

**AN OPEN-LABELED, MULTICENTRIC, POST-MARKETING SURVEILLANCE (PMS)
TO SUBSTANTIATE THE SAFETY AND EFFICACY OF SINAREST LEVO SYRUP IN
PATIENTS OF COMMON COLD AND ALLERGIC RHINITIS****Dr. Mayuresh Kiran¹, Dr. Pramila Yadav², Mr. Lalit Pawaskar³, Ms. Shruthi George⁴**^{1,3,4}Centaur Pharmaceuticals Pvt. Ltd., Mumbai.²Professor, Pad. Dr. D. Y. Patil Medical College and Hospital, Navi Mumbai.***Corresponding Author: Dr. Pramila Yadav**

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ABSTRACT

Introduction: The common cold is the most frequently encountered disease in medical practice. Patients continue to use medications that produce symptomatic relief because of the epidemiological relevance and the intensity of symptoms of flu-like syndromes and the common cold. This is a Phase IV study evaluated the efficacy and safety of Sinarest Levo Syrup in treatment of common cold and allergic rhinitis. **Methodology:** Of 172 enrolled, 152 patients completed the study. Efficacy assessment was made by reduction in TSS and four point Likert-type scales. Safety assessment was made by analyzing the adverse events during trial. **Results:** there was reduction in TSS from 7.65 (baseline) to 3.61 (day 3) and 1.28 (day 5). One point reduction in Likert-type symptom scale from Moderate to Mild took just 3 days. Nearly all the patients had >50% reduction in symptom score at all visit and majority of patients had complete relief from the symptom. 27 episodes of adverse events occurred and were of mild intensity. **Conclusion:** Sinarest Levo Syrup is safe and effective in the treatment of common cold and allergic rhinitis.

KEYWORDS: Phenylephrine, Levocetirizine, Common Cold, Allergic Rhinitis, Total Symptom Score (TSS), Likert-type symptom severity scale.

INTRODUCTION AND BACKGROUND

Common cold is a self-limiting disease but is responsible for significant absenteeism in schools and job. Providing symptom control would reduce the number of days missed due to common cold, hence the treatment is directed towards symptom control only.^[1]

When the aetiology is presumably bacterial, treatment is based on the use of antibiotics and medication for symptomatic relief. However, the most common clinical entities, the common cold and the flu-like syndrome, have a viral aetiology, for which symptomatic treatment remains, in most cases, the standard recommendation. This syndrome affects the upper airways, sometimes in association with low-grade fever and systemic symptoms and usually presents with at least two of the following symptoms: cough, dysphonia, throat discomfort, sore throat, nasal congestion, rhinorrhoea, sneezing, headaches, myalgia and fever.^[2,3] Symptoms usually peak at 2 to 3 days and have a mean duration of 7 to 10 days.^[4]

Levocetirizine is one of the most often recommended and used 2nd generation antihistaminic agents. The primary action of Levocetirizine 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 Levocetirizine would be translated to its anti-allergic and anti-inflammatory action in the nasal mucosa. Levocetirizine being a 2nd generation antihistaminic, has lower potential to cause sedation and drowsiness as adverse effects. Levocetirizine is thus useful to control the symptoms of common cold like - Running Nose and Sneezing.^[7]

A combination of Levocetirizine and phenylephrine is often used to treat common cold and allergic rhinitis. Cochrane has reviewed the combination of antipyretic, decongestant and antihistaminics,^[8] however there is dearth of clinical data available for this combination hence a Phase IV (Post-Marketing Surveillance) study was conducted to document the efficacy and safety of the combination of Phenylephrine and Levocetirizine in the treatment of common cold and allergic rhinitis.

METHODOLOGY

This Phase IV clinical study was conducted at 12 Centers, 3 centers at each region (North, South, East, West or Central, from October 2016 to December 2016. A total of 181 enrolled, 172 patients were recruited for the study, out of which all the 152 patients completed the study. 20 patients were lost to follow-up.

Inclusion and Exclusion Criteria

This study included patients of both the gender having age between ages 6 to 20 years. Patients with confirmed diagnosis of common cold or allergic rhinitis (having 4 out of the 9 symptoms of headache, fever, bodyache, nasal congestion, rhinorrhea, sneezing, sore throat, dysphonia and malaise) present for not more than 48 hours were included in the study. Only the patients who would strictly adhere to the protocol were recruited for the study.

Study Intervention

Patients were given 50 ml free sample bottle of Sinarest Levo Syrup and advised to be taken the dose as per the following table.

Age	Weight	Dose of Sinarest Levo Syrup
Children above 12 years	30 to 60 kg	5 to 10 ml twice daily
Children 6-11 years	16.5 to 51.7 kg	2.5 to 5 ml twice daily

Study procedure

The study duration was decided to be 5 days. Patients of common cold and allergic rhinitis satisfying the inclusion and exclusion criteria were recruited for the study. A detailed medical history was taken and physical examination (including the vital signs, systemic and general examination) was conducted by the investigators. Patients were dispensed Sinarest Levo Syrup of the study drug by the investigator. Patients were asked to maintain a symptoms diary and note any adverse events occurring during the study duration.

Three visits were planned for the patients recruited in this study – V0 (baseline visit) on day 1, V1 (reevaluation visit) on day 3 and V2 (conclusion visit) on day 5. Total symptom score and adverse events occurring were noted during each visit along with medical history and physical examination. Investigators were asked to discontinue the study drug in case of severe adverse event and with discretion, clinical experience in case of mild to moderate adverse events.

Concomitant therapy

No Pharmacological intervention and medication including antibiotics, topical decongestants (sprays/drops and aromatic oils), multi-vitamins and multi-minerals were allowed during the study duration, other than study drug.

Non-Pharmacological interventions like steam inhalation and drinking of warm/hot water at regular intervals 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 – 4 on TSS), Moderate (5 – 8 on TSS) and Severe (9 – 10 on TSS).

The secondary assessment was number of patients having no symptoms (0 on TSS) on day 5 and number of patients having more than 50% reduction in TSS.

Safety assessment

Patients were asked for any adverse event and the same if present was noted in the case record form during each post-dose visit. These adverse events were classified into serious adverse events and non-serious adverse events. Naranjo's scale of probability was used to classify the adverse event as drug related or non-drug related. Adverse events were followed up by the investigators till their resolution.

Regulatory matters

The study drug in combination has been approved for manufacturing and marketing (with minor change in composition). The said 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.

All the patients participating in this study read and signed the informed consent form, voluntarily. The protocol, case record form, informed consent form, investigators undertaking, investigators CV, investigators medical registration certificates (including post-graduation certificates) and ethics committee registration certificates were submitted to the office of Drug Controller General of India (DCGI), Central Drugs Standard Control Organization (CDSCO) and are registered under ref. no. 29394.

RESULTS

A total of 172 patients were recruited at centers across India, 152 patients completed the study and were analyzed. Other demographic characteristics are in Table.1.

Table 1: Demographic Characteristics of the patients recruited for the study.

Mean Age of Patients (years)	13.5
Males	88 (51.75%)
Females	84 (48.25%)
Mean BMI (kg/m ²)	20.71
Patients with Common Cold / Allergic Rhinitis	135/37

Efficacy analysis

Mean of Total Symptom Score (TSS) was recorded at all the visits (V0, V1 & V2) and thus the reduction on TSS was calculated. The mean TSS at V0 or the baseline visit was 7.65, which was reduced to 3.61 at V1 or day 3 and further reduced to 1.284 on V2 or day 5 (Figure 1). The

reduction in TSS corresponded with the improvement in general and physical examination of the patients.

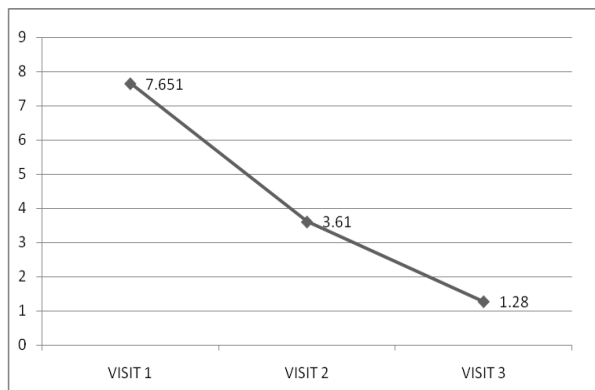


Figure 1: Reduction in TSS at each visit.

Extrapolating the data to the Likert-type symptom scale, at V0 or baseline the mean TSS corresponds to Moderate symptoms which was reduced to Mild in V2 or Day 5.

Out of 152 patients, 63 patients had a TSS of 0 i.e. no symptoms on Likert-type symptom scale and another 32 had the TSS of 1 (Figure 2) at the end of 5 days.

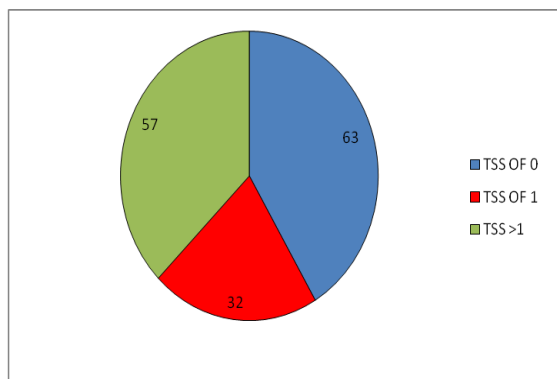


Figure 2: No. of Patients with TSS Score.

More than 50% reduction in TSS was seen in 132 patients from V0 to V1 and in 152 patients from V1 to V2.

Safety analysis

The overall incidence of reported study drug related adverse effects was 34 seen in 21 patients. The list of adverse events with the number of episodes is mentioned in Table 2.

Table 2: Adverse Events and their Incidence.

Adverse Events	No. of Episodes
Sedation and Drowsiness	21
Hyperacidity	3
Nausea	3
Dizziness	6
Palpitation	1
Total	34

Majority of adverse effects were study drug related with Sedation and Drowsiness.

DISCUSSION

Common cold is a self-limiting disease but is responsible for significant absenteeism in schools and job. Providing symptom control would reduce the number of days missed due to common cold, hence the treatment is directed towards symptom control only.^[9]

In author’s knowledge, this is the first clinical study of the combination of Phenylephrine and Levocetirizine in treatment of common cold and allergic rhinitis. Strength of this clinical study is that Total Symptom Score (TSS) is used as the parameter for efficacy assessment and extrapolated to Likert-type symptom scale. TSS has 11 grades for symptom assessment compared to 4 with Likert-type symptom scale, making TSS more sensitive. The data of TSS is extrapolated to Likert-type symptom scale which is internationally accepted scale for common cold symptom assessment.

There was a reduction in Total Symptom Score (TSS) in all the patients in this Phase IV Post Marketing Surveillance Study. The TSS reduced from 7.65 to 3.61 in 3 first days and from 3.61 to 1.28 in the next 2 days. The overall reduction in TSS in 5 days was 83.28%. One point reduction in Likert-type symptom scale from Moderate to Mild took just 3 days with the study drug. Majority of patients had no (TSS score of 0) to very less (TSS score of 1) at the end of 5 study days. Nearly all the patient had more than 50% reductions in symptoms at every visit.

A total of 34 (22.14%) adverse events were related to study drug. Sedation and drowsiness was a major adverse effect which can be contributed to the antihistaminic Levocetirizine present in the combination. Levocetirizine being a 2nd generation antihistaminic, it still produces sedation and drowsiness in some patients. The vital signs (Blood Pressure, Respiratory rate and Pulse rate) showed no significant change from the baseline readings which are particularly important as Phenylephrine, a vasoconstrictor is a component of the study drug.

Picon et al.,^[5] conducted a Phase III clinical study of a combination of an antipyretic, Phenylephrine and Chlorpheniramine maleate (different antihistaminic than the study drug in this trial) in treatment of common cold, in Brazilian population.^[8] Efficacy and Safety of the combination were evaluated in 146 patients and were compared with placebo. The reduction 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. The reduction in placebo arm was from a baseline score of 14.23 to 4.64 at the end of 10 days. The number, type and distribution of adverse events were similar in both the groups. The study concluded that the combination of Phenylephrine and Chlorpheniramine maleate is better

than placebo in the treatment of common cold and flu-like syndrome in adults.

A Cochrane review^[6] analysed 32 studies or meta-analysis of 8930 patients for the treatment of common cold, inferring that antihistamine-analgesic-decongestant combinations have some general benefit in adults and older children in treatment of common cold. Phenylephrine and Levocetirizine are mentioned in the list provided for decongestant and antihistamine.

The symptomatic treatment of the common cold has been evaluated in Cochrane meta-analyses. The first included 32 studies with a total of 8930 patients and investigated the administration of antihistamines in the common cold. Results showed that monotherapy did not improve symptoms in either children or adults.^[11] The combined use of antihistamines and decongestants may alleviate symptoms in adults, but results are heterogeneous.^[10,11]

Another meta-analysis investigated the use of nasal decongestants in the common cold in 286 adults, and found no benefit for the relief of nasal congestion.^[12] Another recent meta-analysis⁷ suggests that a triple combination of antihistamine, decongestant and analgesic provided some general benefit in adults and older children.

Eccles *et al.*,^[7] suggests the rationale for combining multiple drugs in treatment of common cold to provide relief from multiple symptoms. Further it suggests, there is no evidence that multi-symptom relief medicines are inherently less safe than single-active ingredient medicines. Multi-symptom relief combination products containing several active ingredients provide an effective, safe, economic and convenient option of treating the multiple symptoms of common cold.

The limitation of the study was common cold being a self-limiting disease, may resolve spontaneously. The cause for reduction in symptoms may not be solely attributed to the study drug. We have tried to minimize this limitation by keeping the study duration for 5 days as opposed to earlier study (with Chlorpheniramine as antihistaminic) where it was 10 days. Several papers suggest common cold resolves in about 7 days,^[9] so the benefit offered on day 5 would be majorly due to the study drug.

CONCLUSION

A combination of Sinarest Levo Syrup, an FDC of Phenylephrine Hydrochloride 10 mg + Levocetirizine 2.5 mg provides optimum symptomatic relief and is safe for the treatment of common cold.

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Disclosure

Dr. Mayuresh Kiran, principal investigator of this study is an employee of Centaur Pharmaceuticals Pvt. Ltd. This study was conducted as a part of Sinarest Levo Syrup Pharmacovigilance activity for manufactured and marketed by Centaur Pharmaceuticals Pvt. Ltd. in accordance with Pharmacovigilance Program of India (PvPI).

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