NEW DRUG APPROVAL

Brand Name	Zoryve™
Generic Name	roflumilast
Drug Manufacturer	Arcutis Biotherapeutics, Inc.

New Drug Approval

FDA approval date: July 29, 2022

Review designation: Standard

Type of review: Type 3 - New Dosage Form; NDA 215985

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Psoriasis is a common chronic, recurrent, immune mediated disease of the skin and joints. It can have a significant negative impact on the physical, emotional, and psychosocial wellbeing of affected patients. Psoriasis is found worldwide but the prevalence varies among different ethnic groups. It has a strong genetic component but environmental factors such as infections can play an important role in the presentation of disease. There are several clinical cutaneous manifestations of psoriasis but most commonly the disease presents as chronic, symmetrical, erythematous, scaling papules and plaques.

The commonest form of psoriasis is plaque psoriasis in which patients may have sharply circumscribed, round-oval, or nummular (coin-sized) plaques. The lesions may initially begin as erythematous macules (flat and <1 cm) or papules, extend peripherally, and coalesce to form plaques of one to several centimetres in diameter. A white blanching ring, known as Woronoff's ring, may be observed in the skin surrounding a psoriatic plaque. With gradual peripheral extension, plaques may develop different configurations including:

- psoriasis gyrata—in which curved linear patterns predominate
- annular psoriasis—in which ring-like lesions develop secondary to central clearing
- psoriasis follicularis—in which minute scaly papules are present at the openings of pilosebaceous follicles.

The molecular genetic basis of psoriasis is complex with evidence that multiple genes are involved. Seven major psoriasis susceptibility loci have been reported. Many investigators have established that a major susceptibility locus for psoriasis is at 6p21, referred to as PSORS1 and is overrepresented in all populations tested

Although psoriasis occurs worldwide, its prevalence varies considerably. In the USA, approximately 2% of the population is affected. High rates of psoriasis have been reported in people of the Faroe Islands, where one study found 2.8% of the population to be affected. The prevalence of psoriasis is low in certain ethnic groups such as the Japanese and may be absent in aboriginal Australians and Indians from South America. Psoriasis can present at any age and has been reported at birth and in older people of advanced age. Accurate determination of the age of onset of psoriasis is problematic, as studies which do so typically rely on a patient's recall of the onset of lesions or determine the onset from the physician's diagnosis as recorded on the initial visit. Data based on patient recall can be inaccurate; determining onset based on first visit to a physician could underestimate the time of disease occurrence, as minimal disease may be present for years before a consultation is sought. A bimodal age of onset has been recognised in several large studies. The mean age of onset for the first presentation of psoriasis can range from 15 to 20 years of age, with a second peak occurring at 55–60 years.

Topical therapy as monotherapy is useful in psoriasis patients with mild disease. Topical agents are also used as adjuvant for moderate-to-severe disease who are being concurrently treated with either ultraviolet light or systemic medications. Emollients are useful adjuncts to the treatment of psoriasis. Use of older topical agents such as anthralin and coal tar has declined over the years. However, they are cheaper and can still be used for the treatment of difficult psoriasis refractory to conventional treatment. Salicylic acid can be used in combination with other topical therapies such as topical corticosteroids (TCS) and calcineurin inhibitors for the treatment of thick limited plaques to increase the absorption of the latter into the psoriatic plaques. Low- to mid-potent TCS are used in facial/flexural psoriasis and high potent over palmoplantar/thick psoriasis lesions. The addition of noncorticosteroid treatment can also facilitate the avoidance of long-term daily TCS. Tacrolimus and pimecrolimus can be used for the treatment of facial and intertriginous psoriasis. Tazarotene is indicated for stable plaque psoriasis usually in combination with other therapies such as TCS. Vitamin D analogs alone in combination with TCS are useful in stable plaques over limbs and palmoplantar psoriasis. Topical therapies for scalp psoriasis include TCS, Vitamin D analogs, salicylic acid, coal tar, and anthralin in various formulations such as solutions, foams, and shampoos. TCS, vitamin D analogs, and tazarotene can be used in the treatment of nail psoriasis.

Efficacy

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%. 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. 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 1: 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%).

Safety

ADVERSE EVENTS

The most common adverse reactions that led to discontinuation of Zoryve™ was application site urticaria (0.3%). Table 2 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 2. 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.

WARNINGS & PRECAUTIONS

N/A

CONTRAINDICATIONS

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

Clinical Pharmacology

MECHANISMS 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.

Dose & Administration

ADULTS

Apply topically to the affected area(s) once daily.

PEDIATRICS

Age 12 to 17 years- refer to adult dosing.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

No roflumilast dosage adjustments are needed for patients with renal impairment.

HEPATIC IMPAIRMENT

Moderate to severe hepatic impairment (Child-Pugh class B or C): Use is contraindicated.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

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