

**SAFETY AND EFFICACY FOR THE COMBINATION OF CHLORPHENIRAMINE MALEATE AND PHENYLEPHRINE IN THE SYMPTOMATIC TREATMENT OF ALLERGIC RHINITIS IN PAEDIATRIC POPULATION: PHASE IV CLINICAL TRIAL****Dr. Mayuresh Kiran<sup>\*1</sup> and Lalit Pawaskar<sup>2</sup>**<sup>1</sup>Vice-President, Medical Services and Pharmacovigilance, Centaur Pharmaceuticals Pvt. Ltd.<sup>2</sup>Executive, Pharmacovigilance, Centaur Pharmaceuticals Pvt. Ltd.**\*Corresponding Author: Dr. Mayuresh Kiran**

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Article Received on 20/12/2018

Article Revised on 10/01/2019

Article Accepted on 31/01/2019

**ABSTRACT**

**Introduction:** Allergic rhinitis, a trivial illness causing significant degree of morbidity can alter the social life of patients affecting school performance and has a prevalence of up to 40% in the pediatric population. FDC of Chlorpheniramine Maleate, an anti-histaminic and Phenylephrine, a nasal decongestant is much celebrated in the treatment of Allergic Rhinitis in Children. **Methodology:** Of 193 registered, 172 patients completed the study. Safety assessment was made by inspecting the adverse events during trial. Efficacy assessment was made by decrease in TSS and extrapolating to four point Likert type scales. **Results:** Reduction in mean TSS was from 6.19 at baseline to 3.09 at day 3 and 0.75 at day 5. One point reduction in Likert-type symptom scale from Moderate to Mild took just 3 days and was further reduced to less than mild at day 5. Nearly all the patients had >50% reduction in symptom score at day 3 and day 5. At day 3 and day 5 there was reduction of 49.95 % and 87.88 % respectively in mean TSS as compared to baseline. 35 episodes of adverse events occurred and were of mild intensity including sedation and drowsiness being dominantly seen. **Conclusion:** A combination of Chlorpheniramine Maleate and Phenylephrine was found to be safe as well as effective in the treatment of Allergic Rhinitis in paediatric population.

**KEYWORDS:** Allergic Rhinitis, Chlorpheniramine Maleate, Phenylephrine, Paediatric population.**INTRODUCTION**

Allergic rhinitis (AR) is a skewed immune reaction to common antigens in the nasal mucosa often undiagnosed despite high ubiquity. It has become a global health problem that constantly affects a large part of the general population, especially children. Its global prevalence continues to increase, with over 500 million individuals affected worldwide. Nearly 20-30% of the Indian population suffers from Allergic Rhinitis.<sup>[1]</sup> The prevalence of AR is increasing in countries with previously low prevalence while plateauing in areas of highest prevalence of up to 40% in children, although it frequently goes untreated and unrecognized.<sup>[2]</sup>

According to Joint Task Force guidelines set forth by the American Academy of Allergy, Asthma and Immunology (AAAAI), American College of Allergy, Asthma and Immunology (ACAAI) and the Joint Council on Allergy, Asthma and Immunology, AR can be classified as seasonal, perennial and episodic.<sup>[3]</sup> This can have humongous negative consequences, particularly in children, since it is associated with numerous comorbidities and complications that have a compelling health impact on quality of life.

Recently, the document Allergic rhinitis and its impact on asthma (ARIA), developed in collaboration with the WHO depicted how a disease so frequently affecting human race is way more disastrous and its complications and sequelae should be the subject of extensive research.<sup>[4]</sup> Often the child's parents will ruminate on comorbid diseases only and will not acknowledge or be concerned by symptoms of their child's allergic rhinitis.<sup>[5]</sup> Allergic rhinitis if poorly controlled, may contribute to the development of other co-morbidities including acute and chronic sinusitis nasal polyps, otitis media/otitis media with effusion, and even to asthma thereby resulting in hospitalization of the patient.<sup>[6]</sup> A survey by All India Co-ordinated Project on Aeroallergens and human health, New Delhi, 2000, cited that of the 20-30% of the population suffering from Allergic Rhinitis, 15% are likely to develop Asthma.<sup>[7]</sup>

Cardinal symptoms of this clinically defined symptomatic condition in children subsume watery rhinorrhoea, nasal obstruction, nasal itching and sneezing.<sup>[8]</sup> In India, the ISAAC phase I conceded that 12.5% children in 6-7 year age-group and 18.6% in the 13-14 year age-group had nasal symptoms alone, while

allergic rhinoconjunctivitis was seen in 3.2% and 6.3% children in these age-groups respectively.<sup>[1]</sup> The signs and symptoms of allergic rhinitis overlap with those of other conditions. Monotherapy may be scanty to relieve all the symptoms of Allergic rhinitis, thence multiple drug combinations subsuming a first generation Antihistamine are used to treat these varieties of Symptoms.<sup>[9]</sup>

Phenylephrine is a sympathomimetic primarily used as a systemic nasal decongestant.<sup>[6]</sup> The mechanism by which decongestants bring off their action is by activation of postjunctional alpha-adrenergic receptors found on precapillary and post capillary blood vessels of the nasal mucosa. Activation of these receptors by distinct binding of the sympathomimetic agent to the binding site of the receptor or by enhanced release of norepinephrine leads to vasoconstriction. Such vasoconstriction leads to shrinkage of the tissue by decreasing blood flow through the nasal mucosa.<sup>[9]</sup> Chlorpheniramine maleate (CPM) is one of the most often recommended and used 1<sup>st</sup> generation antihistaminic agents. The primary action of CPM is competitive binding to the H1 receptors of the vascular tunica medius in the nasal mucosa to prevent the histamine vasoreactive response. The anti-histaminic action of CPM would be translated to its anti-allergic and anti-inflammatory action in the nasal mucosa. The additional anti-cholinergic action of CPM may be responsible for decrease in the nasal discharge, which is infective. Thus CPM is useful to control the symptoms of common cold like - Running Nose and Sneezing.

Eccles *et al.*, stated that Multi-ingredient combination products for multi-symptom relief are formulated to simply, safely and simultaneously treat multiple symptoms when used as directed.<sup>[10]</sup>

Monotherapy has a shortfall to provide relief of all the symptoms and other co-morbidities if any of Allergic Rhinitis. Hence, multiple drug combinations including an Antihistamine and Nasal Decongestant are used to these indications.

However due to the inadequacy of clinical data available for this combination of Phenylephrine and Chlorpheniramine Maleate a Phase IV Post-Marketing study was conducted to document the efficacy and safety of this combination in the treatment of Common Cold ad Allergic Rhinitis.

## METHODOLOGY

This Phase IV Clinical trial enrolled volunteers at 12 Pediatric Specialty centers in various cities in India, from October 2016 to January 2017. A total of 193 patients were recruited for the study, out of which 172 patients completed the study. 21 patients were lost to follow-up.

### Inclusion and Exclusion Criteria

The study subsumed patients of both gender between the age of 6 to 11 years. Patients included in the study were

diagnosed of Allergic Rhinitis having 4 out of the 9 symptoms of Headache, fever, bodyache, nasal congestion, rhinorrhoea, sneezing sore throat, dysphonia and malaise) extant for not more than 48 hours were embodied in the study. Only the patients who would strictly cohere to the protocol were recruited for the study.

Patients with any intricacy due to common cold like otitis media, tonsillitis, sinusitis etc. were excluded from the study since that avail use of antibiotics also would prolong the treatment duration. Patients with hypersensitivity to the individual study drugs were also excluded from the study drug.

### Study Intervention

A combination of Phenylephrine Hydrochloride 5mg, Chlorpheniramine Maleate 1mg, Sodium Citrate 60 mg and Menthol 1mg per 5 ml was provided by the sponsor free of cost to the patient Study dosage and administration – Patients and Guardians were instructed to take the dose as per the table 1.

**Table 1: Dose of the study drug combination for pediatric population of different age and weight.**

Weight	Age	Dose
10.2 to 20.8 kg	1 - 6 years	2.5 – 5 ml
20.7 to 32.5	6 - 10 years	5 ml bd

### Study procedure

The study stretch was decided to be 5 days. Patients of Allergic Rhinitis satisfying the inclusion and exclusion criteria were recruited for the study. An itemized medical history was taken and physical examination (including the vital signs, systemic and general examination) was conducted by the investigators. Patients were given free samples by the investigator and asked to take as per the table 1. Patients were asked to maintain a diary to record any adverse events occurring during the study duration. Three visits were outlined for the patients recruited in this study – V1 (baseline visit) on day 1, V2 (re-evaluation visit) on day 3 and V3 (conclusion visit) on day 5. Total symptom score and adverse events occurring were esteemed during each visit along with medical history and physical examination. Investigators were asked to stop the study drug combination in case of severe adverse event and with discretion, clinical experience contingent upon mild to moderate adverse events.

### Concomitant therapy

No Pharmacological intervention and medication including, topical decongestants (sprays/ drops and aromatic oils), antibiotics, multi-vitamins and multiminerals were allowed during the study duration, other than study drug. Non-Pharmacological interventions like drinking of warm/hot water at regular intervals and steam inhalation were allowed and encouraged during the study duration.

### Efficacy assessment

The primary assessment was reduction in Total Symptom Score (TSS) which was a score of all the symptoms on an eleven-point scale (0 to 10) where 0 is no symptoms and 10 is maximum tolerated symptoms. The TSS was further extrapolated to the Likert-type symptom severity scale with 4 grades – no symptoms (0 on TSS), mild (1 – 3 on TSS), Moderate (4 – 6 on TSS) and Severe (7 – 10 on TSS). The secondary assessment was done by calculating the average TSS at all the visits and average percentage reduction in the TSS at visit 2 and visit 3 as compared to baseline.

### Safety assessment

Patients were questioned for any adverse events and the same if present was noted in the case record form during each post-dose visit. Patients with any adverse events if present were recorded in the case report form after thorough investigation. These adverse events were categorized into non-serious or serious adverse events. Naranjo's scale of probability was used to classify the adverse event as non-drug related or drug related. Adverse events were followed up by the investigators till the symptoms subside.

### Regulatory matters

The study drug in combination has been approved for manufacturing and marketing in 2005. The Drug controller has already approved the combination in 2015. The forenamed combination is available under various brands but is classified as schedule H drug in India, i.e. to be sold in presence of prescription of registered medical practitioners only. Patients engaged voluntarily read and signed the informed consent form.

## RESULTS

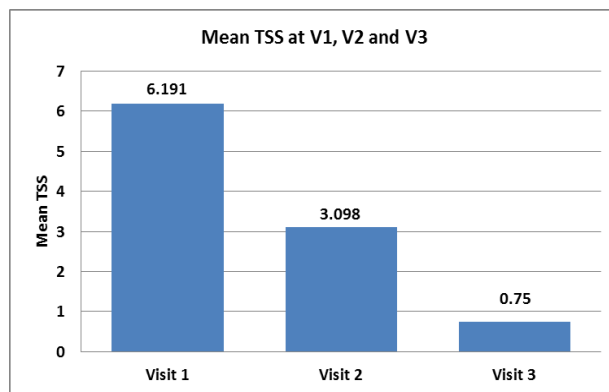
A total of 193 patients were recruited at 12 centers across India, 172 patients completed the study and were analyzed. Other demographic characteristics are in Table 1.

**Table 2: Demographic Characteristics of the patients recruited for the study.**

Mean Age of Patients(years)	8 years
Males	105
Females	67

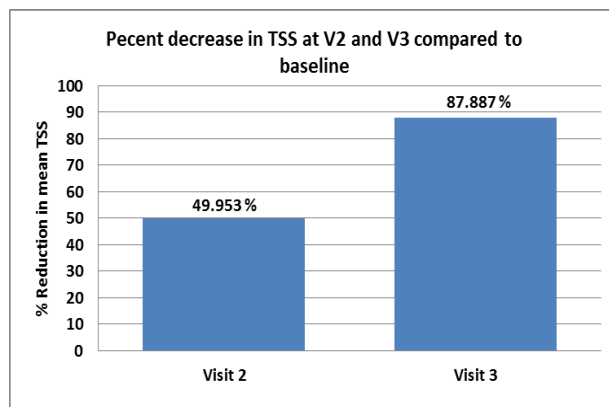
### Efficacy analysis

Mean of Total Symptom Score (TSS) was recorded at all the visits (V1, V2 & V3) and thus the reduction on TSS was calculated. The mean TSS at V0 or the baseline visit was 6.19, which was reduced to 3.09 at V2 or day 3 and further reduced to 0.75 on V3 OR day 5 (Figure 1). The reduction in TSS corresponds with the improvement in general and physical examination of the Patients.



**Figure 1: Mean TSS score at baseline, V1 (day 3) and V2 (day 5).**

At visit 2 and visit 3 there was 3.098 % and 0.75 % decrease in the mean TSS as compared to the baseline respectively as shown in the figure 2.



**Figure 2: Percent reduction in TSS at visit 2 and visit 3 as compared to baseline**

### Safety analysis

The overall incidence of reported study drug related adverse effects were 35 seen in 24 patients. The list of adverse events with the number of episodes is mentioned in Table 3.

**Table 3: List of adverse events, no of episodes and no. of patients experienced adverse events.**

Adverse Events	No. of Episodes	No of patients	% of patients
Sedation and Drowsiness	22	16	9.302 %
Dizziness	13	9	5.232 %
Total	35	24	13.952 %

## DISCUSSION

While considered by many as a trivial disease, allergic rhinitis is a global health problem with considerable economic & societal burdens. About 40 % of the world's population is atopic, and allergic rhinitis is the commonest of preservation of this atopic tendency. In author's knowledge this was the first clinical trial conducted to study the efficacy and safety of a fixed-

dose combination of Phenylephrine Hydrochloride, Chlorpheniramine Maleate, Sodium Citrate and Menthol in reducing the symptoms of Allergic Rhinitis in Indian children. Strong arm of this clinical study is that Total Symptom Score (TSS) is used as a criterion for efficacy reckoning and that this data of TSS is extrapolated to Likert-type symptom scale which is the internationally acknowledged scale for common cold symptom assessment. What makes TSS more impressionable is that it has 11 grades for symptom assessment compared to Likert-type symptom scale which has 4 grades, thus increasing the sensitivity of the study.

At baseline (V1) average TSS was 6.19 which was reduced to 3.09 at visit 2 (reevaluation visit) and was further reduced to 0.75 at visit 3 which was the conclusion visit. So at V2 and V3 there was reduction of 49.95 % and 87.88 % compared to the baseline respectively. So from baseline to visit 3 there was reduction of overall 87.88 % in mean TSS which proves that the study drug combination was efficacious in the symptomatic treatment of allergic rhinitis.

A Cochrane review analysed 32 studies or meta-analysis of 8930 patients for the treatment of Common Cold, construing that antihistamine-analgesic decongestant combinations have some general advantage in adults and older children in treatment of Common Cold.<sup>[11]</sup> Paracetamol, Phenylephrine and Levocetizine are specified in the list provided for antihistamine-analgesic-decongestant.

In the clinical trial duration there were total 35 episodes of adverse events seen in total 24 patients. All the adverse events were of non-serious nature including dizziness, sedation and drowsiness.

Kiran M et al.<sup>[12]</sup> conducted a Phase IV clinical study of a combination of Paracetamol, Phenylephrine and Chlorpheniramine Maleate essentially in the Treatment of Common Cold and allergic rhinitis. Safety and Efficacy of the Combination were gauged in 187 patients. Efficacy assessment was made by reduction in Total Symptom Score and four point Likert-type scales with reduction in TSS from 6.58(baseline) to 3.76(day 3) and 1.78 (day 5) showing 50% reduction in symptom score at all visit. Safety assessment was made by analysing the adverse events during trial the study concluded that the combination of Paracetamol, Phenylephrine and Chlorpheniramine maleate is safe and effective in the treatment of Common Cold and allergic Rhinitis.

Picon et al.<sup>[9]</sup> conducted a Phase III clinical study in Brazilian population with a consolidation of Paracetamol, Phenylephrine and Chlorpheniramine maleate (different strength capsule) in treatment of Common Cold, in Brazilian population. Efficacy and Safety of the combination were evaluated in 146 patients and were compared with placebo. The curtailment of

symptom score in the combination (test) arm was from baseline score of 14.09 to 3.54 at the end of 10 days study period. At the end of 10 days the reduction in placebo arm was from a baseline score of 14.23 to 4.64. The distribution, type and number of adverse events were analogous in both the groups. The study ceased that the combination of Paracetamol, Phenylephrine and Chlorpheniramine maleate is better than placebo in the treatment of Common Cold and flulike syndrome in adults.

Eccles et al.,<sup>[10]</sup> theorize the rationale for bringing together multiple drugs in treatment of common cold to provide relief from multiple symptoms. The treatment of common cold by bringing together various drugs to provide relief from multiple symptoms. Furthermore, it is suggested that there is a lack of proof that multi-symptom relief medicines are innately less safe than single active ingredient medicines. Multi-symptom relief combination products containing several active ingredients that provide an effective, safe, economic and convenient option of treating the multiple symptoms of common cold.

Kiran M et al.<sup>[13]</sup> conducted a Phase IV study evaluating the efficacy and safety of a combination of Paracetamol, Phenylephrine and Levocetizine in Treatment of Common Cold and Allergic rhinitis on 201 patients (adults). Efficacy assessment was made by curtailment in TSS score which was from 6.82(baseline) to 3.63(day 3) and 1.14(day 5). The study showed >50% reduction in symptom score at all visit and patients in majority had complete relief from the symptom. Thus, the combination of Paracetamol, Phenylephrine and Levocetizine is safe and effective in the treatment of Common Cold and Allergic rhinitis was concluded.

A combination of Nasal Decongestants conjoined Anti-Histamines and NSAID is much celebrated in treatment of Common Cold and has ample clinical data including the aforementioned studies.

Condition like allergic rhinitis is essentially afebrile and associated with less pain therefore does not warrant the use of NSAID. Furthermore, NSAID expedite adverse effects like gastritis, vomiting, nausea and rarely even hepatic failure.

## CONCLUSION

A combination of Chlorpheniramine Maleate 1mg and Phenylephrine Hydrochloride 5mg provides symptomatic relief and is safe for the treatment of Allergic Rhinitis in the paediatric population.

## ACKNOWLEDGEMENTS

Somashekar A R, Somashekar A R, Prashant Gade, Yuvaraja Shetty, Sunil Subbiah, Anand Gurav, Praful Shanbhag, Umesh Ch Mishra, S R Panigrahi, Sreenivas

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Common Cold and Allergic Rhinitis: Phase IV Clinical Study. *International Journal of Current Research in Medical Sciences*, 2017; 3(01): 53-59.

## DISCLOSURES

This study was conducted as a part of Pharmacovigilance activity for Sinarest AF Syrup marketed by Centaur Pharmaceuticals Pvt. Ltd. in accordance with Pharmacovigilance Program of India (PvPI).

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