International Journal of Research in Dermatology
Selvakumar MD. Int J Res Dermatol. 2025 Jan;11(1):68-73
http://www.ijord.com

DOI: https://dx.doi.org/10.18203/issn.2455-4529.IntJResDermatol20243880

Review Article

Crisaborole in dermatology

Monisha Devi Selvakumar*

Department of Dermatology, Tirupur Aadhaar Medical Centre, Tirupur, Tamil Nadu, India

Received: 23 September 2024
Accepted: 19 October 2024

***Correspondence:**
Dr. Monisha Devi Selvakumar,
E-mail: monishadevi0507@gmail.com

ABSTRACT

Crisaborole, though initially approved for the treatment of mild to moderate atopic dermatitis, has found its application in treatment of various other inflammatory dermatological conditions including psoriasis, vitiligo, stasis dermatitis, inflammatory verrucous epidermal nevus and more. This is due to the involvement of enzyme phosphodiesterase-4 and cyclic adenosine monophosphate (cAMP) in the pathogenesis of these disorders. Sources of study material included PubMed, National Library of Medicine, DermNet, Journal of the American Academy of Dermatology, manufacturer prescribing information and article bibliographies.This review article was prepared to show that crisaborole can be effectively used in treating those inflammatory dermatological disorders (as off-label indications) which are unresponsive to their first line treatment options. The side effects are minimal and tolerable. The only limitation is that the number of studies and case reports with crisaborole are very limited. Crisaborole seems to have promising results in the management of various inflammatory dermatological conditions with minimal side effects.

Keywords: Atopic dermatitis, Crisaborole, Psoriasis, Phosphodiesterase-4, Vitiligo

INTRODUCTION

Crisaborole is a non-steroidal, anti-inflammatory phosphodiesterase-4 (PDE-4) inhibitor. Inhibition of PDE-4 leads to increase in cAMP (cyclic adenosine monophosphate) levels thus controlling inflammation. Also, the presence of boron in the molecule facilitates effective penetration of crisaborole through the human skin.[1] Crisaborole was first approved by the US Food and Drug Administration (US-FDA) on 14 December, 2016, with the labelled indication for topical treatment of mild to moderate Atopic dermatitis. It was indicated from age 2 years and above.[2] Apart from atopic dermatitis, crisaborole has found to be efficacious in the treatment of various other dermatological disorders as well such as psoriasis, eczema, vitiligo, alopecia areata, morphea, stasis dermatitis and few more. This is due to involvement of PDE-4 enzyme as a part of their pathogenesis.

Sources of study material included PubMed, National Library of Medicine, DermNet, Journal of the American Academy of Dermatology, manufacturer prescribing information and article bibliographies. Key words used for searching for articles and reports included "Crisaborole", "Atopic dermatitis", "crisaborole in dermatology", "phosphodiesterase-4 inhibition and skin", "crisaborole and hand eczema", "crisaborole and stasis dermatitis".

Pharmacology of crisaborole

Crisaborole is a boron containing PDE-4 inhibitor. The boron atom attaches in a competitive and reversible manner to the bimetal center of the enzyme PDE-4, thereby inhibiting the enzyme. This results in increased intracellular cyclic adenosine monophosphate (cAMP) levels. Increased cAMP reduces the production and

effects of inflammatory mediators including interleukin (IL)-4 and IL-13.[2]

PHARMACOKINETICS

Absorption

The pharmacokinetics of crisaborole was investigated in 33 pediatric subjects of age 2 to 17 years with mild to moderate AD and a mean body surface area involvement in the range of 27% to 92%. In this study, subjects applied approximately 3 mg/cm^2 of crisaborole ointment twice daily for a period of 8 days.[3,4]

Time to maximum plasma concentrations (T max) after application was consistent over the 8 days at 3 hours (range: 3-24 hours). Steady state of systemic concentrations of crisaborole were achieved by day 8.[4]

Distribution

Crisaborole is 97% bound to human plasma proteins.[3]

Metabolism

Crisaborole is substantially metabolized into 2 inactive metabolites. The major metabolite is 5-(4-cyanophenoxy)-2-hydroxyl benzyl alcohol (metabolite 1) and is formed via hydrolysis. Metabolite 1 is further metabolized into downstream metabolites, among which 5-(4-cyanophenoxy)-2-hydroxyl benzoic acid (metabolite 2), formed via oxidation, is another major metabolite.[3]

Elimination

Renal excretion is the major route of elimination.[3]

Dosage and administration

Crisaborole is available as 2% ointment and is for topical use only. Patients are advised to apply a thin layer twice a day to the affected area(s). No dosage adjustment is recommended for special populations, including patients with hepatic or renal impairment.[3] There is no data available regarding its safety in pregnancy, lactation and geriatric patients.

Adverse effects

The most commonly reported adverse effects are application site erythema, burning or stinging.[2]

Co-application with emollients

To understand the penetration of crisaborole into skin when used along with an emollient, a study was conducted using an ex-vivo model of healthy abdominal human skin. Here, crisaborole was applied either alone, 15 minutes before, immediately after or 15 minutes after application of the emollient. The amount of crisaborole delivered into the skin and through the skin into the receptor solution was determined by liquid chromatography tandem mass spectrometry.[5] It was observed that crisaborole was most effective when applied atleast 15 minutes before the emollient.[5]

Although an ex-vivo model was used, the results of this study can help in explaining to the patients about the importance of applying crisaborole directly on the skin followed by emollients, especially to reduce the adverse effects such as stinging or burning sensation.

INDICATIONS OF CRISABOROLE

Atopic dermatitis

Crisaborole has been approved by the US-FDA for use in patients with atopic dermatitis (AD) and can be used above the age group of 2 years.

However, a study was conducted later to show the safety and efficacy of crisaborole in age group 3 months and above. In this study, 137 infants in the age group of 3 months to 24 months with mild to moderate atopic dermatitis were treated with crisaborole twice a day for 28 days. It was observed that crisaborole was well tolerated and effective, with 22 patients (16.1%) reporting adverse events. Application site pain (3.6%), application site discomfort (2.9%) and erythema (2.9%) were most frequently reported.[6] This study shows that crisaborole can be safely used in children above 3 months of age.

Another study was conducted in 19 pediatric patients in age group 2 to 16 years with atopic dermatitis. Crisaborole application was advised twice a day and follow up was done on a weekly basis. At the end of the study (day 29), there was a significant reduction in severity of AD indicated by investigator's static global assessment (ISGA) score.[7] Individual markers for clinical signs of AD, including erythema, exudation, excoriation, induration and lichenification, also showed statistically significant improvements. Crisaborole ointment was well tolerated. 6 out of 19 patients reported a localized burning sensation, which was manageable.[7]

A randomised, double-blind, vehicle controlled, phase III study was conducted where 270 patients in the age group of 3 months to 18 years were divided into two groups (135 into crisaborole and 135 into vehicle groups). Patients were instructed to apply crisaborole twice a day up to 52 weeks and were followed up every 4 or 8 weeks. At the end of the study, it was observed that the mean number of flare-free days was significantly greater for patients treated with crisaborole, with a difference of 34.6 days.[8] Also, the mean number of flares was significantly lower in patients in crisaborole group. Only one patient (0.7%) in the crisaborole group and three (2.2%) in the

vehicle group discontinued the treatment because of adverse events.[8]

All these above studies show that crisaborole can be safely used in pediatric patients above 3 months of age. The adverse effects were usually mild in most patients. Also, being a non-steroid, crisaborole can be safely prescribed for a longer duration.

Psoriasis

Psoriasis is a chronic inflammatory disease where multiple mediators are involved in its pathogenesis such as tumour necrosis factor (TNF), Interferon alpha, interleukins 17, 22, 2, 36, 8, 23, chemokines CCL20 and CXCL10, vascular endothelial growth factor (VEGF) and many others. These inflammatory mediators are released secondary to increased intracellular cAMP levels in cells. Therefore, inhibition of cAMP levels can help in control of the disease.[9]

A double-blind, randomised, vehicle-controlled study was conducted in 21 participants with intertriginous (n=12), facial (n=5) and anogenital psoriasis (n=4). The study was conducted in two phases. In phase 1, participants were randomized 2:1 to receive treatment with either crisaborole 2% ointment twice daily (n = 14) or vehicle ointment twice daily (n = 7).[10] On day 29, participants were eligible for phase 2, in which all participants received open-label crisaborole 2% ointment twice daily until day 57. Participants were evaluated at screening and on days 7, 14, 29, 43 and 57. At day 57, participants from the crisaborole group had achieved an 81% change in Target Lesion Severity Scale (TLSS) score compared with baseline, with 71% of participants reaching clinical clearance. There were no reports of application site reactions.[10]

Vitiligo

PDE-4 enzyme has been found to be involved in the pathogenesis of vitiligo. To prove this, a study was done to evaluate the PDE-4 levels in lesional skin and serum of 20 vitiligo patients and was compared with 20 healthy controls. A 4 mm punch biopsy was taken from lesional skin of the cases and remains of abdominoplasty operations from controls. 5 ml venous blood samples were collected from both groups, centrifuged, the serum extracted and kept at −80°C. PDE4 levels in tissues and serum were measured using the immunoassay LANCE Ultra cAMP kit. At the end of this study, it was observed that the level of PDE-4 was higher in both tissue and serum of the vitiligo patients, compared to the controls.[11]

A 71-year-old male patient with recalcitrant generalized atopic dermatitis with progressive depigmentation of his forearms and dorsal aspects of his hands (Body surface area 10%) was started on crisaborole 2% ointment twice a day for his eczema and vitiliginous patches. There were significant improvements noticed in both eczema and repigmentation of his patches were noticed following 10 months application of crisaborole. After 22 months, further increase in repigmentation was noted on the hands. Patient tolerated the treatment well with no adverse effects.[12]

In another report, a Hispanic male in his 40's with a diagnosis of persistent vitiligo for more than 20 years, had presented with depigmented spots on ears and glans penis. Due to failure of past treatment options such as topical steroids and calcineurin inhibitors, he was started on crisaborole 2% ointment twice a day. Patient refused to apply the ointment to the glans penis, but had applied to his ears. On follow-up after 1 month, scattered perifollicular repigmentation was observed on his ears while the penile lesions remained unchanged. Subsequently, patient was lost to follow-up.[13]

Seborrheic dermatitis

In treatment of seborrheic dermatitis (SD), inhibition of PDE-4 enzyme leads to increased cAMP levels in the cells, thereby suppressing the pro-inflammatory molecules.[14]

A study was conducted in 30 patients aged 18 to 80 years, with mild to moderate facial SD. They were treated with crisaborole 2% ointment twice daily for 4 weeks. By week 4, 83.3% of patients showed a significant reduction in the investigator global assessment scale to clear or almost clear, with improvements in erythema, scaling, dryness and pruritus. Only one patient discontinued crisaborole after 2 weeks due to complaints of headache and facial pain.[15]

Inflammatory linear verrucous epidermal nevus (ILVEN)

Studies have shown the possibility of involvement of cellular immunologic processes in the pathogenesis of ILVEN.

A 9-year-old girl with biopsy proven ILVEN and who had previously failed with topical therapies (triamcinolone, pimecrolimus, mometasone, calcipotriene) responded well with crisaborole 2% ointment.[16]

In another report, a 5year old boy with inflammatory linear verrucous epidermal nevus was treated successfully with twice daily application of crisaborole 2% ointment.[17] Although only 2 case reports were found, crisaborole seems to be a promising option to control ILVEN even when other treatment options fail. Also, due to the safety profile, it can be given for a long duration.

Vulvar leukoplakia

A study was conducted with a total of 100 patients with vulvar intraepithelial non-neoplastic lesions (biopsy

proven). The pathological results included vulvar lichen simplex chronicus and vulvar lichen sclerosus. These patients were randomly divided into observation group (n=50) and control group (n=50). Observation group was advised to apply crisaborole 2% ointment and control group was advised to apply vitamin E, twice a day and followed up after 2 weeks. At the end of the study, the effective response rate was 92% in observation group and 52% in control group. There were two cases in the observation group with local pain and ulceration, which subsided after withdrawing crisaborole. The control group had no adverse effects.[18]

Morphea

A single-arm, open-label, pilot study was conducted in 7 adult patients with active morphea involving <20% total body surface area. These patients were advised to apply crisaborole 2% ointment on the active plaques, twice a day for 12 weeks. A 4 mm punch biopsy analysis was done at baseline and at 12 weeks from a sentinel plaque. It was observed by a dermatopathologist that there was a reduction in histologic dermal fibrosis in 5 out of 7 patients. 6 out of 7 patients had a clinical reduction in the size and induration of the sentinel plaque.[19]

Although only small sample was taken in the above study, it shows that crisaborole can be an option in patients who have failed to show results with other treatment options or who cannot tolerate other medications such as topical steroids.

Chronic hand eczema

Cyclic adenosine monophosphate (cAMP) induces the expression of the anti-inflammatory cytokine IL-10 which reduces the levels of pro-inflammatory cytokines such as TNFα and INF-γ. These mediators appear to be involved in chronic hand eczema and several other diseases like psoriasis.[20]

A retrospective review involving 251 patients observed that crisaborole was a successful treatment option for chronic hand eczema, with 72.2% of individuals experiencing an improvement in their symptoms.[21]

Stasis dermatitis

In stasis dermatitis, inflammation leads to eczema, which if progresses can either present with oozing and crusting (acute eczema) or lichenification (chronic eczema). PDE-4 enzyme inhibition reduces the inflammation by decreasing the cytokine production, thereby controlling the symptoms.

In a study, 65 participants (aged 45 years and above) with stasis dermatitis, were randomly assigned into two groups-32 received vehicle and 33 received crisaborole. The participants in the respective groups were advised to apply the vehicle and crisaborole twice a day up to 6 weeks. They were followed up periodically.[22] At the end of the study, it was observed that crisaborole-treated participants had significantly reduced total sign score from baseline versus vehicle.[22] 4 participants from each group discontinued treatment due to adverse effects.[22]

Alopecia areata

PDE-4 is highly increased in human alopecia areata lesions on scalp, representing a potential therapeutic target.[23] Hence, crisaborole can be tried in patients with alopecia areata having limited patches.

Rosacea

A 68-year-old woman with a history of rosacea was advised patch testing due to recurrent facial eruptions. Patch testing was positive to Kathon CG (found in the patient's laundry product). Since topical corticosteroids were unsuccessful, treatment with crisaborole ointment was started along with ceramides containing cream as needed. Her skin condition markedly improved within two weeks.[24]

Irritant contact dermatitis

A 29-year-old neonatal intensive care unit (NICU) nurse developed hand dermatitis in the last one year, due to frequent use of hand sanitizer. Patch test was negative and she had no history of atopy. She was clinically better when she was on holiday. Since she refused topical corticosteroids due to its possible side effects, crisaborole 2% ointment was started. Within eight weeks the condition had resolved. The ointment was well tolerated.[24]

Knuckle pads

A 45-year-old male patient with a 6-year history of asymptomatic thick plaques on extensor aspects of knuckles and ankles, not responsive to other medications such as triamcinolone injections, clobetasol creams, responded well to twice daily application of crisaborole 2% ointment within 2 weeks.[25]

As there are no specific treatments for knuckle pads so far, crisaborole seems to be a promising treatment option.

Necrobiotic xanthogranuloma with associated multiple myeloma

A patient with generalized NXG associated with multiple myeloma achieved a complete response from treatment with crisaborole ointment 2%, a topical, nonsteroidal, phosphodiesterase-4 (PDE-4) inhibitor.[26]

CONCLUSION

Crisaborole has been shown to be safe and effective in mild to moderate atopic dermatitis and can be prescribed

in children from 3 months of age. It has been tried in various other inflammatory dermatological conditions such as psoriasis, vitiligo, seborrheic dermatitis and few more. Although the number of studies is very limited, with predominantly case reports and studies of small sample size of various diagnoses, crisaborole seems to have promising results with minimal side effects. Many new studies are being published with crisaborole. In all the case reports published so far, crisaborole was started when other common treatment options failed to give adequate response in the patients. Hence, crisaborole can be added to the treatment plan in patients with limited or mild to moderate disease.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Dina Coronado B, Zane LT, Coronado D. Crisaborole topical ointment, 2%: a nonsteroidal, topical, anti-inflammatory phosphodiesterase 4 inhibitor in clinical development for the treatment of atopic dermatitis. J Drugs Dermatol. 2016;15(4):390-6.
2. McDowell L, Olin B. Crisaborole: a novel nonsteroidal topical treatment for atopic dermatitis. J Pharm Technol. 2019;35(4):172-8.
3. Eucrisa® (crisaborole) ointment, 2%, for topical use. New York, NY: Anacor Pharmaceuticals/Pfizer. 2017.
4. Zane LT, Kircik L, Call R, Tschen E, Draelos ZD, Chanda S, Van Syoc M, et al. Crisaborole topical ointment, 2% in patients ages 2 to 17 years with atopic dermatitis: A phase 1b, open-label, maximal-use systemic exposure study. Pediatr Dermatol. 2016;33(4):380-7.
5. Draelos ZD, Ports WC, Vlahos B, Yeoh T, Wu-Linhares D, Brown MB, et al. Skin permeation and penetration of crisaborole when coapplied with emollients. J Am Acad Dermatol. 2020;1;83(6):1801-3.
6. Schlessinger J, Shepard JS, Gower R, Su JC, Lynde C, Cha A, et al. Safety, effectiveness and pharmacokinetics of crisaborole in infants aged 3 to< 24 months with mild-to-moderate atopic dermatitis: a phase IV open-label study (CrisADe CARE 1). Am J Clin Dermatol. 2020;21:275-84.
7. De A, Chakraborty D, Grisilda BN, Chaudhuri S, Godse K, Dhar S. Efficacy and safety of crisaborole ointment in pediatric atopic dermatitis: A 4-week open-label study. Ind J Skin Aller. 2024;3(1):60.
8. Eichenfield LF, Gower RG, Xu J, Alam MS, Su JC, Myers DE, et al. Once-daily crisaborole ointment, 2%, as a long-term maintenance treatment in patients aged≥ 3 months with mild-to-moderate atopic dermatitis: a 52-week clinical study. Am J Clin Dermatol. 2023;24(4):623-35.
9. Wittmann M, Helliwell PS. Phosphodiesterase 4 inhibition in the treatment of psoriasis, psoriatic arthritis and other chronic inflammatory diseases. Dermatol Ther. 2013;3:1-5.
10. Hashim PW, Chima M, Kim HJ, Bares J, Yao CJ, Singer G, et al. Crisaborole 2% ointment for the treatment of intertriginous, anogenital and facial psoriasis: a double-blind, randomized, vehicle-controlled trial. J Am Acad Dermatol. 2020;1;82(2):360-5.
11. Nagui N, Gaballah B, Rashed L, Sany I. Evaluation of phosphodiesterase 4 enzyme levels in lesional skin and serum of vitiligo patients. J Egypt Women's Dermatol Soc. 2021;1;18(3):186-90.
12. Tam I, Kahn JS, Rosmarin D. Repigmentation in a patient with vitiligo on crisaborole 2% ointment. JAAD Case Rep. 2021;1;11:99-101.
13. Tausend W, Hoyer P, Arnold M, Wagner K, Ross L, Goodwin BP, et al. Successful treatment of vitiligo with crisaborole 2% ointment. Skin J Cutan Med. 2019;11;3(2):111-3.
14. Jackson JM, Alexis A, Zirwas M, Taylor S. Unmet needs for patients with seborrheic dermatitis. J Am Acad Dermatol. 2022;17:213.
15. Peña SM, Oak AS, Smith AM, Mayo TT, Elewski BE. Topical crisaborole is an efficacious steroid-sparing agent for treating mild-to-moderate seborrhoeic dermatitis. J Europ Acad Dermatol Venereol. 2020;1;34:12.
16. Terrell J, Hogeling M. 44569 Improvement of ILVEN with Crisaborole Use. Journal of the American Academy of Dermatology. 2023;89(3):179.
17. Barney E, Prose NS, Ramirez M. Inflammatory linear verrucous epidermal nevus treated successfully with crisaborole ointment in a 5-year-old boy. Pediatric dermatology. 2019;36(3):404-5.
18. Li L. Clinical efficacy evaluation of crisaborole ointment in the treatment of vulvar leukoplakia. Revista da Associação Médica Brasileira. 2023;17;69:97-100.
19. Petty AJ, Emge DA, Blanchard SK, Selim MA, Scoggins K, Liu B, et al. Pilot, open-label, single-arm clinical trial evaluating the efficacy of topical crisaborole for steroid refractory morphea. J Am Acad Dermatol. 20231;89(2):390-2.
20. Tancredi V, Buononato D, Caccavale S, Di Brizzi EV, Di Caprio R, Argenziano G, et al. New perspectives in the management of chronic hand eczema: lessons from pathogenesis. International J Mol Sci. 2023;27;25(1):362.
21. Kahn JSM, Grossman-Kranseler JS, Zancanaro p. Topical Crisaborole in the Treatment of Atopic Hand Dermatitis: A Retrospective Chart Review. Dermatitis. 2021;32:141-3.
22. Silverberg JI, Kirsner RS, Margolis DJ, Tharp M, Myers DE, Annis K, et al. Efficacy and safety of crisaborole ointment, 2%, in participants aged≥ 45 years with stasis dermatitis: Results from a fully decentralized, randomized, proof-of-concept phase

2a study. J Am Acad Dermatol. 2024;1;90(5):945-52.
23. Renert-Yuval Y, Guttman-Yassky E. The changing landscape of alopecia areata: the therapeutic paradigm. Advances in therapy. 2017;34:1594-609.
24. Lynde CW, Bergman J, Fiorillo L, Guenther L, Joseph M, Grant JK, et al. Use of Topical Crisaborole for Treating Dermatitis in a Variety of Dermatology Settings. Supplement to STL. 2020;1;25(3).
25. Liang Y, Liang J, Huang Q, Tian X, Shao L, Xia M, et al. Knuckle pads successfully treated with 2% crisaborole ointment combined with triamcinolone acetonide and neomycin plaster: a case report. Clinical, Cosmetic and Investigational Dermatol. 2023;31:1893-7.
26. Henning C, Meyers S, Swift R, Eades B, Bussell L, Spektor TM, et al. Efficacy of topical use crisaborole 2% ointment for treatment of necrobiotic xanthogranuloma associated with multiple myeloma. Clinical Lymphoma Myeloma and Leukemia. 2020;1;20(8):e492-5.

Cite this article as: Selvakumar MD. Crisaborole in dermatology. Int J Res Dermatol 2025;11:68-73.