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Efficacy and Safety for the combination of Montelukast and Levocetirizine in patients of allergic rhinitis: Post Marketing Surveillance study

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Abstract

Introduction: When patients exposes to allergen, histamine gets released from mast cells due to hypersensitivity towards allergens. Antihistamines can be used to treat allergic rhinitis as it blocks histamine receptors from nerve terminals that produces relief from allergic rhinitis. As monotherapy of antihistamines cannot reduce all the symptoms of allergic rhinitis like nasal congestion or inflammation, hence antihistamines can be combined with leukotriene receptor antagonist like Montelukast which inhibits leukotriene, allows the patient to breathe normally and reduces swelling. This post marketing surveillance study was conducted to evaluate the efficacy and safety for allergic rhinitis patients for the fixed dose combination of Montelukast 10 mg and Levocetirizine 5 mg per tablet (investigational product) in Indian Population. **Method**: Out of 180 enrolled trial subjects, 164 trial subjects completed the study. Efficacy was evaluated by decrease in total symptom score (TSS) where trial subjects were asked to rate the symptoms on 11 point scale ranging from 0 (no symptoms) to 10 (severe symptoms) which was further extrapolated to four-point Likert-type-symptom-severity scale. Safety was analysed by the reported adverse events. **Results**: Reduction in TSS was from 6.60 (day 1) to 3.28 (day 5) to 0.56 (day 10). Nearly all the trial subjects had more than 50% reduction in TSS at all visits and the majority of trial subjects had complete relief from the symptoms. Also, no serious or unexpected adverse event was observed during study. **Conclusion**: The investigational product was found to be efficacious and safe for the treatment of allergic rhinitis.

Keywords: Allergic rhinitis, Montelukast, Levocetirizine, Efficacy, Safety

INTRODUCTION

Allergic rhinitis, also known as hay fever is a form of nasal inflammation caused by the action of immune system to allergens present in the air to which the patient has been exposed. Allergic rhinitis (AR) is characterized by nasal swelling, rhinorrhoea, nasal/ocular pruritus, sneezing and postnasal discharge, which may be recurrent or chronic. These symptoms are caused by allergen-induced IgE-mediated allergic inflammation in the nasal mucosa. When allergens get exposed to nasal mucosa of the patients, the cell bound immunoglobulin E get cross linked due to mast cells which leads

to allergic rhinitis. An early phase response also develops due to cysteine leukotriene that results into sneezing, postnasal discharge, congestion, inflammation etc.[1] Allergic rhinitis is a common condition that places a significant burden on both individuals and society.[2] Symptom onset is often within minutes following exposure and they can affect sleep, the ability to work and the ability to concentrate at work or school. Allergens those causes reactions may be seasonal or persistent. Pollen grains and mold etc. are seasonal allergens, while dust bugs, pet dander and rodents etc are perennial allergens.[3,4] In United States, the most common diagnosis identified in the 2000 Otolaryngology Workforce survey was allergic rhinitis (AR), which was one of the most common conditions seen by otolaryngologists.[2] Its occurrence and poor control are of worldwide concern.[5] The guidelines for AR treatment present a step-by-step approach that combines allergen (trigger) avoidance, medical management and immunotherapy in serious, extreme cases of AR.[6] The type and severity of individual patient symptoms should direct drug treatment for allergic rhinitis, which should relieve nasal inflammation, sneezing and rhinorrhoea during the day and night, as well as physician preferences. As allergens induced symptoms like pruritus, sneezing etc are occurred because of release of histamine from mast cells can be treated by antihistamines which blocks the release of histamines from nasal mucosa. Monotherapy of antihistamines is insufficient to treat all the symptoms of AR. Symptoms like nasal swelling, nasal congestion due to viscous mucus can be severe which develops due to cysteine leukotriene receptor. Hence to reduce those symptoms, Leukotriene receptor antagonists like Montelukast can be added with antihistamines to reduce airway swelling, nasal congestion etc.[7] So the combination of Levocetirizine and Montelukast can be used for the medical management of allergic rhinitis.

Levocetirizine is a selective, active oral histamine H1R antagonist that is indicated for the therapeutic treatment of allergic rhinitis in adults and children over the age of two years. It acts as an inverse agonist, lowers the activity of histamine H1 receptors by which it inhibits the release of histamine and reduces the symptoms of allergic rhinitis.[8] Adults and children of age 12 years and older than 12 years can take 5 mg once a day in the evening. Children aged 6 to 11 years old can take 2.5 mg once a day in the evening. Levocetirizine have a higher affinity for the histamine H1 receptor than Cetirizine (2-fold; $p<0.01$) or Dextrocetirizine.[9] As Levocetirizine is a first line agent which helps to cure primary symptoms of AR which mainly excludes nasal swelling and nasal congestion. Hence Montelukast, a Leukotriene receptor antagonists can be combined with Levocetirizine to treat allergic rhinitis.

Montelukast can be used for the treatment of allergic rhinitis and asthma. Montelukast is an effective, selective and orally active leukotriene receptor antagonist that acts by blocking the cysteinyl leukotrienes D4 (LTD4) at cysteinyl leukotriene receptor that prevents airway edema with contraction of smooth muscles which increases the secretion of thick and viscous mucus. It is prescribed for prophylaxis and long-term care in patients aged 2 years and older. Montelukast inhibits the cysteinyl leukotriene receptor 1 and is a selective leukotriene receptor antagonist.[10,11]

So according to the above mentioned information the combination of Montelukast with antihistamines can provide reduction of day and night time allergic rhinitis

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symptoms.[12] So this post marketing surveillance study was conducted to determine and document the efficacy and safety of Montelukast in combination with Levocetirizine as a treatment for allergic rhinitis in Indian population.

MATERIALS & METHODS

This post marketing surveillance study was conducted at 12 clinical trial sites across India. The study was conducted with ENT speciality investigators. A total of 180 trial subjects were recruited for the study out of which 164 trial subjects completed the study. For the post marketing surveillance study duration of 10 days, trial subjects were requested to visit the clinical trial site on day 5 and day 10 considering the baseline visit as day 1. Visit of the trial subject on day 1 was named as baseline visit or visit 1, on day 5 was named as re-evaluation visit or visit 2 and on day 10 was named as conclusion visit or visit 3.

Inclusion and Exclusion Criteria:

This post Marketing Surveillance study involved patients of both sexes including male and female. Patients having age above 18 and below 65 years with confirmed diagnosis of allergic rhinitis who were ready to strictly adhere to the study procedure were recruited for the study.

Patients hypersensitive to investigational product were excluded. Also, pregnant or lactating women or patients who could not adhere to the study, like psychologically or mentally ill patients were excluded from study.

Investigational product:

The Investigational product used for the post marketing surveillance study was the fixed dose combination of Montelukast 10 mg and Levocetirizine 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 the trial subjects at no cost by the investigator.

Study design

Total 180 trial subjects were enrolled for post marketing surveillance study at 12 clinical trial sites across India as it was a multicentric post marketing surveillance study. Post marketing surveillance study was of non-randomized and non-comparative nature. The investigational product and its composition was known to all trial subjects and clinical research staff from the side of sponsor and investigators.

Study Procedure

Patients with the confirmed diagnosis of allergic rhinitis who met the inclusion and exclusion criteria were recruited for the study by the investigator. A detailed medical history was obtained from all enrolled trial subjects, which was followed by a thorough clinical examination. All the trial subjects were given 10 tablets of investigational products and were asked to take in the dose of 1 tablet for a day for a study period of 10 days. Investigator instructed trial subjects to keep a diary of daily symptoms to detect the adverse events if any. Three visits were planned for the trial subjects to determine efficacy and safety as baseline visit/ visit 1 on day 1 (V1), re-evaluation visit/ visit 2 on day 5 (V2) and conclusion visit/ visit 3 on day 10 (V3) on which all the trial subjects were asked to visit the clinical trial site.

Concomitant therapy

In the study duration of 10 days, all the trial subjects were instructed not take any pharmacological intervention other than

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investigational product for the treatment of allergic rhinitis but at the same time non-pharmacological intervention like steam inhalation or drinking of hot water etc. were permitted.

Efficacy Assessment

Efficacy assessment was done by calculating the decrease in the total symptom score (TSS). Trial subjects were asked to rate all the symptoms of allergic rhinitis 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 graded Likert-type symptom severity scale as no symptoms for the TSS value 0, mild intensity symptom for the TSS value 1-3, moderate intensity symptom for the TSS value 4-6 and severe intensity symptom for the TSS value 7-10.

Safety assessment

Trial subjects were asked by the investigators to report any adverse events, if experienced. These adverse events were categorized into serious and non-serious adverse events and causality assessment for the adverse events was done to check the causal relationship between the adverse event and the investigational product.

Regulatory Matters

The Investigational product was approved for manufacturing and marketing in India by the concern regulatory authorities. In India the Investigational product is categorized under the category of schedule H drug i.e., to be sold only in the presence of licensed medical practitioners' prescription.

RESULTS

Twelve ENT speciality clinical trial sites across India were selected for this study. Total 180 trial subjects were recruited for the study out of which 164 trial subjects completed the study as per the study procedure. On visit 1 the mean TSS was 6.60, at visit 2 the mean TSS was reduced to 3.28 which further reduced to 0.56 on visit 3 which was the conclusion visit. The mean TSS score at each visit is graphically presented in Figure 1

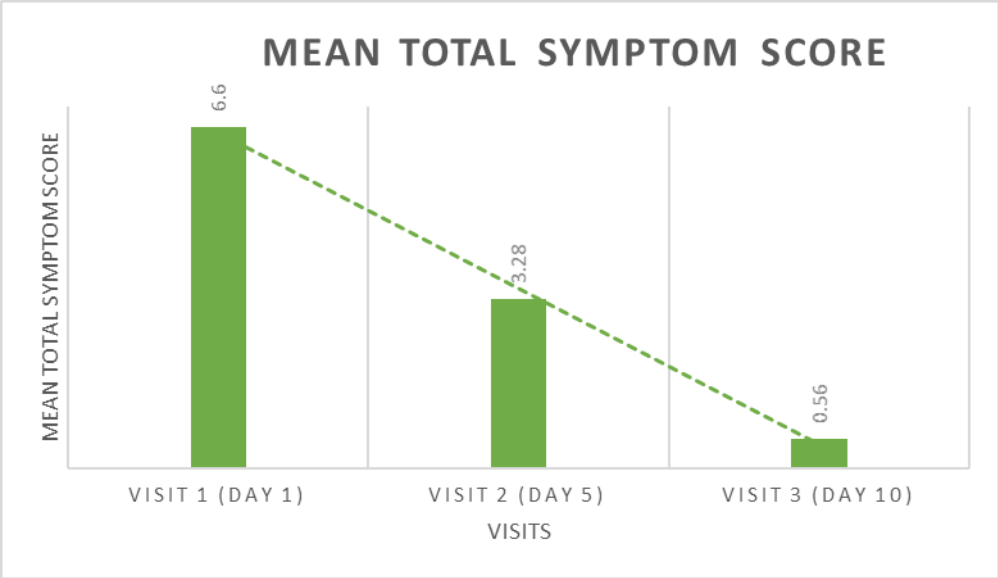

Fig.1: Mean TSS at visit 1, 2 and 3

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The percentage decrease in TSS at visits 2 and 3 as compared to visit 1 was also calculated; at visits 2 (day 5) and 3 (day 10), the mean TSS was reduced by 50.32 % and 91.50 % respectively which is graphically presented in figure 2.

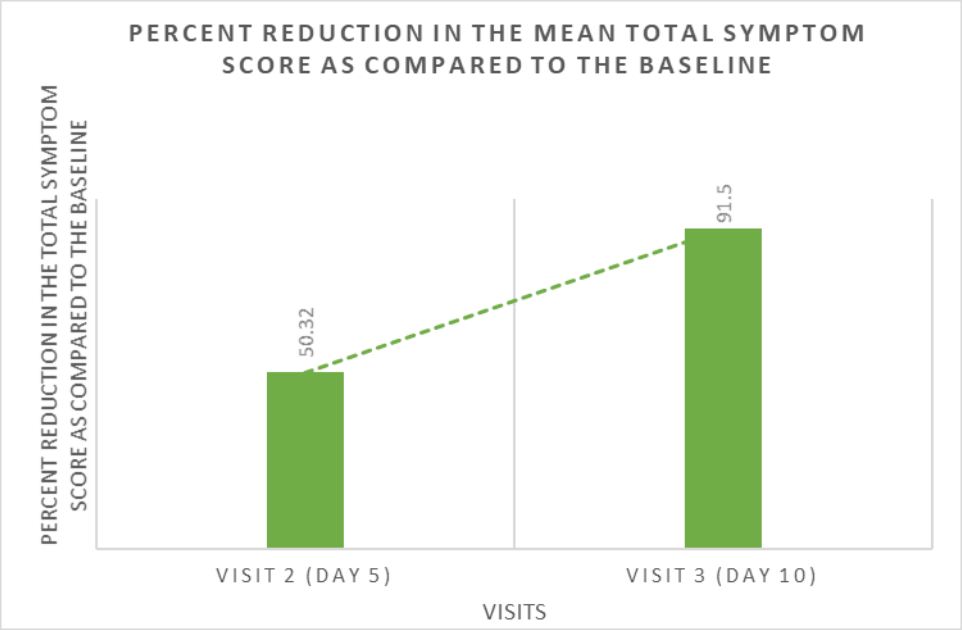

Fig 2: Percent Reduction in mean TSS at visit 2 and 3 as compared to baseline

The data was extrapolated to a Likert-type symptom severity Scale, which was used to monitor the severity of the symptoms at each visit.

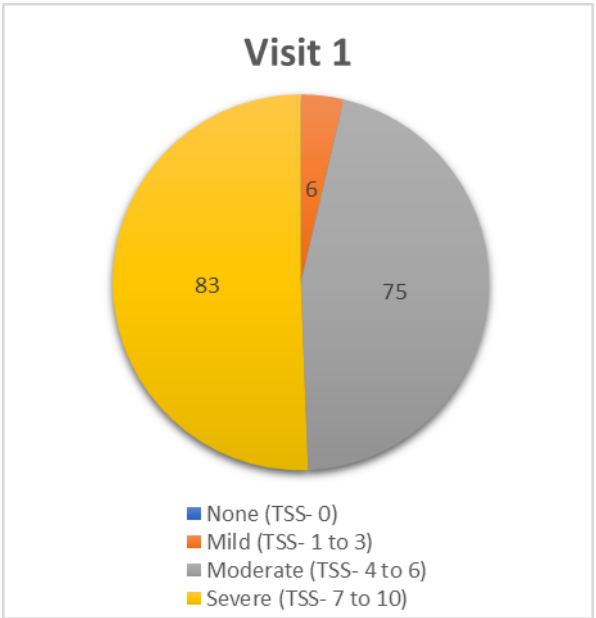

Fig. 3: No of trial subjects of no, mild, moderate and severe intensity symptoms as per the Likert-type symptom severity scale at visit 1.

On baseline visit, day 1, 83 trial subjects had severe intensity symptoms of TSS 7-10, 75 trial subjects had moderate intensity symptoms and 6 trial subjects had mild intensity symptoms of

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TSS 4-6 and 1-3 respectively. 50.60 % of trial subjects had severe intensity symptoms, 45.73% clinical trial subjects had moderate intensity symptoms and 3.65% trial subjects had mild intensity symptoms.

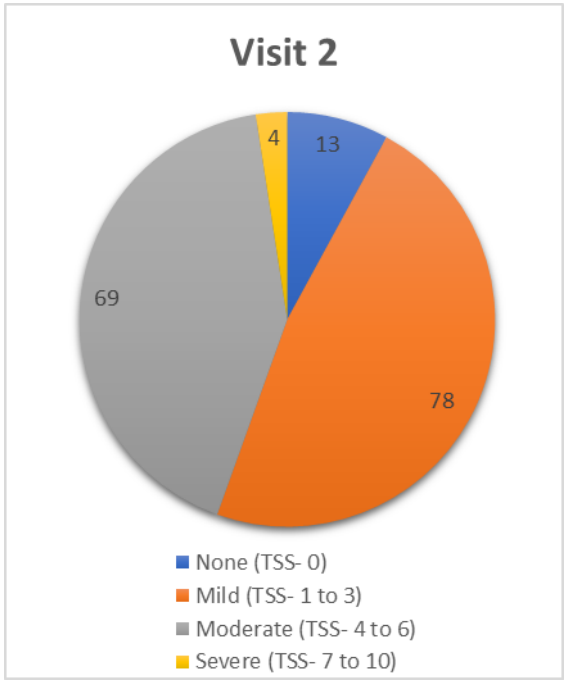

Fig. 4: No of trial subjects of no, mild, moderate and severe intensity symptoms as per the Likert-type symptom severity scale at visit 2.

Trial subjects were re-evaluated on visit 2, i.e., day 5, 78 trial subjects had TSS score 1-3 i.e. 47.56% trial subjects had mild intensity symptoms. 69 trial subjects had TSS score 4-6i.e.42.07% trial subjects had moderate intensity symptoms. 13 trial subjects had no symptom of allergic rhinitis; TSS 0 i.e. they were completely cured whereas only 4 trial subjects had a TSS score of 7-10. So at visit 2, 7.92% of trial subjects were completely recovered and only 2.43% of trial subjects had severe intensity symptoms.

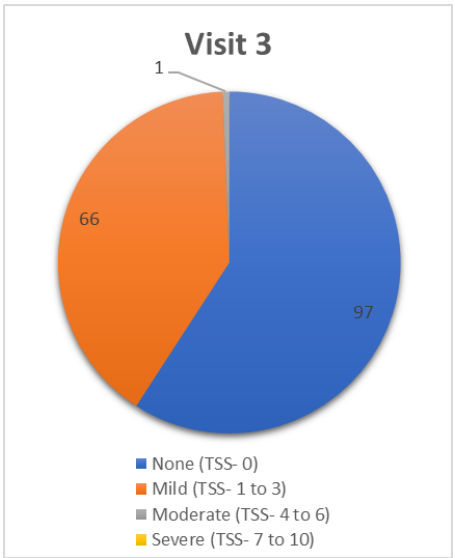

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Fig. 5 No of trial subjects of no, mild and moderate intensity symptoms as per the Likert-type symptom severity scale at visit 3.

At visit 3, not a single trial subject out of 164 had TSS score of 7-10 or severe intensity symptoms of allergic rhinitis. 97 trial subjects had TSS score 0 that showed 59.14 % trial subjects were completely recovered. 66 trial subjects had TSS score 1-3 at the final visit which showed 40.24 % trial subjects had mild intensity symptoms. Only 1 clinical trial subject had a TSS score of 4-6 which showed that 0.60 % trial subjects had moderate intensity symptoms of allergic rhinitis.

Safety Assessment:

Total 8 trial subjects reported 12 episodes of adverse events which are tabulated below in table no 1.

Table 1: List of adverse events, number of episodes and patients.

Adverse Event	Number of episodes	Number of trial subjects
Nausea	4	2
Sedation and drowsiness	7	5
Dryness of mouth	1	1

DISCUSSION

Allergic rhinitis is the most common allergic condition in the general population which causes inflammation of the upper airway mucous membranes. It begins with nasal congestion, which causes breathing through mouth instead of nose, discomfort sleep, awakening sleep at an odd time and it ends with snoring; it progresses to nasal congestion on awakening, results in daytime hallucinations, disturbed behaviour, bad concentration and reduced productivity at school and work. If treatment is not administered, a chronic state of nasal inflammation with nasal obstruction may develop over time, leading to sinusitis, otitis media with effusion, nasal polyps and asthma.[13] For the treatment during one of the previously conducted clinical trial, antihistamines were given as a monotherapy and it was concluded that antihistamines as a monotherapy does not relieves nasal inflammation, rhinorrhoea and sneezing. Leukotriene receptor inhibitors can be added with antihistamines to improve daytime as well as nigh time symptomatic relief. This post marketing surveillance study for the combination of Levocetirizine and Montelukast was conducted to evaluate the efficacy and safety in the patients of allergic rhinitis. For the study, 180 trial subjects were recruited out of which 164 trial subjects completed the study. TSS was used as an efficacy assessment criteria for efficacy evaluation and was extrapolated to the Likert-type symptom severity scale, which is the internationally recognised scale for assessing symptoms. Mean TSS reduced from 6.60 to 3.28 from visit 1 (baseline) to visit 2 which was on day 5 i.e., 50.32 % reduction compared to baseline, and from 3.28 to 0.56 in the next 5 days which was a reduction of 91.50 % as compared to the baseline. The overall reduction in TSS in 10 days was of 91.50 % in all the trial subjects. According to the efficacy assessment data, the fixed-dose combination was found to be efficacious for the therapeutic treatment of allergic rhinitis. Also, only 8 trial subjects reported 12 episodes of adverse events and all of them were of non-serious in nature and mild in intensity. Also, after the benefit risk assessment, the study combination was found to be beneficial to use for the treatment of allergic rhinitis. Below we have discussed

some of the similar kind of studies conducted before.

A randomised, double-blind, placebo-controlled crossover study was conducted by Górska- Ciebiada M et al. to analyse the results of 6 weeks of treatment of chronic AR with Levocetirizine or Montelukast alone or in combination. Patients were randomly allocated to Montelukast or Levocetirizine or both. Washout intervals of two weeks were used to differentiate the treatment periods. Nasal lavage was used to measure eosinophil cationic protein levels. Before treatment, the mean +/- SD nasal symptom score was 7.95 +/- 0.68, 3.02 +/- 0.64 after Levocetirizine, 3.44 +/- 0.55 after Montelukast and 2.14 +/- 0.39 after the combination of Montelukast and Levocetirizine. The combination treatment resulted in the greater improvement in nasal symptoms in comparison to another monotherapy. The combined use of Montelukast and Levocetirizine resulted in greater reduction in eosinophil cationic protein than either agent used alone. So at the end of the study, it was concluded that, for the treatment of chronic AR, combination of Montelukast and Levocetirizine was more effective as compared to monotherapy of Levocetirizine or Montelukast.[12]

Gupta et al conducted prospective, randomized, open label, parallel group study. The investigation was conducted out at the out-patient department of Gian Sagar Medical College and Hospital in District Patiala from July 2008 to April 2010. Adults of 18-60 years old of both sexes, with a clinical history of perennial allergic rhinitis for at least 1 year, who were non-smokers, could read and understand the protocol (middle level education) and were able to give written consent, were eligible for the study. Patients were randomly assigned to receive Levocetirizine 5 mg and Montelukast 10 mg in the treatment group or Levocetirizine 5 mg in the control group once daily at bedtime for 6 weeks during the randomization phase using a random number table. Clinic visits were scheduled at screening (visit 1), after a 14-day run-in duration (visit 2) and every 2 weeks of care for a total of 6 weeks (visit 3, 4, 5). The primary outcome measure was the mean change of the total daytime nasal symptom scores (PDTS), defined as the average score of four daytime nasal symptoms. Night-time nasal symptom scores (PNTS), daytime eye symptom scores (PES), composite symptom scores (PCS) (average score of day and nighttime nasal symptom score) were used to determine secondary outcome. In the Montelukast and Levocetirizine group, the change in total daytime nasal symptom, composite symptoms and nighttime nasal symptom scores were substantially greater than in the Levocetirizine alone group ($p<0.05$). In both classes, the improvement in daytime eye symptom scores was similar but not statistically significant ($p=0.94$). Compared to the monotherapy of Levocetirizine, the combination of Levocetirizine and Montelukast was more efficacious reducing daytime, night time, composite, and daytime eye symptom ratings.[14]

CONCLUSION

The fixed dose combination of Montelukast 10 mg and Levocetirizine 5 mg per tablet was found to be efficacious as well as safe for the treatment of allergic rhinitis.

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Disclosure

This study was conducted as a part of Pharmacovigilance activity for an Investigational product whose brand name is MtNL Tablet which is a fixed dose combination of Montelukast sodium equivalent to Montelukast 10 mg and Levocetirizine dihydrochloride 5 mg per tablet which is a product of Centaur Pharmaceuticals Pvt. Ltd.

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Montelukast 10 mg and Levocetirizine dihydrochloride 5 mg per tablet which is available in Indian market under the brand name of MtNL, Conflict of Interest: None declared