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# Real world Efficacy and Tolerance of Bepotastine, a new 2nd generation antihistamine, in Pruritis and other symptoms associated with cutaneous disorders. (BEREAL study)

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**ABSTRACT**

Bepotastine besilate is a selective histamine H1-receptor antagonist and a second-generation non-sedating antihistamine approved for relief from pruritis in various dermatological disorders.

*Aim*: To study the real world efficacy and tolerance of bepotastine in cutaneous disorders associated with pruritus and other symptoms (redness, wheal and angioedema), by assessing patient's perceived symptomatic improvement.

*Methodology*: Adult patients presenting clinically with any of the symptoms: pruritis, redness, wheal or angioedema, associated with skin conditions, were evaluated to record patient's end of treatment perception of improvement in the presenting symptoms, as well as tolerance to treatment, in response to bepotastine 10mg twice a day. Adverse events if any were recorded, assessed and managed.

*Results*: Overall for each symptom, complete or significant relief was obtained by >80% patients (P<0.001). Average treatment duration was 21 days or less in 80% patients. Patients achieving complete relief was maximum between 14-21 days. The adverse event rate was low at 0.3%.

*Conclusion*: Bepotastine 20mg/day, is an effective and well tolerated treatment for improving pruritis and other symptoms: erythema, wheal and angioedema, associated with cutaneous disorders, with an optimum treatment duration of 14-21 days.



## Introduction:

Pruritis is a common symptom, of many skin conditions like chronic urticaria, eczema, atopic dermatitis, and psoriasis, which affects the patient's day to day life[1]. Itching maybe often associated with redness (erythema), wheals and sometimes angioedema.[2,3]Bepotastine besilate is a selective histamine H1-receptor antagonist and a second-generation non-sedating antihistamine. It has also been studied to have additional actions like mast cell stabilization, inhibition of eosinophilic infiltration, Inhibition of leukotriene B4, IL-5, PAF and Substance P all of which may contribute to its anti-pruritic effects.[4,5] Bepotastine tablet was approved in Japan for use in the treatment of allergic rhinitis and uriticaria/puritus in the year 2000 and 2002, respectively. Bepotastine besilate 10 mg tablet was

approved in India in 2017, for the treatment of allergic rhinitis and itching associated with cutaneous disorders

(eczema/dermatitis, and dermal pruritus) in adult patients.

This is the first real world data from India on the effect of bepotastine in patients who have cutaneous conditions with pruritis with or without other symptoms of redness, wheal and angioedema. It is also the first time that patient's self-assessment of perceived improvement has been used to assess the benefit of bepotastine in patients' skin condition and quality of life.

**Methodology:**

4775 adult patients presenting clinically in the Dermatologist's out-patient department, with any of the symptoms: pruritis, redness, wheal or angioedema, were evaluated with a questionnaire to record patient's treatment perception of improvement in the presenting symptoms, as well as tolerance to treatment. Each patient was treated with bepotastine 10mg twice a day, and asked to follow up weekly. Patient's improvement perception was assessed on a 4 point rating scale as 'No improvement', 'Slightly improved', Significantly improved, and 'Complete relief'. Each patient's duration of treatment was also recorded. Adverse events if any were recorded, assessed and managed. All data was obtained in accordance with ethical principles and with patient consent.

**Results:**

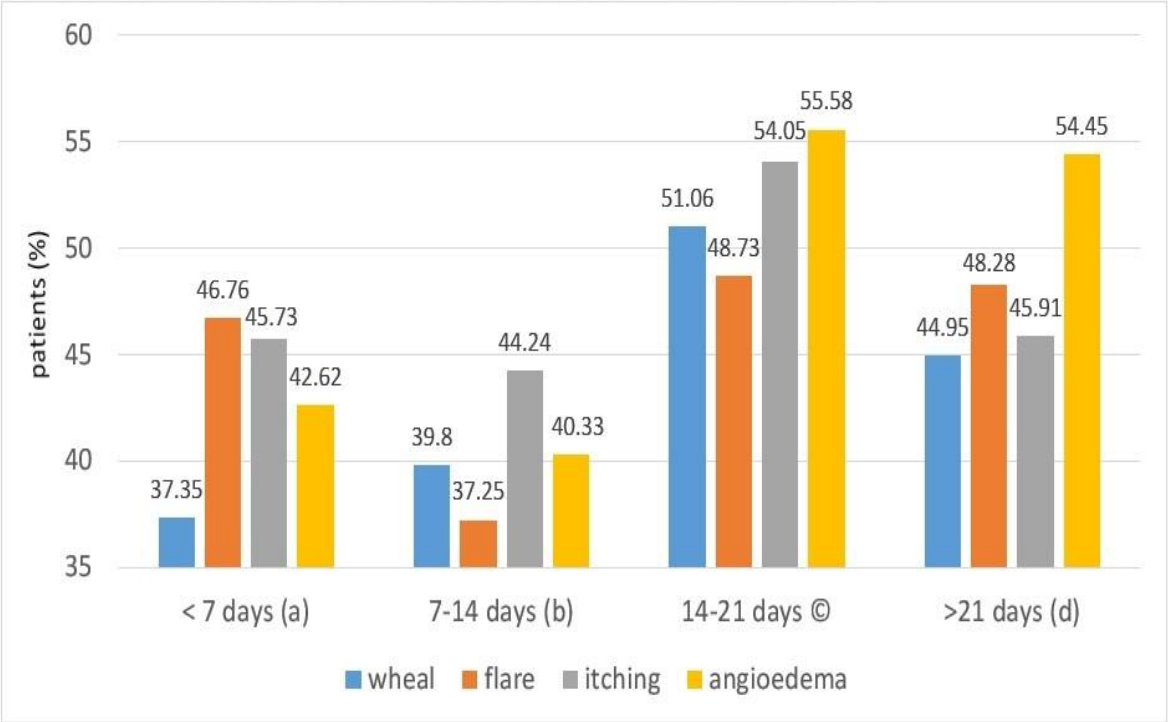
Out of 4775 patients, 144 patients were lost to follow up and 4631 patients completed the study. 3415 patients participated in the evaluation of their perceived symptomatic improvement to treatment. 88% patients presented with pruritis while 71%, 61% and 33% patients presented with wheal, erythema and angioedema respectively. After treatment with bepotastine 10mg twice daily, complete relief from itching and redness was achieved in 47.68% and 45.56% patients respectively, while significant reduction was seen in 38.45% and 38.08% patients respectively. Complete and significant relief from wheal was seen in 44.58% and 38.45% patients respectively, while complete and significant relief from angioedema was seen in 48.53% and 32.85% patients respectively. ($P<0.001$ for all mentioned values versus no improvement - Figure 1). Overall for each symptom, complete or significant relief was obtained by >80% patients, with >87% for pruritis.

Average treatment duration was 14-21 days in 39% patients and 7-14 days in 32%. Only 20% patients took the treatment beyond 21 days while 9% were treated for less than 7 days. Duration of treatment was seen to have an effect on symptomatic relief obtained (Figure 2). More number of patients achieved complete relief when treated for 14-21 days or >21 days, than when treated for less than 14 days. Maximum number of patients achieved complete relief from pruritus, redness, wheal, and angioedema at 14-21 days.

The adverse event rate was 0.3%. Mild sedation was seen in 7 cases. Gastrointestinal upset, nausea or acidity was seen in 5 patients while 1 patient complained of headache. All adverse events were mild, resolved spontaneously and did not require bepotastine discontinuation or any additional treatment

. ***Figure 1: Patient's perception of improvement in signs and symptoms:***

***Figure 2: Effect of treatment duration on number of patients showing complete relief:***




Wheal: significant for c vs a (P=0.0011); c vs b (P<0.0001) and c vs d (P=0.043)
Redness: significant for a vs b (P=0.032), c vs b (P<0.0001) and d vs b (P=0.0003)
Itching: significant for c vs a (P=0.017) and c vs d (P=0.0034)
Angioedema: significant for c vs b (P<0.0001) and d vs b (P=0.0007)

**Discussion:**

Oral bepotastine is a highly selective second-generation histamine H1 receptor antagonist and has shown long-lasting, dose-dependent antihistaminic and antiallergic activity in vitro and in vivo[4,5]. Bepotastine has been seen to exhibit mast cell stabilization and Leukotriene B4 inhibition which contribute to its anti-pruritic and anti-inflammatory actions. Suppression of nitric oxide production in vascular endothelial cell, may lead to suppression of itch induced by substance P. Bepotastine decreases PAF and antigen induced eosinophilic infiltration and cutaneous reaction, as well as suppresses production of pro-inflammatory cytokines like interleukin-5 and interleukin-1a. Bepotastine's action on inhibition of intercellular adhesion molecule-1 (ICAM-1) expression in human epidermal keratinocytes and vascular endothelial cells decreases recruitment and infiltration of inflammatory cells.

Bepotastine is rapidly absorbed after oral administration with onset of action within half hour and T max of 1.2 hours.[4,6,] Its pharmacokinetics is not significantly affected by food. It shows a 55% blood protein binding with minimal hepatic metabolism which is not CYP dependent.elimination half life is 2.4 hours with 80% oral bepotastine excreted in urine unchanged. Bepotastine does not appear to accumulate in the body due to stable elimination half life with repeated dosing.

Brain penetration of bepotastine is restricted by P-glycoprotein (P-gp) which makes it a non-sedating antihistamine[7]. However due to high membrane permeability and absorption of bepotastine in the upper small intestine, (where P-gp expression is minimal), almost complete absorption takes place here which is unaffected by intestinal P-gp.

Short- and long-term clinical and post marketing studies have shown 10mg twice-daily bepotastine to be effective and well tolerated in the treatment of allergic rhinitis, chronic urticaria or pruritus associated with skin conditions (eczema/dermatitis, prurigo or pruritus cutaneus)[2].

A 1 week phase 3 trial versus placebo with bepotastine 20 mg/day showed higher efficacy than

placebo in improving the level of itching on a 5-point itching scale and improving the level of eruption on a 4-point eruption scale, ($p< 0.0001$ for both)[8]. Global improvement ratings were

significantly better with bepotastine. No significant difference was seen in adverse event rate between bepotastine and placebo.

In a 2 week phase 3, comparative study, Bepotastine 20mg/day was as effective as terfenadine 120mg/day in the treatment of chronic urticaria (final global improvement rating of moderate or greater: 77.1% vs 73.0%).[9] Similar number of bepotastine and terfenadine recipients had an improvement from baseline of two or more grades in itching (74.0% vs 73.7%) or eruption (69.5% vs 68.6%), based on a 5-grade scale. Patient perception of treatment utility was 74.2% with bepotastine 20 mg/day and 68.6% with terfenadine 120mg/day. Adverse event rate was comparable. (12.4% vs 16.1%).

In a long term study in Chronic urticaria, efficacy of bepotastine was maintained up to 12 weeks with final global improvement rating of moderate or greater in 87.3% receiving bepotastine 20 mg/day (increasing over time from 71.8% at week 2 to 90.0% at week 12)[10].

In a post-marketing surveillance study of the efficacy of bepotastine in the treatment of skin conditions, rating of satisfactory or almost satisfactory was reported by 84.3% (N= 549) of Chronic urticaria and 92.7% (N=1101) of patients with pruritus associated with skin disease [11].

A, 2-week trial to study the efficacy of bepotastine 20 mg/day in adult patients with pruritus associated with skin disease: eczema/dermatitis, prurigo, and pruritus cutaneous, showed a final global improvement rating of moderate or greater in 64.7% (63.1%, 73.2%, and 60.0% in eczema/dermatitis, prurigo and pruritus cutaneous respectively)[12]. Patient perception of treatment utility of extremely useful or useful was in 62.2%. Severity of pruritus from moderate or severe at baseline in all patients improved to mild, slight or no symptoms in 70–81% of patients.

In 2 small separate studies, bepotastine significantly reduced mean day and night-time VAS scores for pruritus, scratch mark, erythema and dryness at 2 and 4 weeks in patients of senile pruritus and weekly (up to 4 weeks) VAS scores for itch sensation in patients with pruritic skin disorders[13,14].

In a group of atopic dermatitis patients strongly positive for specific IgE against Dermatophagoides farina (DF) antigen. The flare, wheal and itch responses to scratch test of DF antigen were examined at baseline and at 1 and 2 h after the oral administration of 10 mg of bepotastine besilate.[15] The itch, flare and wheal responses were significantly inhibited as early as 1 h and getting more pronounced at 2 h after oral administration of bepotastine besilate.

A study comparing bepotastine to fexofenadine showed that attenuation of histamine induced itch was seen 30 min after the administration of each drug and thereafter until 6 h, and bepotastine suppressed flare formation after only 30 min following drug administration which was sooner than fexofenadine[16].

In a 4 week study in patients of Atopic Dermatitis, chronic eczema, chronic urticaria and cutaneous pruritis, significant improvement was seen in VAS scores (27.3+/-26 vs 60.7+/-20.1) and HRQoL at 4 weeks versus baseline[17].

The results of our study have been in accordance with past studies, establishing real world in-clinic treatment utility assessed by patients' perceived improvement in symptoms as well as assessing drug tolerance. More than 80% have shown overall complete relief or significant improvement in symptoms with bepotastine. Optimal treatment duration was seen to be 14-21 days in this study. Over all adverse event rate has been very low showing good real world tolerance for bepotastine.

**Conclusion:**

Bepotastine is a new non sedative and effective treatment option for patients having cutaneous conditions with pruritis and other symptoms like erythema, wheal and angioedema. Adverse events rates are low and if present, are mild, without usually needing treatment discontinuation.

Real world data from day to day clinical practice with emphasis on patients' symptomatic relief and satisfaction adds further credence to data from randomized control drug trials. More such real world studies also assessing detailed HRQoL along with improvement in symptom scores, are recommended.

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