 0.3%, during labor and delivery. There are no human studies that have investigated effects of ZORYVE foam, 0.3%, 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 (21 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 (2 times 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 (7 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 (20 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 (18 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 (11 and 34 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 (11 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 (34 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 (68 times the MRHD on a mg/m^2 basis).

8.2 Lactation

Risk Summary

There are no data on the presence of roflumilast or its metabolite 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 be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZORYVE foam, 0.3%, and any potential adverse effects on the breastfed infant from ZORYVE foam, 0.3%, or from the underlying maternal condition.

Clinical Considerations

To minimize potential exposure to the breastfed infant via breast milk, use ZORYVE foam, 0.3%, on the smallest area of skin and for the shortest duration possible while breastfeeding. To avoid direct infant exposure, advise breastfeeding women not to apply ZORYVE foam, 0.3%, directly to the nipple or areola. If applied to the patient's chest, avoid exposure via direct contact with the infant's skin.

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. The concentration of roflumilast in animal milk does not necessarily predict the concentration of drug in human milk.

8.3 Fertility

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.

8.4 Pediatric Use

Seborrheic Dermatitis

The safety and effectiveness of ZORYVE topical foam, 0.3%, for the treatment of seborrheic dermatitis have been established in pediatric patients 9 years of age and older. Use of ZORYVE foam, 0.3%, in this age group is supported by data from two 8-week, vehicle-controlled trials which included 32 subjects 9 to 17 years of age, of whom 17 received ZORYVE foam, 0.3%, and from

open-label trials of up to 52 weeks which included 23 pediatric subjects treated with ZORYVE foam, 0.3% *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14)]*.

The safety and effectiveness of ZORYVE foam, 0.3%, in pediatric patients below the age of 9 years have not been established.

Plaque Psoriasis

The safety and effectiveness of ZORYVE topical foam, 0.3%, for the treatment of plaque psoriasis of the scalp and body have been established in pediatric patients 12 years of age and older. Use of ZORYVE foam, 0.3%, in this age group is supported by data from two 8-week, vehicle-controlled trials which included 12 subjects 12 to 17 years of age, of whom 8 received ZORYVE foam, 0.3%. Use of ZORYVE foam, 0.3%, in pediatric patients 12 years of age and older is also supported by data from an open-label trial of 8 weeks duration which included 7 subjects 12 to 17 years of age treated with ZORYVE foam, 0.3%.

The safety and effectiveness of ZORYVE foam, 0.3%, in pediatric patients below the age of 12 years with plaque psoriasis have not been established.

8.5 Geriatric Use

Seborrheic Dermatitis

Of the 683 subjects with seborrheic dermatitis exposed to ZORYVE foam, 0.3%, or vehicle for up to 8 weeks in the controlled clinical trials, 98 (14%) were 65 years of age or older, and 33 (5%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Plaque Psoriasis

Of the 734 subjects with plaque psoriasis of the scalp and body exposed to ZORYVE foam, 0.3%, or vehicle for up to 8 weeks in the controlled clinical trials, 82 (11%) were 65 years of age or older, and 21 (3%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

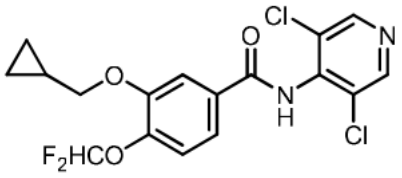
Oral roflumilast 250 mcg once daily for 14 days was studied in subjects with hepatic impairment. The systemic exposure of roflumilast and roflumilast N-oxide were increased in subjects with moderate (Child-Pugh B) hepatic impairment. ZORYVE foam, 0.3%, is contraindicated in patients with moderate to severe liver impairment (Child-Pugh B or C). No dosage adjustment is needed in patients with mild (Child-Pugh A) hepatic impairment *[see Contraindications (4), Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

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

The chemical name of roflumilast is 3-cyclopropylmethoxy-*N*-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)benzamide with a molecular formula of $C_{17}H_{14}Cl_2F_2N_2O_3$ and the molecular weight of 403.21.

The structural formula of roflumilast is:



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

Each gram of ZORYVE topical foam, 0.3%, contains 3 mg of roflumilast in a foam 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. ZORYVE topical foam, 0.3%, is dispensed from an aluminum can pressurized with propellant (butane, isobutane, and propane).

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 foam, 0.3%, in the treatment of seborrheic dermatitis and plaque psoriasis is unknown.

12.3 Pharmacokinetics

Absorption

Seborrheic Dermatitis

The pharmacokinetics of ZORYVE foam, 0.3%, was investigated in 10 adult and 10 pediatric (11 to 16 years of age) subjects with seborrheic dermatitis. In this study, a mean dose of approximately 4.1 g of ZORYVE foam, 0.3%, was applied once daily for 15 days to a mean ± SD body surface area (BSA) involvement of 6.5 ± 1.08% and 5.5 ± 1.27% in adult and pediatric subjects, respectively. Plasma concentrations of roflumilast were quantifiable in all but two subjects at Day 15. Plasma concentrations of roflumilast N-oxide were quantifiable in all subjects at Day 15. Following application of ZORYVE foam, 0.3%, the plasma concentration versus time profile was relatively flat, with mean peak-to-trough ratios of 1.68 and 1.62 for roflumilast and roflumilast N-oxide, respectively.

In adults, the mean ± SD maximum concentration (C_{max}) was 2.2 ± 1.6 and 13.8 ± 9.0 ng/mL for roflumilast and the N-oxide metabolite, respectively. The mean ± SD systemic exposure (AUC_{0-24}) was 36.6 ± 23.7 and 261 ± 190 h·ng/mL for roflumilast and the N-oxide metabolite, respectively. In pediatric subjects, the extrapolated mean ± SD AUC_{0-24} (based on pre-dose concentration) was 25.1 ± 30.2 and 253 ± 404 h·ng/mL for roflumilast and the N-oxide metabolite, respectively.

Plaque Psoriasis

The pharmacokinetics of ZORYVE foam, 0.3%, was investigated in 19 adults and 7 pediatric subjects 12 to 16 years of age with plaque psoriasis of the scalp and body. The entire scalp (BSA of approximately 4.5%) was treated in addition to the mean ± SD BSA involvement on the body of 25.0 ± 7.88% and 10.4 ± 0.54% in adults and pediatric subjects, respectively. In this study, the mean daily dose administered in adults was 10.3 g and in pediatric subjects from 12 to 16 years of age was 5.3 g of ZORYVE foam, 0.3%, once daily for 15 days. Following application of ZORYVE foam, 0.3%, the plasma concentration versus time profile was flat, with mean peak-to-trough ratios of approximately 1.2 for both roflumilast and roflumilast N-oxide.

In adults, the mean ± SD C_{max} was 4.48 ± 2.28 and 29.9 ± 17.5 ng/mL for roflumilast and the N-oxide metabolite, respectively, on Day 15. The mean ± SD AUC_{0-24} was 90 ± 58.7 and 567 ± 436 h·ng/mL for roflumilast and the N-oxide metabolite, respectively, on Day 15. In pediatric subjects, the extrapolated mean ± SD AUC_{0-24} (based on pre-dose concentration) was 35.5 ± 41.4 and 270 ± 293 h·ng/mL for roflumilast and the N-oxide metabolite, respectively, on Day 15.

Distribution

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

Elimination

The plasma clearance after short-term intravenous infusion of roflumilast is on average about 9.6 L/h. Following topical administration, the mean half-lives of both roflumilast and the N-oxide metabolite were in the range of 3.6 to 5 days.

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 3 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 7-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 drug.

Specific Populations

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

Patients with 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 *[see Contraindications (4)]*.

Patients with Renal Impairment

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

Drug Interaction Studies

Clinical Studies

No formal drug-drug interaction studies were conducted with roflumilast topical foam, 0.3%.

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 *[see Drug Interactions (7)]*.

Erythromycin: In an open-label crossover study in 16 healthy volunteers, the co-administration of CYP3A4 inhibitor erythromycin (500 mg 3 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 co-administration 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 co-administration 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 co-administration 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 co-administration of a dual CYP 3A4/1A2 inhibitor cimetidine (400 mg twice daily for 7 days) with a single oral dose of 500 mcg 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, co-administration 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, roflumilast and roflumilast N-oxide therapeutic plasma concentrations 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 (11 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 (10 and 15 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 (4 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 fertility study, oral roflumilast decreased fertility rates in male rats at 1.8 mg/kg/day (20 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 (7 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 (17 times the MRHD on a mg/m^2 basis).

14 CLINICAL STUDIES

14.1 Seborrheic Dermatitis

Two randomized, double-blind, vehicle-controlled trials (STRATUM [NCT04973228] and Trial 203 [NCT04091646]) enrolled a total of 683 adult and pediatric subjects with seborrheic dermatitis involving the scalp, face, and/or body with an Investigator Global Assessment (IGA) of moderate or severe (IGA of 3 or 4 on a 5-point scale from 0 to 4). In each trial, subjects were randomized 2:1 to receive ZORYVE foam, 0.3%, or vehicle foam applied once daily for 8 weeks. The combined trial population was 50% male, 79% White, 11% Black, 5% Asian, and 5% other races; for ethnicity, 79% identified as non-Hispanic/Latino and 21% identified as Hispanic/Latino. In Trial STRATUM, the trial population ranged in age from 9 to 87 years, including 7% of subjects who were 9 to 17 years of age and 12% of subjects who were 65 years of age or older. At baseline, 94% of subjects had an IGA score of 3 (moderate), and 6% had an IGA score of 4 (severe). At baseline, 67% of subjects had a Worst Itch-Numeric Rating Scale (WI-NRS) score of 4 or higher on a scale of 0 to 10. In Trial 203, the trial population ranged in age from 18 to 85 years, including 18% who were 65 years of age or older. At baseline, 93% of subjects had an IGA score of 3

(moderate), and 7% had an IGA score of 4 (severe). At baseline, 81% of subjects had a Worst Itch-Numeric Rating Scale (WI-NRS) score of 4 or higher on a scale of 0 to 10.

The primary endpoint was the proportion of subjects who achieved IGA treatment success at Week 8 (Table 3). Success was defined as a score of “Clear” (0) or “Almost Clear” (1), plus a 2-grade improvement from baseline.

Table 3: IGA Treatment Success at Week 8 in Adult and Pediatric Subjects 9 Years of Age and Older with Moderate to Severe Seborrheic Dermatitis in Trial STRATUM and Trial 203

	STRATUM		Trial 203	
	ZORYVE foam, 0.3%	**Vehicle foam**	**ZORYVE foam, 0.3%**	**Vehicle foam**
Number of subjects randomized	**N=304**	**N=153**	**N=154**	**N=72**
IGA success*	79.5%	58.0%	73.1%	40.8%
Difference from Vehicle (95% CI)†	20.6% (11.2%, 30.0%)		33.8% (20.3%, 47.4%)	

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 pooled site and baseline IGA strata.

In Trial STRATUM, among subjects with a baseline WI-NRS score of at least 4 (67% of subjects), there was a higher percentage of subjects who achieved a reduction of at least 4 points from baseline at Week 8 in the group who received ZORYVE foam, 0.3%, compared to the group who received vehicle foam (62.8% vs. 40.6% for a treatment difference of 25.7% and 95% CI of (13.4, 38.1)).

14.2 Plaque Psoriasis

Two randomized, double-blind, vehicle-controlled trials (ARRECTOR [NCT05028582] and Trial 204 [NCT04128007]) enrolled a total of 736 adult and pediatric subjects 12 years of age and older with mild to severe plaque psoriasis of the scalp and body. In each trial, subjects were randomized 2:1 to receive ZORYVE foam, 0.3%, or vehicle foam applied once daily for 8 weeks. The combined trial population was 55% female, 85% White, 5% Black, 6% Asian, and 4% other races; for ethnicity, 79% identified as non-Hispanic/Latino and 19% identified as Hispanic/Latino. The median age was 47 years (range 12 to 87 years).

In Trial ARRECTOR, the trial population ranged in age from 12 to 87 years, including 2% of subjects who were 12 to 17 years of age and 13% of subjects who were 65 years of age or older. At baseline, 86% of subjects had a Scalp Investigator Global Assessment (S-IGA) score of 3 (moderate) on a 5-point scale of 0 to 4, and 14% had an S-IGA score of 4 (severe); 28% of subjects had a Body Investigator Global Assessment (B-IGA) score of 2 (mild), 67% of subjects had a B-IGA score of 3 (moderate), and 5% had a B-IGA score of 4 (severe). At baseline, 76% of subjects had a Scalp Itch-Numeric Rating Scale (SI-NRS) score of 4 or higher on a scale of 0 to 10 and 73% had a Worst Itch-Numeric Rating Scale (WI-NRS) score of 4 or higher.

In Trial 204, the trial population ranged in age from 12 to 87 years, including 1% of subjects who were 12 to 17 years of age, and 9% who were 65 years of age or older. At baseline, 11% of subjects had an S-IGA score of 2 (mild), 76% of subjects had an S-IGA score of 3 (moderate), and 13% had an S-IGA score of 4 (severe); 36% of subjects had a B-IGA score of 2 (mild), 59% of subjects had a B-IGA score of 3 (moderate), and 5% had a B-IGA score of 4 (severe). At baseline, 89% of subjects had an SI-NRS score of 4 or higher on a scale of 0 to 10.

In both trials, S-IGA treatment success, a primary endpoint in ARRECTOR and Trial 204, and B-IGA treatment success, a primary endpoint in ARRECTOR, were defined as a score of “Clear” (0) or “Almost Clear” (1), plus a 2-grade improvement from baseline.

Table 4: S-IGA and B-IGA Treatment Success at Week 8 in Adult and Pediatric Subjects 12 Years of Age and Older with Plaque Psoriasis of the Scalp and Body in Trial ARRECTOR and Trial 204

	Trial ARRECTOR		**Trial 204**	
	ZORYVE foam, 0.3%	**Vehicle foam**	**ZORYVE foam, 0.3%**	**Vehicle foam**
Number of subjects randomized	**N=281**	**N=151**	**N=200**	**N=104**
S-IGA success*	66.4%	27.8%	56.7%	11.0%
Difference from Vehicle (95% CI)†	37.1% (27.1%, 47.1%)		47.7% (37.9%, 57.5%)	
B-IGA success*	45.5%	20.1%	39.0%	7.4%
Difference from Vehicle (95% CI)†	24.8% (15.0%, 34.6%)		32.4% (23.3%, 41.6%)	

Abbreviations: CI = Confidence Interval

*S-IGA treatment success and B-IGA treatment success were defined as a score of “Clear” (0) or “Almost Clear” (1), plus a 2-grade score improvement from baseline at Week 8 (Multiple Imputation).

†Treatment difference and 95% CI are based on the CMH method stratified by pooled site and baseline IGA strata.

SI-NRS success and WI-NRS success were defined as a reduction of at least 4 points from baseline with a baseline score of at least 4. In Trial ARRECTOR, among subjects with a baseline SI-NRS score of at least 4 (75% of subjects), a higher percentage of subjects achieved SI-NRS success at Week 8 in the group who received ZORYVE foam, 0.3%, compared to the group who received vehicle foam (65.3% vs. 30.3% for a treatment difference of 35.4% and 95% CI of (23.9, 47.0)). In Trial ARRECTOR, among subjects with a baseline WI-NRS score of at least 4 (72% of subjects), a higher percentage of subjects achieved WI-NRS success at Week 8 in the group who received ZORYVE foam, 0.3%, compared to the group who received vehicle foam (63.1% vs. 30.1% for a treatment difference of 32.8% and 95% CI of (20.3, 45.2)).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ZORYVE (roflumilast) topical foam, 0.3%, is a white to off-white foam. It is supplied in a 60-gram pressurized aluminum can (NDC 80610-430-60).

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].

Do not freeze.

Store upright.

Flammable. Contents under pressure. Do not puncture or incinerate. Do not expose to heat or store at temperatures above 49°C (120°F) *[see Warnings and Precautions (5.1)]*.

17 PATIENT COUNSELING INFORMATION

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

Administration Instructions

Advise patients or caregivers that ZORYVE foam, 0.3%, is for topical use only and is not for ophthalmic, oral, or intravaginal use *[see Dosage and Administration (2)]*.

Instruct patients or caregivers to shake the can of ZORYVE foam, 0.3%, prior to each use *[see Dosage and Administration (2)]*.

Instruct patients or caregivers to wash hands after applying ZORYVE foam, 0.3% *[see Dosage and Administration (2)]*.

Flammability

Because the propellants in ZORYVE foam, 0.3%, are flammable, instruct the patient to avoid fire, flame, and smoking during and immediately following application *[see Dosage and Administration (2), Warnings and Precautions (5.1)]*.

Lactation

Advise patients to use ZORYVE foam, 0.3%, on the smallest area of skin and for the shortest duration possible while breastfeeding. Instruct patients who are breastfeeding not to apply ZORYVE foam, 0.3%, directly to the nipple or areola to avoid direct infant exposure. Instruct patients to avoid inadvertent contact of treated areas with infant skin *[see Use in Specific Populations (8.2)]*.

Marketed by:
Arcutis Biotherapeutics, Inc.
Westlake Village, CA 91361

For more information on ZORYVE foam, call 1-805-418-5006 or visit http://www.zoryve.com.

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Patient Information
ZORYVE® (zor-EEV)
(roflumilast) topical foam, 0.3%

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

What is ZORYVE foam?

ZORYVE foam is a prescription medicine used on the skin (topical) to treat:

- seborrheic dermatitis in adults and children 9 years of age and older.
  It is not known if ZORYVE foam is safe and effective in children with seborrheic dermatitis under 9 years of age.
- plaque psoriasis of the scalp and body in adults and children 12 years of age and older.
  It is not known if ZORYVE foam is safe and effective in children with plaque psoriasis of the scalp and body under 12 years of age.

Do not use ZORYVE foam if you have certain liver problems.

Before using ZORYVE foam, 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 foam will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if ZORYVE foam passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with ZORYVE foam.
  Breastfeeding women using ZORYVE foam should use it on the smallest area of the skin and for the shortest time needed. Do not apply ZORYVE foam directly to the nipple or areola to avoid contact with your baby. Avoid direct skin contact of treated areas with your baby if ZORYVE foam is applied to your chest.

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 foam?

- Use ZORYVE foam exactly as your healthcare provider tells you to use it. See the “Instructions for Use” provided with this leaflet for directions about how to apply ZORYVE foam.
- Shake the can of ZORYVE foam before each use.
- Apply a thin layer of ZORYVE foam 1 time a day to the affected areas of your body and scalp when they are not wet. Rub the foam in completely.
- Wash your hands after applying ZORYVE foam. If someone else applies ZORYVE foam for you, they should wash their hands after applying it.

What should I avoid while using ZORYVE foam?

ZORYVE foam is flammable. Avoid fire, flame, and smoking during and right after you apply ZORYVE foam.

What are the possible side effects of ZORYVE foam?

The most common side effects of ZORYVE foam in people treated for seborrheic dermatitis include:

- common cold
- nausea
- headache

The most common side effects of ZORYVE foam in people treated for plaque psoriasis include:

- headache
- diarrhea
- nausea
- common cold

These are not all of the possible side effects of ZORYVE foam.

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 foam?

- Store ZORYVE foam at room temperature between 68°F to 77°F (20°C to 25°C).
- ZORYVE foam is flammable. Keep away from heat and flame.
- The contents in ZORYVE foam are under pressure. **Do not** puncture or burn the can. **Do not** expose the can to heat or store at temperatures above 120°F (49°C).

- **Do not** freeze.
- Store the can upright.

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

General Information about the safe and effective use of ZORYVE foam.

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

What are the ingredients in ZORYVE foam?

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.

Propellants: butane, isobutane, and propane.

Marketed by:
Arcutis Biotherapeutics, Inc.
Westlake Village, CA 91361

For more information on ZORYVE topical foam, 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. Revised: 5/2025

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INSTRUCTIONS FOR USE
ZORYVE® (zor-EEV)
(roflumilast) topical foam, 0.3%

This Instructions for Use contains information on how to apply ZORYVE foam.

Read this Instructions for Use before you start using ZORYVE foam and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment. Use ZORYVE foam exactly as your healthcare provider tells you.

Important information you need to know before applying ZORYVE foam:

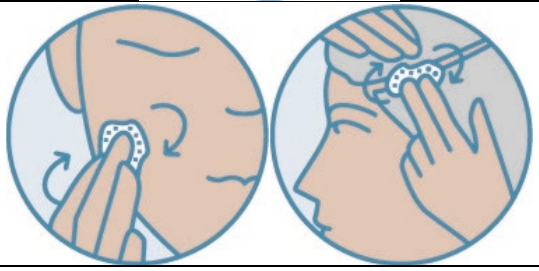
- **ZORYVE foam is for use on skin only (topical use).** ZORYVE foam is not for use in your eyes, mouth, or vagina.
- **ZORYVE foam is flammable.** Avoid fire, flame, and smoking during and right after you apply ZORYVE foam.

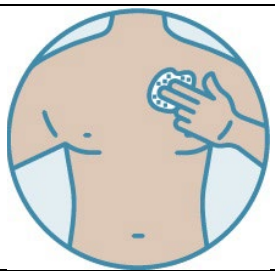
Before applying ZORYVE foam for the first time:

Gently pull back on the nozzle to break the plastic piece at the base.

Applying ZORYVE foam:

Apply a thin layer of ZORYVE foam **1 time a day** to the affected areas of your body and scalp when they are not wet.

Step 1: Shake. • Shake the can well before each use.	
Step 2: Dispense. • Turn the can upside down and press the nozzle. • Dispense a small amount into your hand.	
Step 3: Apply. • Use enough ZORYVE foam to cover all affected areas with a thin layer. Rub the foam in completely. • If you are treating your scalp, part the hair so that ZORYVE foam can be applied directly to the affected area on the skin.	

• Wash your hands after applying the medicine. If someone else applies ZORYVE foam for you, they should wash their hands after applying it.	

Storing ZORYVE foam

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- ZORYVE foam is flammable. Keep away from heat and flame.
- The contents in ZORYVE foam are under pressure. **Do not** puncture or burn the can. **Do not** expose the can to heat or store at temperatures above 120°F (49°C).
- **Do not** freeze.
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