

**ZORYVE- roflumilast aerosol, foam**  
**Arcutis Biotherapeutics, Inc.**

-----

**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**

----- **INDICATIONS AND USAGE** -----

ZORYVE 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)

----- **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  $\geq 1\%$  of patients) are nasopharyngitis, nausea, and headache. (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](http://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)

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

**Revised: 12/2023**

---

**FULL PRESCRIBING INFORMATION: CONTENTS\***

**1 INDICATIONS AND USAGE**

**2 DOSAGE AND ADMINISTRATION**

**3 DOSAGE FORMS AND STRENGTHS**

**4 CONTRAINDICATIONS**

**5 WARNINGS AND PRECAUTIONS**

5.1 Flammability

**6 ADVERSE REACTIONS**

6.1 Clinical Trials Experience

**7 DRUG INTERACTIONS**

**8 USE IN SPECIFIC POPULATIONS**

8.1 Pregnancy

- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment

## **11 DESCRIPTION**

## **12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

## **13 NONCLINICAL TOXICOLOGY**

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

## **14 CLINICAL STUDIES**

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

## **17 PATIENT COUNSELING INFORMATION**

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

---

## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

ZORYVE<sup>®</sup> foam, 0.3%, is indicated for the treatment of seborrheic dermatitis in adult and pediatric patients 9 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 on skin 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 [see *Dosage and Administration (2)*].

## 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 (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.

The combined trial population was 79% White, 11% Black, and 5% Asian; for ethnicity, 79% identified as non-Hispanic/Latino and 21% identified as Hispanic/Latino. Fifty percent (50%) were male and 50% were female. The median age was 41 years (range 9 to 87 years). The median body surface area (BSA) affected was 2.5%.

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  $\geq 1\%$  of Subjects with Seborrheic Dermatitis Treated with ZORYVE Foam, 0.3%, for 8 Weeks in Trial 203 and Trial STRATUM**

<b>Adverse Reaction</b>	<b>ZORYVE foam, 0.3% (N=458) n (%)</b>	<b>Vehicle foam (N=225) n (%)</b>
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.

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.

## 7 DRUG INTERACTIONS

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

### Drugs that Inhibit Cytochrome P450 (CYP) Enzymes

The co-administration 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. 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 30 and 26 times the maximum recommended human dose (MRHD), respectively. Roflumilast induced post-implantation loss in rats at oral doses greater than or equal to 10 times the MRHD. Roflumilast induced stillbirth and decreased pup viability in mice at oral doses 16 and 49 times the MRHD, respectively. Roflumilast has been shown to adversely affect pup post-natal development when dams were treated with an oral dose 49 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 (30 times the MRHD on a mg/m<sup>2</sup> 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 (3 times the MRHD on a mg/m<sup>2</sup> 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 (10 times the MRHD on a mg/m<sup>2</sup> basis). Roflumilast did not cause fetal structural abnormalities at maternal oral doses up to 1.8 mg/kg/day (29 times the MRHD on a mg/m<sup>2</sup> 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 (26 times the MRHD on a mg/m<sup>2</sup> 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 (16 and 49 times the MRHD on a mg/m<sup>2</sup> basis, respectively). Roflumilast induced delivery retardation in pregnant mice at maternal oral doses greater than 2 mg/kg/day (16 times the MRHD on a mg/m<sup>2</sup> basis). Roflumilast decreased pup rearing frequencies at a maternal oral dose of 6 mg/kg/day during pregnancy and lactation (49 times the MRHD on a mg/m<sup>2</sup> 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 (97 times the MRHD on a mg/m<sup>2</sup> 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.

## **8.4 Pediatric Use**

The safety and effectiveness of ZORYVE 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 pediatric 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%. The adverse reaction profile was consistent with that observed in adults [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.

## 8.5 Geriatric Use

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.

## 8.6 Hepatic Impairment

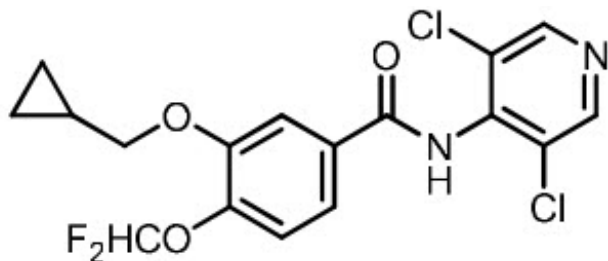
Oral roflumilast 250 mcg once daily for 14 days was studied in subjects with hepatic impairment. The systemic exposure of roflumilast and roflumilast N-oxide were increased in subjects with moderate (Child-Pugh B) hepatic impairment. ZORYVE foam, 0.3%, is contraindicated in patients with moderate to 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<sub>17</sub>H<sub>14</sub>Cl<sub>2</sub>F<sub>2</sub>N<sub>2</sub>O<sub>3</sub>, 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 cetareth-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 is unknown.

### **12.3 Pharmacokinetics**

#### Absorption

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  $\pm$  SD body surface area (BSA) involvement of  $6.5 \pm 1.08\%$  and  $5.5 \pm 1.27\%$  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  $\pm$  SD maximum concentration ( $C_{max}$ ) was  $2.2 \pm 1.6$  and  $13.8 \pm 9.0$  ng/mL for roflumilast and the N-oxide metabolite, respectively. The mean  $\pm$  SD systemic exposure ( $AUC_{0-24}$ ) was  $36.6 \pm 23.7$  and  $261 \pm 190$  h•ng/mL for roflumilast and the N-oxide metabolite, respectively. In pediatric subjects, the extrapolated mean  $\pm$  SD  $AUC_{0-24}$  (based on pre-dose concentration) was  $25.1 \pm 30.2$  and  $253 \pm 404$  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.

#### 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 3.6 and 4.4 days, 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 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 (9 to 87 years), 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*

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.

### *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 (20 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 (18 and 27 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 (7 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 (29 times the MRHD on a mg/m<sup>2</sup> 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 (10 times the MRHD on a mg/m<sup>2</sup> 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 (24 times the MRHD on a mg/m<sup>2</sup> basis).

## 14 CLINICAL STUDIES

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 included 79% White, 11% Black, and 5% Asian; for ethnicity, 79% identified as non-Hispanic/Latino and 21% identified as Hispanic/Latino. Fifty percent (50%) were male and 50% were female. 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 2). Success was defined as a score of "Clear" (0) or "Almost Clear" (1), plus a 2-grade improvement from baseline.

**Table 2: IGA Treatment Success at Week 8 in Subjects 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

<b>Number of subjects randomized</b>	<b>N=304</b>	<b>N=153</b>	<b>N=154</b>	<b>N=72</b>
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)).

## **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).

### 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, call 1-805-418-5006 or visit <http://www.zoryve.com>.

© 2023 Arcutis Biotherapeutics, Inc. All rights reserved.

v1

<b>Patient Information ZORYVE® (zor-EEV) (roflumilast) topical foam, 0.3%</b>
<b>Important information: ZORYVE foam is for use on the skin (topical use) only.</b> Do not use ZORYVE foam in or on your eyes, mouth, or vagina.
<b>What is ZORYVE foam?</b> 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 under 9 years of age.
<b>Do not use ZORYVE foam if</b> you have certain liver problems.
<b>Before using ZORYVE foam, tell your healthcare provider about all of your medical conditions, including if you:</b> <ul style="list-style-type: none"><li>• have liver problems.</li><li>• are pregnant or plan to become pregnant. It is not known if ZORYVE foam will harm your unborn baby.</li><li>• 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 it 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.</li></ul>
<b>Tell your healthcare provider about the medicines you take,</b> including prescription and over-the-counter medicines, vitamins, and herbal supplements.
<b>How should I use ZORYVE foam?</b> <ul style="list-style-type: none"><li>• 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.</li><li>• Apply a thin layer of ZORYVE foam 1 time a day to the affected areas on skin and scalp when they are not wet. Rub the foam in completely.</li><li>• Wash your hands after applying ZORYVE foam. If someone else applies it for you, they should wash their hands after applying it.</li></ul>
<b>What should I avoid while using ZORYVE foam?</b> <b>ZORYVE foam is flammable.</b> Avoid fire, flame, and smoking when applying and right after you apply it.
<b>What are the possible side effects of ZORYVE foam?</b> <b>The most common side effects include:</b> <ul style="list-style-type: none"><li>• common cold</li></ul>

- nausea
- headache

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 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 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 you have. It may harm them. You can ask your healthcare provider or pharmacist for information about ZORYVE foam that is written for health professionals.

#### **What are the ingredients in ZORYVE foam?**

**Active ingredient:** roflumilast

**Inactive ingredients:** cetareth-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, 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: 12/2023

v1

## **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 when applying and right after you apply it.

**Before Applying ZORYVE foam for the first time:**



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

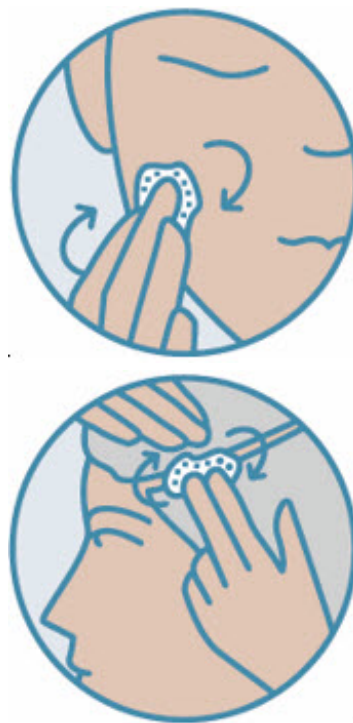
**Applying ZORYVE foam:**

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

<p><b>Step 1: Shake.</b></p> <ul style="list-style-type: none"><li>• Shake the can well before each use.</li></ul>	A circular illustration showing a hand holding the white foam canister and shaking it. Curved lines around the canister indicate the motion of shaking.
<p><b>Step 2: Dispense.</b></p> <ul style="list-style-type: none"><li>• Turn the can upside down and press the nozzle.</li><li>• Dispense a small amount into your hand.</li></ul>	A circular illustration showing a hand holding the white foam canister upside down. The nozzle is pressed against the palm of another hand, and a small amount of white foam is being dispensed.

### 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.



### Storing 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 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.

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

For more information, call 1-844-692-6729 or visit <http://www.zoryve.com>.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.  
Issued: 12/2023

v1

### PRINCIPAL DISPLAY PANEL - 60 g Can Carton

NDC 80610-430-60

ZORYVE®  
(roflumilast)  
topical foam, 0.3%

Rx Only  
60 grams

For Topical Use Only





**Z ZORYVE**  
(roflumilast)  
topical foam, 0.3%

NDC 80610-430-60

NDC 80610-430-60

**Each gram contains:**

3 mg (0.3%) roflumilast in a white to off-white foam base containing cetareth-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. Contains propellant (butane, isobutane, and propane).

**Z ZORYVE**  
(roflumilast)  
topical foam, 0.3%

Rx Only | 60 grams

For Topical Use Only

**Recommended Dosage:**

See prescribing information.

**Not for oral, ophthalmic, or intravaginal use**

**Store upright. Shake before use.**

**Turn can upside down to dispense.**

**Keep out of reach of children.**

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.

Warning: Flammable. Avoid fire, flame, and smoking during and immediately following application. Contents under pressure. Do not puncture or incinerate. Do not expose to heat or store at temperatures above 49°C (120°F).

**Z ZORYVE**  
(roflumilast)  
topical foam, 0.3%

Rx Only | 60 grams

For Topical Use Only

**Manufactured for:**

Arcutis Biotherapeutics, Inc.  
Westlake Village, CA 91361



©2023 Arcutis Biotherapeutics, Inc.  
All rights reserved.

603200



630163

GTIN 00380610430603  
SN 00000000000000  
EXP YYYY-MMM-DD  
LOT AAAA-A

# ZORYVE

roflumilast aerosol, foam

## Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:80610-430
<b>Route of Administration</b>	TOPICAL		

## Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
roflumilast (UNII: 0P6C6ZOP5U) (roflumilast - UNII:0P6C6ZOP5U)	roflumilast	3 mg in 1 g

## Inactive Ingredients

Ingredient Name	Strength
cetareth-10 phosphate (UNII: 099WOY1SA3)	
CETOSTEARYL ALCOHOL (UNII: 2DMT128M1S)	
cetearyl phosphate (UNII: 4O6GCK4CTJ)	
diethylene glycol monoethyl ether (UNII: A1A1I8X02B)	
hexylene glycol (UNII: KEH0A3F75J)	
isopropyl palmitate (UNII: 8CRQ2TH63M)	
methylparaben (UNII: A2I8C7HI9T)	
propylparaben (UNII: Z8IX2SC1OH)	
WATER (UNII: 059QF0KO0R)	
sodium hydroxide (UNII: 55X04QC32I)	
white petrolatum (UNII: B6E5W8RQJ4)	
hydrochloric acid (UNII: QTT17582CB)	
butane (UNII: 6LV4FOR43R)	
isobutane (UNII: BXR49TP611)	
propane (UNII: T75W9911L6)	

## Product Characteristics

<b>Color</b>	WHITE (off white)	<b>Score</b>	
<b>Shape</b>		<b>Size</b>	
<b>Flavor</b>		<b>Imprint Code</b>	
<b>Contains</b>			

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:80610-430-60	1 in 1 CARTON	12/15/2023	
1		60 g in 1 CAN; Type 0: Not a Combination Product		

2	NDC:80610-430-93	1 in 1 CARTON	06/12/2024	10/31/2024
2		25 g in 1 CAN; Type 0: Not a Combination Product		
<b>Marketing Information</b>				
<b>Marketing Category</b>	<b>Application Number or Monograph Citation</b>		<b>Marketing Start Date</b>	<b>Marketing End Date</b>
NDA	NDA217242		12/15/2023	

**Labeler** - Arcutis Biotherapeutics, Inc. (080642948)

Revised: 2/2025

Arcutis Biotherapeutics, Inc.