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POST-MARKETING SURVEILLANCE STUDY TO SUBSTANTIATE THE EFFICACY AND SAFETY FOR THE COMBINATION OF PHENYLEPHRINE AND LEVOCETIRIZINE IN THE PATIENTS OF ALLERGIC RHINITIS IN INDIAN POPULATION

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ABSTRACT

Introduction: Allergic rhinitis is most commonly encountered disease in clinical practises. Allergic rhinitis is developed due to release of histamine from mast cells due to hypersensitivity to any of the allergen to which the patient has been exposed. This study was conducted to test the efficacy and safety for the treatment of allergic rhinitis patients for the fixed dose combination of Phenylephrine 10 mg and Levocetirizine 2.5 mg per tablet in Indian population. **Methodology:** Out of 165 enrolled, 150 trial subjects completed the study. Efficacy assessment was made by total symptom score for which the trial subjects were asked to rate the symptoms on 11-point scale ranging from 0 means no symptoms at all to 10 means the maximum tolerated symptoms. Total symptom score was further extrapolated to four-point Likert-type symptom severity scale. Reported adverse events by the recruited trial subjects during the study were used to determine the safety of the Investigational product. **Results:** Reduction in Total Symptom Score was from 6.98 (baseline) to 3.15 (day 3) to 0.60 (day 5). Nearly all trial subjects had >50% reduction in total symptom score at all visits and most of the trial subjects had complete relief from the symptom of allergic rhinitis. Also, no serious or un-expected adverse event was reported during the study. **Conclusion:** Combination of Phenylephrine and Levocetirizine was found efficacious as well as safe for the treatment of allergic rhinitis.

KEYWORDS: Phenylephrine, Levocetirizine, Allergic Rhinitis.

INTRODUCTION

Allergic rhinitis is also known as hay fever which is an inflammation in the nose which occurs when immune system overreacts to allergens present in the air. Pruritus, sneezing, rhinorrhoea, nasal congestion etc are symptoms of allergic rhinitis which is a common inflammatory disorder of the nasal mucosa.[1] These symptoms can be developed due to release of histamine from mast cells in nasal mucosa. Histamines promotes the flow of blood in the region of body where the allergen is present until they exit the mast cells. This triggers inflammation, which allows patients' immune system's chemicals to interfere and repair the damage.[2,3] The cause of an allergic rhinitis is mainly dependent on factors such as season, age and/ allergen types etc. Despite of its reputation as a seasonal disturbance, allergic rhinitis can cause minimal persistent mucosal inflammation that interacts with infective inflammation, makes patients more vulnerable to viral colds.[4] Allergic rhinitis has a significant impact on social life, school performance and work productivity particularly in severe cases. Symptoms of rhinitis also have a negative influence on academic success.[5] Adults normally can have an annual average of two to four episodes and young children can have as many as six to eight episodes. As allergen induced symptoms like pruritus, sneezing etc occurs because of release of histamine from mast cells and nasal mucosa, the allergic rhinitis can be treated by antihistamines which blocks the release of histamines from nasal mucosa. Monotherapy of antihistamines can be insufficient to treat all the symptoms of allergic rhinitis as nasal congestion is commonly experienced by the allergic rhinitis patients which is generally caused due to swelling of nasal mucosa due to release of histamine. Earlier, NSAIDs was used to reduce the swelling effect of mucosa but it was found that NSAIDs can lead to produces side effects like nausea, hepatic failure, vomiting and gastritis etc.[6] Hence, nasal decongestant can be added with antihistamines to reduce the congestion effect in mucosa.

The combination of antihistamine like Levocetirizine and nasal decongestant like Phenylephrine can be used for the treatment of allergic rhinitis as Levocetirizine blocks the histamine activity and nasal congestion produced by the histamine can be reduced by Phenylephrine.

Antihistamines are indicated for the treatment of allergic rhinitis.[7] Levocetirizine is a fast-acting H1-antihistamine that is highly selective.[8] It blocks histamine binding to receptors or minimises histamine receptor activity on nerves, vascular smooth muscle, glandular cells, endothelium and mast cells, suppresses the histamine-induced wheal response (swelling) and flare response (vasodilation).[9] Phenylephrine hydrochloride is a nasal decongestant used to alleviate nasal inflammation caused by a cold or allergic rhinitis for a limited period. Phenylephrine has both indirect and direct sympathomimetic effects as a vasoconstrictor. The most important direct effect is agonism at alpha1 adrenergic receptors on the capacity of nasal mucosa to blood vessels, that produces vasoconstriction, reduces the amount of fluid that can enters the nose, throat, and sinus linings and reduces inflammation of nasal membrane.[10] The therapeutic dose of phenylephrine hydrochloride 10 mg has neither major stimulant effect on the heart's beta 1-adrenergic receptors, nor does it activates the bronchi or peripheral blood vessels beta 2-adrenergic receptors.[11]

This post-marketing surveillance study was conducted to test and document the efficacy and safety for the fixed dose combination of Phenylephrine 10 mg and Levocetirizine 2.5 mg per tablet for the indication of allergic rhinitis in Indian population.

METHODOLOGY

This post marketing surveillance study was conducted at eleven clinical trial sites all across India. Total 165 trial subjects were recruited for this post marketing surveillance study out of which 150 trial subjects completed the study. For the post marketing surveillance study the duration was of 5 days, trial subjects were asked to visit the clinical trial site at day 3 (visit 2) and day 5 (visit 3) considering the baseline visit as day 1 (visit 1).

Inclusion and Exclusion Criteria

Trial subjects of both the genders including male and female were recruited for the post marketing surveillance study. Trial subjects recruited were of age between 18 to 65 years. The study only recruited trial subjects who had a confirmed diagnosis of allergic rhinitis and had symptoms like congestion, rhinorrhoea, sneezing, pruritis. Only trial subjects who were strictly willing to follow the study procedure were recruited for the study.

Trial subjects who were hypersensitive to the investigational products were excluded. Hypertensive patients were excluded from the study because the Phenylephrine present in the investigational product could cause vasoconstriction and can cause increase in blood pressure. This study excluded pregnant and lactating women, as well as patients with psychological issues.

Study Intervention

Investigational product used for the post marketing surveillance study was the fixed dose combination of Phenylephrine Hydrochloride 10 mg and Levocetirizine 2.5 mg per tablet. The Investigational product was provided by the sponsor to the investigator at no cost and those Investigational products were dispensed to trial subjects at no cost by the investigator.

Study design

PMS study was conducted on 165 trial subjects and at 11 clinical trial sites since it was a multicentric post marketing surveillance study. Study design was of non-randomized, non-comparative and open label nature and all participants, clinical research personnel, trial subjects, and any other people involved in the study, whether from the side of the investigator, trial subjects or the sponsor were aware of the investigational product, its composition, mechanism of action and the study procedure.

Study Procedure

Trial subjects were enrolled for the study as per inclusion and exclusion criteria. All eligible patients were informed about the study procedures and the investigational product by the investigator in an understandable language by the investigators. Trial subjects were asked for their consent and if they were found to be ready to give his/ her consent for the post marketing surveillance study then the consent for the study was taken by the investigator on the informed consent form and then trial subjects were recruited for the study. A detailed medical history was obtained from all enrolled trial subjects, which was followed by thorough clinical examination. Each trial subject was provided 10 tablets of the investigational product at baseline visit only and were advised to take the dose as twice a day for a study period of 5 days. Trial subjects were instructed to keep a diary of daily symptoms to detect the adverse event if any. For the trial subjects recruited in this study, three visits were planned: visit 1 on day 1, visit 2 on day 3 and visit 3 on day 5. Efficacy and safety evaluation was done on day 3 and day 5. Investigators were asked to discontinue the Investigational product in the event of any significant adverse event and inconsistency.

Concomitant therapy

In the study duration, pharmacological intervention or medications including topical decongestants (sprays/drops and aromatic oils) or antibiotics or any other medication than Investigational products were not permitted but at the same time non-pharmacological interventions were permitted.

Efficacy Assessment

In the post marketing surveillance study duration of 5 days the efficacy assessment was done by calculating the decrease in the mean total symptom score (TSS). To measure the TSS, trial subjects were asked to rate their TSS on TSS scale which was an eleven-point scale ranging from 0 to 10 where 0 was no symptom to 10 was the highest tolerated symptoms. The TSS was further extrapolated with 4 grades as no symptoms (0 on TSS), mild (1-3 on TSS), moderate (4-6 on TSS) and severe (7-10 on TSS) intensity symptoms to the Likert-type symptom severity scale.

Safety assessment

Trial subjects were asked for any adverse events and the same, if present, were reported during each post-dose visit. All the reported adverse events were analysed for safety assessment of the investigational product.

Regulatory Matters

The Investigational product was approved for manufacturing and marketing in India. In India the Investigational product is categorised under the category of schedule H drug. All the trial subjects were recruited in the study in compliance regulatory guidelines.

RESULTS

Total 165 trial subjects were recruited out of which 150 trial subjects completed the study. On visit 1, at day 1 mean TSS was 7.026. On revaluation visit on day 3, the mean TSS was reduced to 3.153, which was further reduced to 0.606 on day 5 which was conclusion visit. Figure 1 shows a graphical presentation of the mean TSS score at every visit.

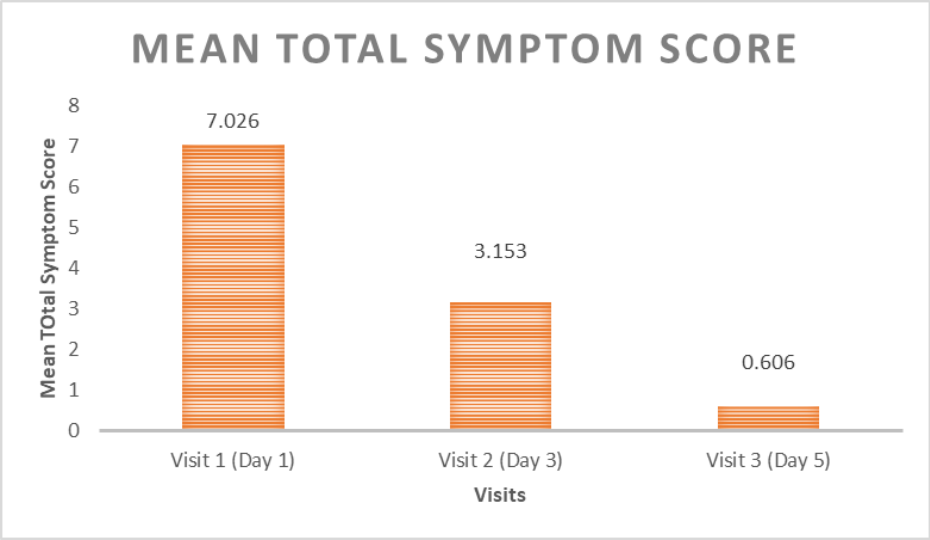

Fig.1: Mean TSS at visit 1, 2 and 3.

Also, the percentage decrease in mean TSS at visit 2 and 3 as compared to visit 1 was calculated, at visit 2 and visit 3 there was 55.123 % and 91.366 % reduction in the TSS as compared to the baseline which was graphically presented as mentioned below in fig 2.

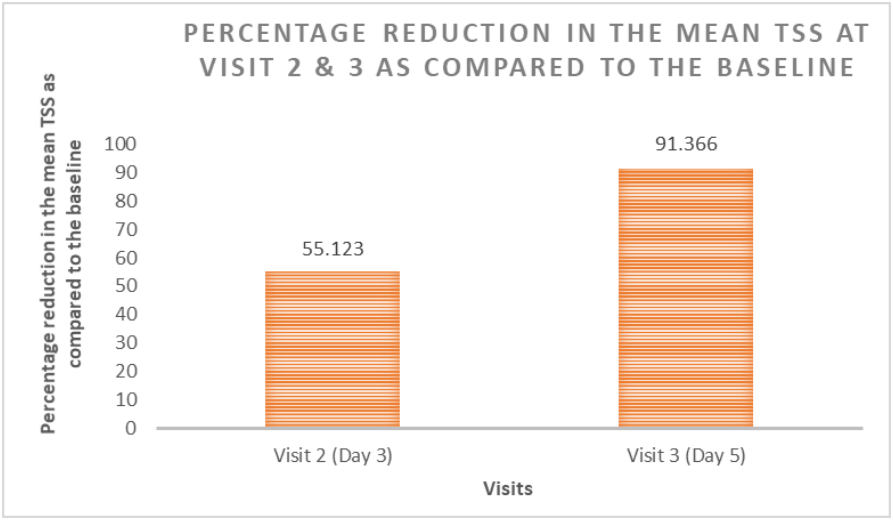

Fig. 2: Percentage reduction in mean TSS at visit 2 and 3 as compared to baseline.

TSS data was further extrapolated to a Likert-type symptom severity scale, which was used to find the severity of the symptoms at each visit according to the mean TSS. The TSS data was extrapolated to Likert-type symptom severity scale as mentioned in the section "Efficacy Assessment".

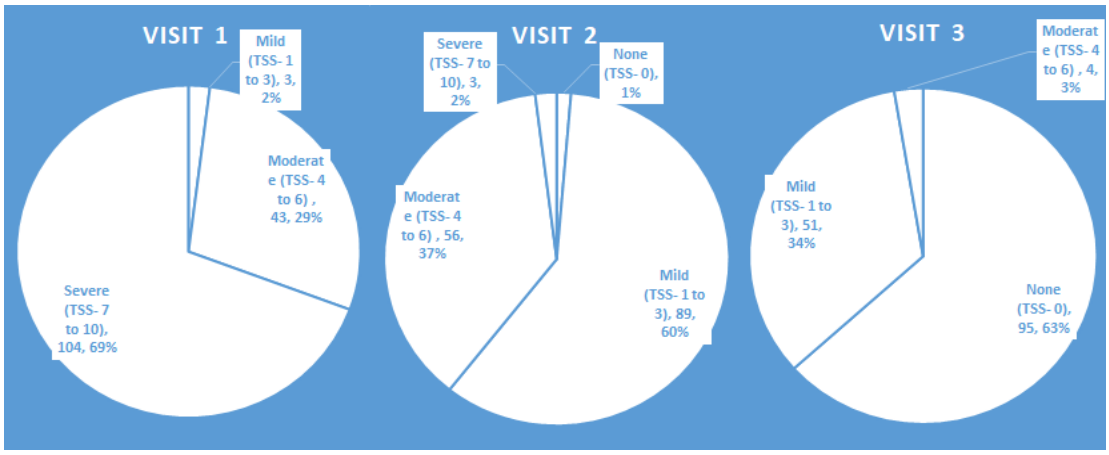

Fig. 3: No of trial subjects of mild, moderate and severe intensity symptoms as per the Likert-type symptom severity scale at visit 1, 2 and 3.

At visit 1 out of 150 trial subjects, 104 (69 %) had severe intensity symptoms of TSS ranging between 7 to 10, 43 (29 %) had moderate intensity symptoms of TSS ranging between 4 to 6 and 3 (2 %) had mild intensity symptoms of TSS ranging from 1 to 3. At re-evaluation visit (day 3), 2 (1 %) trial subjects had no symptom of TSS 0, 89 (60 %) trial subjects had mild intensity symptoms of TSS ranging from 1 to 3, 56 (37 %) trial subjects had moderate intensity symptoms of TSS ranging from 4 to 6 and only 3 (2 %) trial subject had severe intensity symptoms of TSS ranging from 7 to 10. At conclusion visit (day 5), 95 (63 %) trial subjects had no symptom of TSS 0, 51 (34 %) trial subject had mild intensity symptoms of TSS 1 to 3, 4 (3 %) trial subject had moderate intensity symptoms of TSS 4 to 6 and there was no trial subject of severe intensity symptoms of TSS ranging from 7 to 10.

Safety Assessment

All the adverse drug reactions reported by the trial subjects were of expected and non-serious nature. In the population of 165 recruited trial subjects, 20 episodes of adverse drug reactions were reported by 16 trial subjects. Below mentioned adverse drug reactions were reported.

Table no. 1: Adverse drug reactions reported by trial subjects.

Adverse Events	Number of Episodes	No. of Patients
Nausea	2	1
Drowsiness	18	15

DISCUSSION

Allergic rhinitis is most commonly encountered disease in clinical practises. Allergic rhinitis is developed due to release of histamine from mast cells due to hypersensitivity to any of the allergen to which the patient has been exposed. Antihistaminic drugs can be used to treat allergic rhinitis as they block histamine binding to receptors or minimise histamine receptor activity on nerves, vascular smooth muscle, glandular cells, endothelium, and mast cells which supresses the swelling as well as vasoconstriction and give relief from the symptoms.[6] Nasal discharge is generally found to be produced due to allergic rhinitis which can be treated by nasal decongestant like Phenylephrine hydrochloride.[10] This study was conducted to test the efficacy and safety for the treatment of allergic rhinitis patients for the fixed dose combination Phenylephrine 10 mg and Levocetirizine 2.5 mg per tablet in Indian population. Efficacy and safety evaluation was done by the TSS which was further extrapolated to Likert type symptom severity scale and reported adverse events respectively.

During the study, it was found that there was decrease in TSS in all trial subjects. At baseline the mean TSS was 7.02 which was decreased to 3.15 by 55.123 % at day 3, re-evaluation visit and which was further decreased to 0.60 by 91.366 % as compared to the baseline. At baseline 104 (69.33 %), 43 (28.66 %) and 3 (2 %) trial subjects had severe, moderate and mild intensity symptoms of allergic rhinitis as per the Likert-type symptom severity scale respectively. At re-evaluation visit (day 3), 3 (2 %), 56 (37.33 %) and 89 (59.33 %) trial subjects had severe, moderate and mild intensity symptoms respectively of allergic rhinitis and 3 (2 %) trial subjects were found to be completely cured as they had TSS 0. At conclusion visit (day 5), 95 (63.33 %) trial subjects had TSS 0 i.e. they were completely cured, 51 (34 %) trial subjects had mild intensity symptoms and only 4 (2.66 %) trial subjects had moderate intensity symptoms. In the study duration in all the subjects the significant reduction was found in the symptoms of allergic rhinitis after the treatment with the investigational product. Below we have discussed a similar study which was used as a reference for the conduct of this study.

A phase IV clinical trial was conducted by Kiran M et al for the combination of Paracetamol, Levocetirizine and Phenylephrine for the treatment of allergic rhinitis to test the efficacy and safety. The study was conducted in 234 patients. Efficacy was assessed by Total Symptom Score (TSS) and safety was assessed by reported adverse events. A decrease in TSS was found from 6.82 at baseline to 3.63 at day 3 to 1.14 at day 5. A statistically significant reduction was found in 5 days in all the patients who were treated with the study combination. Also, in the study duration no serious or unexpected adverse event was found to be reported. The study concluded that the combination of Paracetamol, Levocetirizine and Phenylephrine was found to be efficacious and safe for the treatment of allergic rhinitis and common cold.[12]

As per the best knowledge of the author of this research article, till time no clinical study was conducted to test the efficacy and safety for the fixed dose combination of Phenylephrine Hydrochloride 10 mg and Levocetirizine 2.5 mg per tablet in Indian patients so this was the first post marketing surveillance study conducted to test the efficacy and safety in Indian population.

CONCLUSION

Safe and optimum relief from the symptoms of allergic rhinitis was found to be provided by the fixed dose combination of Phenylephrine Hydrochloride 10 mg and Levocetirizine 2.5 mg per tablet.

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DISCLOSURE

This post marketing surveillance study was conducted as a part of Pharmacovigilance activity for Sinarest Levo tablet which is a product of Centaur Pharmaceuticals Pvt. Ltd.

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