**Bepotastine Besilate: A Novel Anti-histamine**

**Kiran Godse, Neeti Kumari**
Department of DVL, D.Y. Patil University School of Medicine, Navi Mumbai, Maharashtra, *Department of DVL, Shri Guru Ram Rai Institute of Medical and Health Sciences, Dehradun, Uttarakhand, India*

**Abstract**

Oral bepotastine is a non-sedative second-generation antihistamine with an action on other inflammatory mediators. It also acts as a mast cell stabilizer and leukotrienes inhibitor. Its distribution in the brain is very limited. We explored the currently available literature on bepotastine besilate to assess the pharmacodynamics and pharmacokinetics of the drug and its role in pruritus and urticaria. Bepotastine is generally well tolerated in the elderly population and pediatric patients. Safety of bepotastine in children >2 years of age, pregnant and lactating females is not known. Bepotastine has got very minimal side effect. In comparison to many other second-generation antihistamines, it has got the quicker onset of action, and it maintains its efficacy over the time. It is a promising agent in the treatment of urticaria, allergic rhinitis, and pruritus associated with different skin disorders.

**Keywords:** Allergic rhinitis, bepotastine, pharmacodynamics, pharmacokinetics, pruritus, urticaria

**INTRODUCTION**

Bepotastine is a second-generation non-sedating antihistamine. It possesses a dual mode of action as it also stabilizes mast cell function and suppresses migration of eosinophils into the inflamed tissues.\(^\text{[1-3]}\) At first in 2000 for treatment of allergic rhinitis, an oral formulation of bepotastine was approved in Japan.\(^\text{[3-6]}\) Subsequently, from 2002 onward, it is being used for the treatment of urticaria and pruritus associated with different allergic skin disorders.\(^\text{[7-10]}\)

Bepotastine is generally well tolerated in both adult and pediatric patients with allergic conditions. Histamine along with various cytokines and chemokines, eosinophils, leukotrienes, platelet activating factors, and other inflammatory mediators play a role in pathogenesis of various allergic cutaneous disorders.\(^\text{[11]}\) Second-generation antihistamines are preferable in these disorders as they have got the dual mode of action both as histamine antagonist and mast cell stabilizer.\(^\text{[12]}\) They also exert significantly less sedation as compared to the first-generation antihistamine while maintaining a higher efficacy in improving the pruritus and inflammation associated with cutaneous disorders.\(^\text{[13]}\)

The focus of this review is to examine published clinical and nonclinical literature on bepotastine besilate and to provide its pharmacokinetics and pharmacological result summary and to evaluate the use of its oral twice daily 10 mg formulation in the management of pruritus, urticaria, and different allergic disorders. Currently available medical literature on bepotastine besilate and its use in rhinitis, urticaria and pruritus was explored. Additional references were identified from the reference list of published articles.

**CHEMISTRY**

Bepotastine besilate is a pale yellow crystalline powder with a molecular weight of 547.06Da. It is a piperidine derivative, and its empirical formula is C\(_{21}\)H\(_{25}\)CIN\(_2\)O\(_3\)C\(_6\)H\(_6\)O\(_3\)S. It has been also referred as TAU-284 in some published literature.

**PHARMACODYNAMICS**

**Antihistamine effects**

Bepotastine is a highly selective H1 receptor antagonist and mast cell stabilizer. In *in vitro* assay, it showed a strong affinity for H1R and minimal to no activity against other H2, H3, and H4 receptors. It is a non-sedating antihistamine, unlike first-generation antihistamines.

**Access this article online**

**Quick Response Code:**

Website: www.ijdd.in

DOI: 10.4103/ijdd.ijdd_22_17

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

**How to cite this article:** Godse K, Kumari N. Bepotastine besilate: A novel anti-histamine. Indian J Drugs Dermatol 2017;3:64-8.
receptors such as H3, adrenergic, serotonin, muscarinic, and benzodiazepine.\[^{11}\]

**Mast cell and eosinophil effect**
Bepotastine inhibit IL-5 action or production (approved by in vitro assay in human peripheral blood mononuclear cells) which is a key agent in promoting eosinophil activation and eosinophil-mediated inflammation.\[^{14,15}\]

Bepotastine also stabilizes mast cell. Higuchi et al. approved this by showing similarities in reduced heart failure pathogenesis by viral myocarditis for mast cell-deficient mouse strains infected with murine encephalomyocardiitis virus in comparison to the infected wild strain given bepotastine orally.\[^{16}\]

Yato et al. showed that bepotastine also inhibited production of leukotrienes B4 and 5 hydroxyeicosatetraenoic acid from rat peritoneal mass.\[^{2}\]

**Antiallergic effects**
Bepotastine has a dose-dependent long-lasting effect. A randomized, double-blind, crossover studies done by Ishibashi et al. showed that Bepotastine 10 mg twice daily inhibited histamine-induced wheal and erythema to a significantly greater extent than placebo and maintained the effect for at least 12 h.\[^{17,18}\]

Hashiguchi et al. showed that Bepotastine 10 mg in a single daily dose suppressed nasal and ocular symptoms caused due to exposure of Japanese cedar pollen significantly higher than placebo.\[^{19}\]

Bepotastine inhibited scratching behavior induced by leukotriene B4 and substance P in mice models of pruritus\[^{20}\] and atopic dermatitis.\[^{21}\]

Bepotastine also suppressed nitric oxide production in vascular endothelial cells which may suppress itching caused by substance P.\[^{22}\]

A study done by Ukai et al. showed that when patients with perennial allergic rhinitis a 4-week course of bepotastine 10 mg twice daily dose was given it significantly decreased the mean number of eosinophil in peripheral blood relative to baseline.\[^{23}\]

**Central nervous system effects**
Bepotastine is a selective H1R antagonist with a very limited distribution into the brain.\[^{1}\] This poor ability to penetrate brain of bepotastine owes to P glycoprotein-mediated efflux\[^{24}\] and H1R internalization.\[^{25}\]

In a 1 day trial done by Takahashi et al. showed that 20 mg/day of bepotastine caused lesser subjective sedation and psychomotor impairment at 2 h than olopatadine 10 mg, fexofenadine 120 mg, and cetirizine 10 mg/day.\[^{26}\]

**Other system effects**
When studied on healthy male or elderly volunteer 2.5–40 mg/day dose of bepotastine in single or multiple doses did not cause significant changes in blood pressure, pulse rate, respiratory rate, body temperature, or electrocardiography.\[^{18,27,28}\]

In postmarketing trial in 16 persons with impaired renal function when Bepotastine was given there was only slight changes seen in renal parameters.\[^{29}\]

**Pharmacokinetics**

**Absorption and distribution**
Bepotastine exhibited high oral bioavailability accounting for >85, >70, >80% in rats, dogs, and humans, respectively. Bepotastine is rapidly absorbed after oral administration.\[^{18,27,29}\] After single-dose administration of 10 mg bepotastine, maximum plasma concentration (Cmax) of 101.3 ng/dl was achieved in a mean time of 1.2 h.\[^{18,27,30}\]

Furthermore, increase in Cmax and area under the plasma concentration curve (AUC) values with single dose of bepotastine 2.5–40 mg were linear that suggest dose-proportional pharmacokinetics over that dose range.\[^{27}\]

Repeated doses were associated with only minimal changes in Cmax and AUC values and other pharmacokinetic properties.\[^{31}\]

Although food decreases Bepotastine level, the decrease was only 7% which was not clinically relevant.\[^{18,27}\]

The distribution of bepotastine to the brain is limited.\[^{1,32}\]

**Excretion**
Bepotastine metabolism is very minimal in the body and it is mostly excreted through renal pathway. In a study done by Kadosaka et al. when 20 mg of bepotastine was given in a twice-daily dose only trace amount of metabolite was found in the urine.\[^{31}\]

In a pharmacokinetic study, it was found that the total urinary excretion of unchanged drug after giving 5 mg and 10 mg single dose of bepotastine within 24 h was 76.4% and 84.4% and with a repeated dosing of 20 mg twice daily it was 80.7%.\[^{31}\]

The average half-life of (t\(_{1/2}\)) value after 10 mg was 2.4 h.\[^{27,31}\] Bepotastine is rapidly eliminated after oral administration and its mean plasma half-life displays almost constant value. It does not accumulate in the body as it has got stable mean t\(_{1/2}\) after repeated dosing too.\[^{31}\]

**Pharmacokinetics in pregnancy and lactation**
A study done by Tsukimoto et al. on pregnant and lactating rat showed that transfer of bepotastine to the fetus from maternal blood and also excretion in milk occurs but fetal tissue level are generally lower than maternal plasma level after oral administration.\[^{33,34}\] The US Food and Drug Administration designated pregnancy category of bepotastine is Category C and the drug should be avoided during pregnancy. It should be used only if the potential benefit justifies the potential risk to the fetus.

**Pharmacokinetics in elderly population**
A study done by Kumagai et al. in elderly Japanese volunteers showed that bepotastine pharmacokinetics did not change
significantly with the age, so routine dosage adjustment for elderly persons are not required.\textsuperscript{[38]}

**Bepotastine and renal impairment**

In a postmarketing trial on nephropathic patients, it was found that there was decreased renal clearance in patients with moderate-to-severe renal impairment (CL\textsubscript{CR} 6–50 ml/min) and generally increased values for Cmax and AUC as compared to those with mild renal impairment (CL\textsubscript{CR} 51–70 ml/min) or control with normal renal function (CL\textsubscript{CR} 70 ml/min). Furthermore, in this study, it was found that at the steady state Cmax value was 1.2–1.8 times higher in nephropathic patients.\textsuperscript{[29]} Hence, it requires a lower initial dosing in patients with renal impairment.

**Therapeutics**

Bepotastine in twice daily dose regimen in adult population has been the focus of numerous clinical trials in patients suffering from allergic rhinitis, chronic urticaria, atopic dermatitis/eczema, and pruritus associated with various skin conditions. Our review focuses on data from randomized, double-blind, controlled 1–4-week phase III trial in allergic rhinitis patients\textsuperscript{[18]} or chronic urticarial\textsuperscript{[26]} and noncomparative trial in pruritus.\textsuperscript{[37]} Also supplemented by postmarketing surveillance and some phase II trials and other previous review article on bepotastine.\textsuperscript{[18]}

In 2 Phase II trial in Japan, efficacy of different dose regimen was assessed. In one late Phase II trial, 72 adults were randomized and bepotastine 5, 10.20 mg/day was given. In other early phase II trial, 276 adult patients were given bepotastine 10, 20.40 mg/day for 4 weeks. In these studies, the primary endpoint was based on the final global improvement from baseline ratio (based on 5 grade rating scale as marked, moderate, slight improvement, and no change worsened). With these trials optimum dose of bepotastine as 20 mg/day (administered as 10 mg twice daily) was established although there were no significant between-group efficacy difference was found.\textsuperscript{[38–40]}

In phase III clinical trial in Japanese patients with perennial allergic rhinitis, it was seen that bepotastine 20 mg/day for 4 weeks was significantly more effective than terfenadine 120 mg/day as evaluated by final global improvement rate (\(P = 0.021\)) and a significantly more number of patients given bepotastine had a final global improvement rating of moderate to greater (62% vs. 43.8%, \(P = 0.011\)). However, in these studies at 2 weeks endpoint the difference in improvement rate was not significant.\textsuperscript{[18]}

**Chronic urticaria**

In a phase II clinical trial in urticaria patients in Japan when bepotastine 10 mg twice daily dose was compared with terfenadine 120 mg/day final global improvement rate did not differ significantly.\textsuperscript{[41]} Both were equally effective in 2 weeks trial and also there was also no significant difference seen in final global improvement rating of moderate and greater. The utility rating based on assessments of shift in global improvement rating and overall tolerability was also same.

In long-term treatment study done in Japanese patients with urticaria, bepotastine efficacy was seen to be maintained for up to 12 weeks.\textsuperscript{[18,42]}

In several small noncomparative trials, the efficacy of bepotastine in chronic urticaria was assessed using patient questionnaire, patient diaries or a visual analog scale. In these studies, bepotastine had an effect on itching within 1 or 1.5 h of administration, and it provided sustained improvement in pruritus and all other symptoms of chronic urticaria (wheals, frequency of episodes).\textsuperscript{[18]}

In postmarketing surveillance, bepotastine was found to be very effective in the treatment of urticarial.\textsuperscript{[43]}

In a small double-blinded, randomized crossover study on effects of bepotastine, cetirizine, olopatadine, and fexofenadine on histamine-induced wheal and flare response, sedation, and psychomotor performance showed that among all the drugs olopatadine and cetirizine suppressed most markedly the wheal and flare response while fexofenadine and bepotastine produced a significant but less persistent suppression. In this study, bepotastine showed the least sedative effect and least impairment of psychomotor performance.\textsuperscript{[20]}

In another small randomized, double-blind, crossover study done on healthy volunteer on the response of bepotastine and fexofenadine on histamine-induced wheal and flare response bepotastine was found to be affecting skin symptoms sooner than fexofenadine does. The effect was relatively consistent with the Tmax results. However, in this study, the dose of fexofenadine was 60 mg twice daily which is lower than the usual recommending dose in our country.\textsuperscript{[44]}

**Pruritus associated with skin disease**

In a noncomparative 2-week trial of bepotastine 10 mg twice daily dose in adult patients with eczema, prurigo, and pruritus associated with various skin disorders, it was seen that bepotastine was very effective in treating the pruritus.\textsuperscript{[37]} The severity of rash and specific symptoms of pruritus was improved with bepotastine.

In a study done on patients with senile pruritus bepotastine 10 mg twice daily dose significantly reduced mean day and night time visual analog score (VAS) for itching. VAS is a 10‑cm long line (oriented horizontally or vertically), on which patients indicate the intensity of pruritus by crossing the line at the point that corresponded to their pruritus severity, being informed that the beginning of the scale refers to no pruritus (0 points) and the end to the most severe pruritus, they can imagine (10 points). The study also showed that there was significant decrease in scratch marks, erythema, and dryness score.\textsuperscript{[45]}

A study done by Kawakami et al. showed that when bepotastine besilate was given to the patients with atopic dermatitis pruritus improved markedly and also there was a significant improvement
In Skindex-16 and HRQol (specific quality of life indicator for patients with atopic dermatitis). In this study, authors found that fall in the emotion score after taking bepotastine 10 mg twice daily correlated significantly with fall in VAS scores for pruritus.[46]

In postmarketing surveillance, bepotastine was found to be very effective in the treatment of pruritus associated with various skin disorder.[18]

**TOLERABILITY**

Bepotastine was found to be generally well tolerated in clinical trials and surveillance studies in patients with allergic rhinitis chronic urticaria and itching associated with the various cutaneous disorder.[18]

None of the reported adverse effects were severe in various clinical trials. In postmarketing surveillance drowsiness was the most common adverse effect, and that too was seen in only 1.3% of patients. Others were thirst, nausea, upper abdominal pain, diarrhea, fatigue, vomiting seen in other 0.7% of patients.[18,37,39,41,43]

Bepotastine is also very well tolerated in children.[47] However, safety and efficacy are not well established in children <2 years of age.[48]

Bepotastine is a pregnancy category C drug as animal models showed evidence of teratogenicity.[49] It is unknown if bepotastine excreted in human breast milk or not but based on rat model study, it should be used cautiously in lactating women.

**CONCLUSION**

By reviewing the currently available literature, most of which is in Japanese, we conclude that bepotastine besilate which is now available in India seems to be a promising agent to combat urticaria and pruritus associated with skin disorders due to its non-sedating profile, lesser to no adverse effects and dual mode of action on histamine and other inflammatory mediators. It also has got quick onset of action, and that will be very helpful in many bothersome pruritic skin conditions. Further trials are needed to prove its use in the Indian population in different pruritic skin conditions.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Kato M, Nishida A, Aga Y, Kita J, Kudo Y, Narita H, et al. Pharmacokinetic and pharmacodynamic evaluation of central effect of the novel antiallergic agent betotastine besilate. Arzneimittelforschung 1999;49:1116-24.

2. Yato N, Murata T, Saito N, Takasaki T, Kikuchi M, Tsuzurahara K, et al. Anti-allergic activity of betotastine besilate (TAU-284), a new anti-allergic drug. Nihon Yakurigaku Zasshi 1997;110:119-29.

3. Williams JI, Gow JA, Klier SM, McCue SL, Salapatek AM, McNamara TR, et al. Non-clinical pharmacology, pharmacokinetics, and safety findings for the antihistamine betotastine besilate. Curr Med Res Opin 2010;26:2329-38.

4. Baba S, Sakakura Y, Iwata S. Early phase II study of TAU-284 (betotastine besilate) on perennial allergic rhinitis. J Clin Ther Med 1997;13:1217-35.

5. Baba S, Takasaki T, Baba K. Late phase II clinical study of TAU-284 for perennial allergic rhinitis—Dose finding study by the double-blind method. J Clin Ther Med 1997;13:1259-86.

6. Baba S, Takasaki T, Baba K. Long-term treatment of TAU-284 (betotastine besilate) on perennial allergic rhinitis. J Clin Ther Med 1997;13:1361-82.

7. Maruta H, Nagata M, Koga H, Tajiri S. Clinical evaluation of betotastine besilate (Talion tablets) on chronic urticaria. J New Rem Clin 2004;53:576-82.

8. Ishibashi Y, Harada S, Niimura M. Late phase II study of TAU-284 (betotastine besilate) on chronic urticaria—optimal dose finding study by double-blind technique. J Clin Ther Med 1997;13:1237-57.

9. Ishibashi Y, Harada S, Niimura M. Long-term treatment of TAU-284 (betotastine besilate) on chronic urticaria. J Clin Ther Med 1997;13:1337-59.

10. Kawashima M, Harada S, Kawashima M. Phase III study of TAU-284 (betotastine besilate) on chronic urticaria. A multicenter double blind, comparative study with placebo. J Clin Ther Med 2002;18:501-19.

11. Broide DH. Molecular and cellular mechanisms of allergic disease. J Allergy Clin Immunol 2001;108:S65-71.

12. Bousquet J, Van Cauwenberge P, Bachert C, Canonica GW, Demoly P, Durham SR, et al. Requirements for medications commonly used in the treatment of allergic rhinitis. European Academy of Allergy and Clinical Immunology (EAACI), Allergic Rhinitis and its Impact on Asthma (ARIA). Allergy 2003;58:192-7.

13. Yanai K, Tashiro M, Okamura N. Non-sedating second-generation antihistamines: The penetration through blood-brain barrier measured by PET. Nishinins Hon J Dermatol 2009;71:3-6.

14. Yamaguchi Y, Hayashi Y, Sugama Y, Miura Y, Kasahara T, Kitamura S, et al. Highly purified murine interleukin 5 (IL-5) stimulates eosinophil function and prolongs in vitro survival. IL-5 as an eosinophil chemotactic factor. J Exp Med 1988;167:1737-42.

15. Kaminuma O, Ogawa K, Kikwaka H, Kikuchi M, Naito K, Ikezawa K, et al. A novel anti-allergic drug, betotastine besilate, suppresses interleukin-5 production by human peripheral blood mononuclear cells. Biol Pharm Bull 1998;21:411-3.

16. Higuchi H, Hara M, Yamamoto K, Miyamoto T, Kinoshita M, Yamada T, et al. Mast cells play a critical role in the pathogenesis of viral myocarditis. Circulation 2008;118:363-72.

17. Ishibashi Y, Kawashima M, Harada S. Phase I study of antiallergic agent, TAU-284 (betotastine besilate): study of inhibitory effect on intradermal reaction of histamine. Rinsho Iyaku 1997;13:1187-97.

18. lyseng-Williamson KA. Oral bepotastine: In allergic disorders. Drugs 2010;70:1579-91.

19. Hashiguchi K, Tsuruta S, Suzuki K, Gotoh S, Okubo K, et al. Bepotastine besilate OD tablets suppress nasal symptoms caused by Japanese cedar pollen exposure in an artificial exposure chamber (OHI0 chamber). Expert Opin Pharmacother 2009;10:523-9.

20. Andoh T, Kuraishi Y. Suppression by bepotastine besilate of substance P-induced itch-associated responses through the inhibition of the leukotriene B4 action in mice. Eur J Pharmacol 2006;547:59-64.

21. Tanizaki H, Kambe N, Nakamura Y, Tanaka A, Matsuda H, Miyachi Y, et al. Oral administration of bepotastine besilate suppressed scratching behavior of atopic dermatitis model NC/Nga mice. Int Arch Allergy Immunol 2008;145:277-82.

22. Sanglae B, Shin'ichi S. Suppression effect of bepotastine besilate on oxidative stress (nitric acid: NO). Jpn J Clin Exp Med 2008;85:1045-8.

23. Ukai K, Takeuchi M, Masuda S. Clinical pharmacological study of anti-allergic agent TAU-184 (bepotastine besilate)—the effect on counting of eosinophils in nasal discharge, and the patency improvement of nasal cavity. J Clin Ther Med 1997;13:1401-2.

24. Ohashi R, Kamikozawa Y, Sugiyama M, Fukuda H, Yabuuchi H, Tanai I, et al. Effect of P-glycoprotein on intestinal absorption and brain penetration of antiallergic agent bepotastine besilate. Drug Metab Dispos 2006;34:793-9.
25. Hishinuma S, Sato Y, Kobayashi Y, Komazaki H, Saito M. Intact cell binding for in vitro prediction of sedative and non-sedative histamine H1-receptor antagonists based on receptor internalization. J Pharmacol Sci 2008;107:66-79.

26. Takahashi H, Ishida-Yamamoto A, Iizuka H, Komazaki H, Saito M. Intact cell binding for in vitro prediction of sedative and non-sedative histamine H1-receptor antagonists based on receptor internalization. J Pharmacol Sci 2008;107:66‑79.

27. Yokota H, Mizuuchi H, Maki T, Banno K, Sato T. Phase I study of TAU-284: single oral administration in healthy male volunteers. Journal of Clinical Therapeutics & Medicines 1997;13:1137-53.

28. Kumagai Y, Uchiumi M, Murasaki M. Pharmacokinetics study of TAU-284 in elderly volunteers. Rinsho Iyaku 1997;13:1169-85.

29. Kawashima K, Sakai M, Takatsuka S. Clinical pharmacokinetic study of Talion tablet (bepotastine besilate) in nephropathic patients (post-marketing clinical trial). Rinsho Iyaku 2003;19:637-48.

30. Bielory L, DuttaChoudhury S, McMunn A. Bepotastine besilate for the treatment of pruritus. Expert Opin Pharmacother 2013;14:2553-69.

31. Kadosaka T, Shiraishi K, Mizuuchi H. Phase I study of TAU-284: Repeated oral administration in healthy male volunteers. Rinsho Iyaku 1997;13:1155-68.

32. Tashiro M, Duan X, Kato M, Miyake M, Watanuki S, Ishikawa Y, et al. Brain histamine H1 receptor occupancy of orally administered antihistamines, bepotastine and diphenhydramine, measured by PET with 11C-doxepin. Br J Clin Pharmacol 2008;65:811-21.

33. Ohashi R, Tsukimoto M, Nakamura S, Hotsuka M, Hayashi K, Nishiyama, SI, et al. Pharmacokinetic Studies of Betotastine Besilate (TAU-284)(I): Absorption, Distribution, Metabolism and Excretion after a Single Oral Administration. Drug Metabolism and Pharmacokinetics 1997;12:417-38.

34. Kawashima K, Ohashi R, Nakamura S. Study (II) relating to the internal pharmacokinetics of betotastine besilate (TAU-284): Transfer into the fetus and into milk in rats, and distribution and excretion during repeated administration. Xenobio Metab Dispos 1997;12:439-59.

35. Baba S, Takasaka T, Baba K. Clinical trial of TAU-284 (bepotastinebesilate) on perennial allergic rhinitis: A double blind study in comparison with terfenadine. Rinsho Iyaku 1997;13:1307-35.

36. Kawashima M, Harada S, Nakajima M. Phase III study of TAU-284 (bepotastine besilate) on chronic urticaria: A multicenter double blind comparative study with placebo. J Clin Therap Med 2002;18:13-31.

37. Ishibashi Y, Harada S, Niimura M. Clinical evaluation of TAU-284 (bepotastine besilate) on eczema/dermatitis, prurigo, and pruritus cutaneus. Rinsho Iyaku 1997;13:1383-400.

38. Baba S, Sakakura Y, Iwata S. Early phase II study of TAU-284 (bepotastine besilate) on perennial allergic rhinitis. Rinsho Iyaku 1997;13:1217-35.

39. Baba S, Takasaki T, Baba K. Late phase II clinical study of TAU-284 for perennial allergic rhinitis: Dose finding study by the double-blind method. Rinsho Iyaku 1997;13:1259-86.

40. Ishibashi Y, Harada S, Niimura M. Early phase II study of TAU-284 (bepotastine besilate) on chronic urticaria. Rinsho Iyaku 1997;13:1199-215.

41. Ishibashi Y, Harada S, Niimura M. A multicenter double-blind comparative study: Clinical evaluation of TAU-284 (bepotastine besilate) on chronic urticaria using terfenadine as a control drug. Rinsho Iyaku 1997;13:1287-306.

42. Ishibashi Y, Harada S, Niimura M. Long-term treatment of TAU-284 (bepotastine besilate) on chronic urticaria. Rinsho Iyaku 1997;13:1337-59.

43. Kawashima M. Post-marketing surveillance of Talion tablets (bepotastine besilate) in patients with urticaria and pruritus associated with skin disease (eczema/dermatitis, prurigo, and cutaneous pruritus). J New Rem Clin 2007;56:93-107.

44. Tanizaki H, Ikoma A, Fukuoka M, Miyachi Y, Kabashima K. Effects of bepotastine and fexofenadine on histamine-induced flare, wheal and itch. Int Arch Allergy Immunol 2012;158:191-5.

45. Horikawa T, Ueda M, Nishigori C. Efficacy of bepotastine besilate in the management of senile pruritic diseases. Skin Res 2005;4:475-80.

46. Kawakami T, Kimura S, Haga T, Doi R, Kyoya M, Nakagawa K, et al. Health-related quality of life assessed by the effect of bepotastine besilate in patients with pruritus: Importance of emotions score in atopic dermatitis. J Dermatol 2012;39:527-30.

47. Baba S. Post-marketing surveillance study of Talion tablets on pediatric allergic rhinitis. Rinsho Iyaku 2002;18:1371-87.

48. Hussar DA, Abbas CA. New drugs: Asenapine, iloperidone, and bepotastine besilate. J Am Pharm Assoc (2003) 2010;50:107-10.

49. Bepotastine. LexiDrugs: Lexi-Comp, Inc.; 2013.