Roflumilast (ZORYVE) Foam in Seborrheic Dermatitis National Drug Monograph September 2024

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

Abbreviations: BSA, body surface area; CS, corticosteroid; DB, double-blind; MC, multicenter; RCT, randomized clinical trial; SD, seborrheic dermatitis; TAF, topical antifungal; TCS, topical corticosteroid; VC, vehicle-controlled

FDA Approval Information

Description / Mechanism of Action

- Roflumilast is a phosphodiesterase 4 inhibitor that is 25 to 300 times more potent than crisaborole or apremilast in vitro.[1,2]

Indication Under Review in This Document

- Treatment of seborrheic dermatitis (SD) in adults

Dosage Regimen and Dosage Forms Under Review

- Roflumilast foam should be applied once daily to affected areas on skin and/or scalp when they are not wet.
- Topical foam 0.3% in 60-gram pressurized cans

Efficacy Considerations

- No active-controlled trials have been performed.
- One phase 3, vehicle-controlled, randomized clinical trial (RCT), STRATUM, showed efficacy of roflumilast foam 0.3% in adolescents and adults with SD.[3]
- One phase 2a RCT, similar in design to the phase 3 RCT, provided supportive evidence of efficacy.[4] IGA success at Week 8 was achieved in 104 (73.8%) of 154 roflumilast foam patients and 27 (40.9%) of 72 vehicle foam patients (absolute risk difference: 32.8%; 95% CI 18.5, 45.7).[4]

Phase 3 Randomized Clinical Trial

- Table 1 summarizes the methods of the phase 3 RCT.

Table 1 Methods of Phase 3 RCT

Topic	STRATUM Trial
Study Design	Phase 3 MC DB VC RCT (2:1, stratified by study site and baseline disease severity of 3 or 4 on Investigator Global Assessment [IGA]) (Canada, US)
Major Entry Criteria	Age ≥ 9 y Clinical diagnosis of SD affecting up to 20% of BSA, including scalp, face, trunk, and/or intertriginous areas of ≥ 3 months' duration Stable disease for previous 4 wks at screening
Interventions	Roflumilast foam 0.3% applied once daily to a maximum BSA of 20% (size of hand = 1% BSA) for 8 wks (regardless of lesion clearance)

Topic	STRATUM Trial
	Vehicle foam
Primary Efficacy Measure(s)	IGA Success (0 / Clear or 1 / Almost Clear) plus ≥ 2-point improvement from baseline at Wk 8. Scale: 0 / Clear to 4 / Severe.
Baseline Patient Characteristics	Mean age 42 y (57/ 457 [12%] ≥ 65 y) Male 50%, Not Hispanic or Latino 79%, White 79%, Black / African American 11% IGA 3.1; IGA of 3 / Moderate 93%; 4 / Severe 7% Affected BSA 2.92% (range, 0.2%–20%) Scaling: moderate 84%; severe 16% Erythema: moderate 93%; severe 7%

Results

- Efficacy data are summarized in Table 2.

Table 2 Efficacy results at Week 8

Outcome	Roflumilast Foam	Vehicle	Relative Effect (95% CI)	AAE per 1000 (95% CI)	NNT (95% CI)	Q
IGA Success, n/N (%)	242/304 (79.5)	89/153 (58.0)	1.4 (1.18, 1.58)	214 (124, 305)	5 (4, 9)	M[α]
IGA of 0 / Clear, n/N (%)	154/304 (50.6)	42/153 (27.7)	1.8 (1.39, 2.44)	232 (142, 322)	5 (4, 8)	L[αβ]
WI-NRS Success, n/N (%)	191/304 (62.8)	62/153 (40.6)	1.6 (1.26, 1.91)	223 (128, 318)	5 (4, 8)	M[α]

Source: 3

AAE, Anticipated absolute effect for achieving the outcome; **CFB**, Change from baseline; **NNT**, Number needed to treat for one additional patient to benefit; **Q**, GRADE quality of evidence (H = High, M = Moderate, L = Low, VL = Very low); WI-NRS, worst itch on numerical rating scale (0 / No Itch to 10 / Worst Imaginable Itch)

[α] Downgraded for indirectness (not a patient-reported outcome or clinical outcome).

[β] Downgraded for imprecision (optimal information size not met)

- Subgroup Analyses: None

Onset of Treatment Benefit and Duration of an Adequate Therapeutic Trial

- Onset of effects (earliest significant treatment difference) based on IGA Success was 2 weeks. This was the time point of the first scheduled assessment and may have missed detecting an earlier onset.
- The duration of an adequate therapeutic trial was at least 8 weeks. (IGA Success rate may not have peaked yet at Week 8).

Open-label, Long-term Trial

- An open-label extension trial involving patients who continued roflumilast foam therapy for up to 24 to 52 weeks that is mentioned in the prescribing information[1] has not been published to date.

Safety Considerations

Table 3 Safety Profile from US Prescribing Information

Domain	Comments
Boxed Warnings.	None
Contraindications	Moderate to severe liver impairment (Child-Pugh B or C)
Other Warnings / Precautions.	Flammable
Common Adverse Events (≥ 1%)	Nasopharyngitis, nausea, headache

Table 4 Integrated Safety from the Phase 3 and Phase 2 RCTs

Adverse Event	Roflumilast Foam 0.3%	Vehicle
Serious Adverse Events, n/N (%)	1/458 (0.2)	0/225 (0)
Adverse Events at Least Possibly Related to Study Drug,† n/N (%)	11/458 (2.4)	8/225 (3.6)

Source: 12
† Possibly, probably, or likely related to study drug

- There are no head-to-head trials to inform the relative safety of roflumilast foam vs other topical treatments for SD.
- A 26-week (up to 52 weeks) phase 2, unpublished, open-label study provided long-term safety data.[12]
- PDE4-related adverse events such as psychiatric and gastrointestinal adverse events occurred at significantly lower rates on roflumilast foam than vehicle. Suicidal ideation was reported in one vehicle-treated patient and two patients in the roflumilast foam long-term extension study. There were no reports of suicidal behavior.
- Local adverse events occurred at similar rates in the roflumilast foam and vehicle groups.
- The cream formulation of roflumilast approved in 2022 also had no significant safety concerns.[12]

Evidence Gaps

- Comparative effectiveness with other active therapies
- Efficacy and safety of intermittent maintenance therapy
- Health-related Quality of Life
- Functional ability / Social interactions
- Patient Satisfaction

Network Meta-analyses

- No current network meta-analyses (published within the previous 5 years) have included roflumilast foam trials.

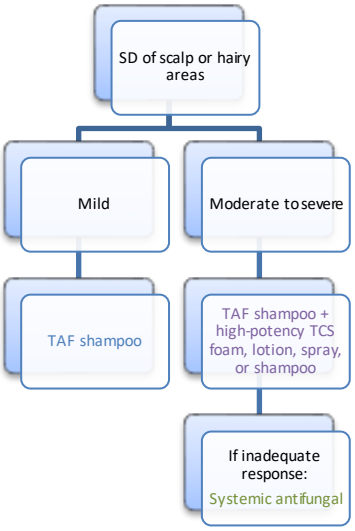
Other Considerations

- **Hair-friendly Formulation**. Roflumilast foam is formulated with moisturizers, without high concentrations of alcohols and sulfate, and is pH-balanced (pH 5.3) and residue-free, thereby reportedly making it suitable for use on all hair types, including curly or coiled hair.[5] Other topical foams and gels may contain high concentrations of drying alcohols that can adversely affect hair color and moisture.
- **Pharmacokinetics**. Roflumilast plasma concentrations were detectable in 18 of 20 patients (10 adult and 10 pediatric) with seborrheic dermatitis at Day 15 following once daily application for 15 days of a mean dose of 4.1 grams to a mean BSA of 6.5% and 5.5% in adults and pediatric patients, respectively.[1] Mean maximum concentration (C_{max}) of roflumilast and its N-oxide active metabolite were 2.2 and 13.8 ng/mL, respectively. Mean systemic exposures (AUC_{0-24}) were 36.6 and 261 h·ng/mL, respectively. (For reference, C_{max} of roflumilast after a single oral dose of roflumilast tablet is 7.5 mcg/L.[6])

Other Therapeutic Options

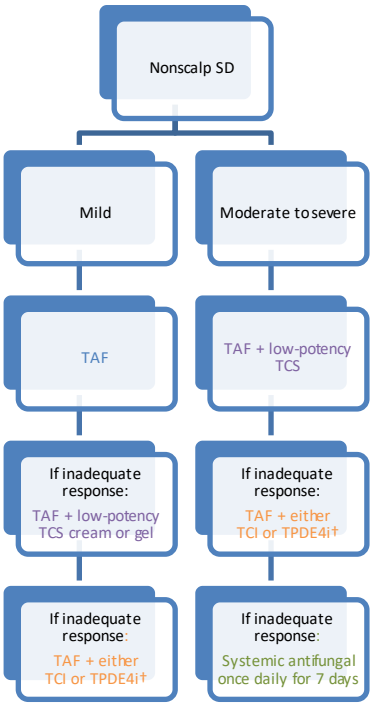
- The place in therapy of SD treatment options is shown in Figure 1 and Figure 2.

Figure 1 General Expert-suggested Treatment Order for SD of Scalp or Hairy Areas



Source: 7
Abbreviations: TAF, topical antifungal; TCS, topical corticosteroid

Figure 2 General Expert-suggested Treatment Order for Nonscalp SD (Face, Trunk, Intertriginous Areas)



Source: 7
Abbreviations: TAF, topical antifungal; TCI, topical calcineurin inhibitor (e.g., pimecrolimus cream 1%, tacrolimus ointment 0.1%); TCS, topical corticosteroid; TPDE4i, topical phosphodiesterase-4 inhibitor (e.g., roflumilast foam or crisaborole ointment)
† TCIs or TPDE4is may be used for facial SD as alternatives in patients requiring frequent use of TCSs. For SD of the trunk and intertriginous areas, TCIs can be used as alternatives to TCSs.

- To prevent relapse, a topical antifungal cream or gel should be continued once or twice weekly. Topical tacrolimus ointment 0.1% once or twice weekly is an alternative maintenance therapy in patients with mild SD who responded to a TCI or in patients with moderate to severe SD.
- Treatments for SD are summarized in Table 5.

Table 5 Topical Treatment Alternatives for SD

Product	On VANF	CFU Place in Therapy	Labelled Use	Expert Suggested Place in Therapy[7†]	Other Considerations
Topical Phosphodiesterase 4 Inhibitors					
Roflumilast foam 0.3%	TBD	TBD	Treatment of SD	2nd-line alternative for SD of the face in patients requiring frequent use of TCSs.	Studied in SD as monotherapy without antifungal, has no active-comparator RCTs, and has not been studied as CS-sparing therapy. For SD, use of crisaborole is supported by a small case series in 30 adults with mild to moderate facial SD.[8] It lacks a vehicle-controlled RCT.
Crisaborole ointment 2%	No	3rd-line after TCS and tacrolimus ointment for atopic dermatitis	Off-label for SD. Treatment of mild to moderate atopic dermatitis	2nd-line alternative for SD of the face in patients requiring frequent use of TCSs.	
Antifungal Products for Primary Therapy					
Hydroxypyridinone					
Ciclopirox olamine cream, suspension 0.77%	No	NA	Off-label for SD. Treatment of tinea pedis, tinea cruris, tinea corporis; dermal candidiasis; tinea (pityriasis) versicolor	**Cream**: 1st-line therapy for SD of the face including for maintenance therapy **Cream, Lotion, Suspension**: 1st-line monotherapy for mild nonscalp SD and 1st-line therapy in combination with low-potency TCS for moderate to severe nonscalp SD	Studied in facial and scalp SD. Gel contains isopropyl alcohol that can strip hair of natural oils; pH not hair-healthy.[5] Shampoo contains sodium laureth sulfate that can affect hair moisture and color.[5]
Ciclopirox gel 0.77% Ciclopirox olamine shampoo 1%	No	NA	Treatment of SD of the scalp Gel: Treatment of superficial tinea	1st-line therapy for mild dermatitis (dandruff) and 1st-line therapy in combination with high-potency TCS (foam, lotion, spray, or shampoo) for moderate–severe SD of the scalp.	
Azoles					
Ketoconazole cream 2%	Yes	NA	Off-label for SD. Treatment of tinea corporis, tinea cruris, tinea pedis, tinea (pityriasis) versicolor, cutaneous candidiasis, SD	**Cream**: 1st-line therapy for SD of the face including for maintenance therapy **Cream, Foam, Gel**: 1st-line therapy for mild nonscalp SD and 1st-line therapy in combination with low-potency TCS for moderate to severe nonscalp SD **Shampoo**: 1st-line monotherapy for mild dermatitis (dandruff) and 1st-line therapy in	Most studies are for scalp SD. The 2% shampoo was effective in treatment[9] and prevention of relapse of SD (off label).[10] Foam contains 58% ethanol, which can make hair dry and fragile[5] Gel contains 34% ethanol, which is less drying but can still reduce hair
Ketoconazole foam, gel 2%	No	NA	Treatment of SD		

Product	On VANF	CFU Place in Therapy	Labelled Use	Expert Suggested Place in Therapy[7†]	Other Considerations
Ketoconazole shampoo 1% (OTC) and 2% (Rx)	Yes	NA	1%: Control flaking, scaling, and itching associated with dandruff Treatment of tinea versicolor	combination with high-potency TCS for moderate–severe SD of the scalp. 1st-line therapy for facial SD affecting areas with hair (beard, mustache).	integrity[5] Shampoo contains cocamide diethanolamine, which is associated with risk of contact dermatitis and potential carcinogenicity[5]
Clotrimazole cream 1%	Yes	NA	Candidiasis Tinea (pityriasis) versicolor	1st-line monotherapy for mild nonscalp SD and 1st-line therapy in combination with low-potency TCS for moderate to severe nonscalp SD	Less frequently mentioned antifungals that could be used for SD. Clotrimazole and miconazole are OTC. Miconazole solution 2% contains acetic acid and laureth-4, which can dry and irritate scalp.[5]
Econazole cream, foam 1%	No	NA	Candidiasis of skin, tinea (pityriasis) versicolor, tinea corporis, tinea cruris, tinea pedis		
Luliconazole cream 1%	No	NA	Tinea corporis, tinea cruris, tinea pedis		
Miconazole nitrate cream, ointment, powder, solution, spray, tincture 2%	Yes	NA	Superficial tinea		
Oxiconazole cream, lotion 1%	No	NA	Tinea (pityriasis) versicolor, superficial tinea, tinea corporis, tinea cruris, tinea pedis		
Sertaconazole cream 2%	No	NA	Interdigital tinea pedis		
Sulconazole cream 1%	No	NA	Superficial tinea		
Other Antifungals					
Selenium sulfide shampoo 1%	Yes	NA	Fights and helps prevent recurrence of flaking and itching due to dandruff	1st-line monotherapy alternative for mild SD.	Limited evidence available. Not FDA approved. Available OTC.
Selenium sulfide shampoo 2.5%	Yes	NA	Treatment of dandruff and SD of the scalp	1st-line monotherapy alternative for mild SD 1st-line alternative in combination with TCSs for moderate to severe SD.	Limited evidence available. Available by Rx.
Pyrithione zinc shampoo 1%	Yes	NA	Relieves flakes and itch associated with dandruff	Same as for selenium sulfide shampoo.	Limited evidence available. Not FDA approved. Less effective than topical

Product	On VANF	CFU Place in Therapy	Labelled Use	Expert Suggested Place in Therapy[7†]	Other Considerations
					ketoconazole.[11]
TCSs for Addition to TAFs					
Low-potency (group 6) shampoo • Fluocinolone acetonide shampoo 0.01%	No	NA	Treatment of SD of the scalp	1st-line add-on alternative in combination with an antifungal shampoo	Prolonged, continuous use of TCSs can cause skin atrophy, hypertrichosis, folliculitis, and telangiectasias. Potent TCSs should not be used on the face. Extensive use of TCSs can cause systemic effects. Other hydrocortisone products are not approved for SD. Other low-potency TCS creams and medium-potency TCSs are nonformulary without CFU. Clobetasol shampoo 0.05% contains sodium laureth sulfate and has a pH of 7–9, both of which can strip hair of natural oils and color and cause dryness or damage.[5]
Lower-mid potency (group 5) • Hydrocortisone butyrate solution 0.1%	No	NA	Relief of inflammatory and pruritic manifestations of SD	1st-line add-on alternative in combination with an antifungal shampoo	
Low-potency TCS cream (group 6 or 7) • Desonide cream 0.05% • Hydrocortisone cream 1% (OTC) and 2.5% (Rx) • Hydrocortisone acetate cream 1% (OTC) and 2.5% (Rx) • Triamcinolone acetonide cream 0.025%	Yes	NA	Treatment of CS-responsive dermatoses	1st-line add-on therapy to TAF cream for nonscalp SD (face, trunk, intertriginous areas)	
Medium-potency TCSs (group 4) • Hydrocortisone valerate ointment 0.2% • Triamcinolone acetonide cream 0.1%, ointment 0.05% and 0.1%	Yes	NA	Treatment of CS-responsive dermatoses	Alternative therapy for SD of the chest or upper back.	
High-potency TCS lotion, spray aerosol, foam, shampoo, gel, or solution (group 2) • Halobetasol propionate lotion 0.01% • Betamethasone valerate aerosol (foam) 0.12% • Desoximetasone spray aerosol 0.25% • Desoximetasone gel 0.05% • Fluocinonide solution 0.05%	No	NA	Treatment of TCS-responsive dermatoses	1st-line alternative in combination with an antifungal shampoo for moderate to severe SD of the scalp or hairy areas	
Super-high potency TCS lotion, spray aerosol, foam, or shampoo (group 1) • Clobetasol foam aerosol, lotion, shampoo, spray, 0.05% • Halobetasol propionate foam 0.05%, lotion 0.01%	No	NA	Treatment of TCS-responsive dermatoses	No specific recommendation for super-high potency TCSs.	

Product	On VANF	CFU Place in Therapy	Labelled Use	Expert Suggested Place in Therapy[7]†	Other Considerations
Topical Nonsteroidal Antiinflammatories for CS-sparing Therapy					
Calcineurin Inhibitors					
Pimecrolimus cream 1%	No	NA	2nd-line therapy for atopic dermatitis	3rd-line therapy added to TAF for mild nonscalp SD (face, trunk, intertriginous areas) after failures of TAF monotherapy (1st–line) and TAF plus low-potency TCS cream or gel (2nd-line). 2nd-line therapy added to TAF for moderate to severe nonscalp SD after failure of TAF plus low-potency TCS. 2nd-line alternative for facial SD in patients requiring frequent use of TCSs. 2nd-line alternative to low-potency TCSs for intertriginous areas.	Limited evidence of effectiveness in moderate to severe facial SD. No recommendation for use in scalp SD. No recommendation to use 0.03% ointment for SD. Associated with transient burning and warming sensations. Lacks TCS adverse effects such as skin atrophy, folliculitis, hypertrichosis, telangiectasias.
Tacrolimus ointment 0.1%	Yes	NA	2nd-line therapy for short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults		
Topical Keratolytics					
Coal tar emulsion	Yes	NA	SD, psoriasis	Traditionally used for softening thick scales. Largely superseded by TAFs.	Infrequently used because of its odor, the potential for staining fabrics and skin, photosensitivity, and potential carcinogenicity.
Coal tar foam	No	NA	Psoriasis		
Coal tar shampoo	Yes	NA	Dandruff		
Coal tar / salicylic acid shampoo	Yes	NA	Dandruff, SD, psoriasis		
Coal tar / salicylic acid cream	No	NA			
Salicylic acid gel 3%	No	NA	SD, psoriasis	Traditionally used for softening thick scales. Largely superseded by TAFs.	Foam, gel, and shampoo 6% are used for hyperkeratotic disorders of the skin.
Salicylic acid shampoo 3%	Yes	NA			
Salicylic acid 2% / sulfur shampoo 2% (SEBEX, SEBULEX)	Yes	NA	Dandruff, SD, psoriasis		
Salicylic acid / sulfur shampoo (METED)	No	NA	Dandruff, SD		

Sources: FDA Multi-discipline Review,[12] UpToDate[7]
† No current (≤ 5 years) society guidelines were available.
CFU, Criteria for Use; TAF, topical antifungal; TCS, topical corticosteroid

Projected Place in Therapy

- **Epidemiology and Prevalence of Seborrheic Dermatitis (SD)**. The etiology of SD is unknown. Body areas often affected by SD usually have larger and more numerous sebaceous glands; however, SD is not a disease of sebaceous glands. Fungi of the *Malassezia* genus are more common in body areas with many sebaceous glands, but *Malassezia* have been only indirectly implicated in the pathogenesis of SD. The observed effectiveness of antifungal agents may be related to an antiinflammatory effect of azoles.[7] The prevalence of clinically significant SD is about 3% and may be much higher if mild cases (i.e., dandruff) are counted. SD is more prevalent in patients with HIV infection (35%) and acquired immunodeficiency syndrome (up to 85%).[7] SD has a chronic, relapsing course. Maintenance therapy is typically needed to prevent recurrence.
- **Potential Place in Therapy Based on the Evidence**. Topical roflumilast foam is the first nonsteroidal, non-antifungal product approved for the treatment of SD. The place in therapy of roflumilast foam in the treatment of SD is uncertain because of a lack of comparative effectiveness studies. Moderate-quality evidence from a short-term (8-week) phase 3 vehicle-controlled trial supports the use of roflumilast foam for achieving IGA success in patients with moderate to severe (mostly moderate) SD who may or may not have had an inadequate response to other topical therapies. Overall, treatment effects in terms of IGA success and worst itch success rates are small and their clinical relevance is uncertain.
- **Potential Place in Therapy in VHA**. Roflumilast may be added to topical antifungal therapy in patients with moderate to severe SD who have an inadequate response, intolerance, or medical inadvisability to combination topical antifungal plus TCS and combination topical antifungal plus topical calcineurin inhibitor. Roflumilast foam may be an alternative to a TCI for maintenance therapy.

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References

[1] ZORYVE (roflumilast) topical foam 0.3% [prescribing information online]. Westlake Village, CA: Arcutis Biotherapeutics. December 2023. Available at: zoryve-foam-pi-hcp.pdf (arcutis.com). Accessed 20 May 2024.

[2] Dong C, Virtucio C, Zemska O, Baltazar G, Zhou Y, Baia D, Jones-Iatauro S, Sexton H, Martin S, Dee J, Mak Y, Meewan M, Rock F, Akama T, Jarnagin K. Treatment of Skin Inflammation with Benzoxaborole Phosphodiesterase Inhibitors: Selectivity, Cellular Activity, and Effect on Cytokines Associated with Skin Inflammation and Skin Architecture Changes. J Pharmacol Exp Ther. 2016 Sep;358(3):413-22. doi: 10.1124/jpet.116.232819. Epub 2016 Jun 27. PMID: 27353073.

[3] Blauvelt A, Draelos ZD, Stein Gold L, Alonso-Llamazares J, Bhatia N, DuBois J, Forman SB, Gooderham M, Green L, Guenthner ST, Hebert AA, Lain E, Moore AY, Papp KA, Zirwas M, Kato S, Snyder S, Krupa D, Burnett P, Berk DR, Chu DH. Roflumilast foam 0.3% for adolescent and adult patients with seborrheic dermatitis: A randomized, double-blinded, vehicle-controlled, phase 3 trial. J Am Acad Dermatol. 2024 May;90(5):986-993. doi: 10.1016/j.jaad.2023.12.065. Epub 2024 Jan 20. PMID: 38253129.

[4] Zirwas MJ, Draelos ZD, DuBois J, et al. Efficacy of Roflumilast Foam, 0.3%, in Patients With Seborrheic Dermatitis: A Double-blind, Vehicle-Controlled Phase 2a Randomized Clinical Trial. *JAMA Dermatol.* 2023;159(6):613–620. doi:10.1001/jamadermatol.2023.0846

[5] Polaskey MT, Woolery-Llloyd H, Osborne D, Burnett P, Hanna D, Chovatiya R. When Patient Diversity Informs Formulation: Reimagining Treatment for Seborrheic Dermatitis. Dermatol Ther (Heidelb). 2024 Apr 27. doi: 10.1007/s13555-024-01161-9. Epub ahead of print. PMID: 38676839.

[6] Roflumilast. IBM Micromedex Solutions. Truven Health Analytics, Inc., Ann Arbor, MI. Accessed May 24, 2024. micromedexsolutions.com

[7] Sasseville D. Seborrheic dermatitis in adolescents and adults. In: UpToDate, Fowler J, Corona R (Eds), UpToDate, Waltham, MA, 2024. (Accessed on 20 May 2024.)

[8] Peña SM, Oak ASW, Smith AM, Mayo TT, Elewski BE. Topical crisaborole is an efficacious steroid-sparing agent for treating mild-to-moderate seborrhoeic dermatitis. J Eur Acad Dermatol Venereol. 2020 Dec;34(12):e809-e812. doi: 10.1111/jdv.16673. Epub 2020 Jun 17. PMID: 32452557.

[9] Green CA, Farr PM, & Shuster S: Treatment of seborrhoeic dermatitis with ketoconazole: II. Response of seborrhoeic dermatitis of the face, scalp and trunk to topical ketoconazole. Br J Dermatol 1987; 116:217-221.

[10] Peter RU & Richarz-Barthauer U: Successful treatment and prophylaxis of scalp seborrhoeic dermatitis and dandruff with 2% ketoconazole shampoo: results of a multicentre, double-blind, placebo-controlled trial. Br J Dermatol 1995; 132:441-445.

[11] Piérard-Franchimont C, Goffin V, Decroix J, Piérard GE. A multicenter randomized trial of ketoconazole 2%; and zinc pyrithione 1%; shampoos in severe dandruff and seborrheic dermatitis. Skin Pharmacol Appl Skin Physiol 2002; 15: 434–441

[12] Center for Drug Evaluation and Research (CDER). Multi-discipline review of roflumilast topical foam 0.3% (ZORYVE). Food and Drug Administration (FDA). December 2023