

**Safety and Efficacy of a topical combination of Neomycin, Clotrimazole, Beclomethasone and Lignocaine for management of Ear Infections: Phase IV Study****Dr. Mayuresh Kiran<sup>1</sup>, Ms. Shruthi George<sup>2</sup>, Mr. Lalit Pawaskar<sup>3</sup>**<sup>1</sup>General Manager, Medical Services, Centaur Pharmaceuticals Pvt. Ltd.<sup>2</sup>Officer, Medical Services, Centaur Pharmaceuticals Pvt. Ltd.<sup>3</sup>Research Associate, Pharmacovigilance, Centaur Pharmaceuticals Pvt. Ltd.**Correspondence Author: Dr. Mayuresh Kiran**, Address: Centaur Pharmaceuticals Pvt. Ltd., Centaur House, Near Grand Hyatt, Vakola, Santacruz (East), Mumbai – 400055.**Conflicts of interest:** None to Declare**Abstract**

**Introduction:** Otitis or ear infection is very common in developing countries like India and is often due mixed pathogens. Multi-drug therapy is often used in the treatment of Otitis. We studied the safety and efficacy of one such combination of anti-bacterial (Neomycin), anti-fungal (Clotrimazole), steroid (Beclomethasone) and local anaesthetic (Lignocaine) in the treatment of middle and external ear infections.

**Methodology:** Total 196 patients were enrolled out of which 160 patients completed the study. Efficacy assessment was made by reduction in Total Symptom Score (TSS) of ear pain, ear discharge and ear itching related to Otitis media with perforation and Otitis Externa. Safety assessment was made by analysing the adverse events through the study.

**Results:** Reduction in mean TSS score was done from 5.73(baseline) to 2.19(day 3) to 0.21(day 5) of ear pain, from 5.63 (baseline) to 1.73 (day 3) to 0.15(day 5) of ear discharge and from 4.84 (baseline) to 1.48(day 3) to 0.13(day 5) of ear itching. Nearly all the patients had >50% reduction in their TSS at all visits in all the parameters. 21 episodes of adverse events occurred and all of them were of mild intensity.

**Conclusion:** A combination of Neomycin, Clotrimazole, Beclomethasone Dipropionate and Lignocaine is safe and effective in the treatment of mixed infection of the external and middle ear (with perforation).

**Keywords:** Neomycin, Clotrimazole, Beclomethasone, Lignocaine, Otitis Media and Otitis Externa

**Introduction**

Ear infection is an umbrella term for a group of complex infective and inflammatory conditions affecting various parts of the ear. Though the ear seems very simple, it is one of the most complex organs in the body. The external part of the ear is only “the edge of the iceberg”.

Otitis Externa (OE) colloquially known as *swimmer's ear* for its preponderance in children and adults who have a history of prolonged water exposure<sup>1</sup>. It is defined as a diffuse inflammation of the external ear canal, which involve the external auditory canal, pinna or tympanic membrane(TM)<sup>2</sup>. Since agents of infection are mostly bacteria, fungi or viruses, it can be accompanied by inflammation, pain and swelling of the skin lining the auditory canal. Otitis Media (OM) or inflammation of the middle ear is one of the complicating sequelae of upper

respiratory tract infections (URTI) and continues to be a substantial public health problem around the world. WHO alleged that 28 thousand deaths every year are attributable to aggravations of OM<sup>3</sup>. Otitis media is a rapid infection of middle ear due to bacterial or fungal invasion. The infection frequently leads to negative pressure and purulent effusion in the middle ear<sup>4</sup>. Complications of OM would be TM rupture (hearing loss), loss of bony tissues in the middle ear, mastoiditis which may lead to external skin fistula or result in meningitis/encephalitis<sup>5</sup>.

American Academy of Otolaryngology published a clinical guideline suggesting the use of topical antimicrobials as first-line treatment in patients having ear infection<sup>6</sup>. External or middle ear infections are often of mixed origins with multiple pathogens invading the ear as many commensals including bacteria and fungi reside in the ear. Initially the infection embarks with individual organism but due to tenacious inflammation other organisms may start infecting as well. In the recent years, opportunistic infections are gaining greater importance due to huge number of immunocompromised patients<sup>7</sup>. When the immunity is reduced, the opportunistic organisms cause superinfections of mixed microbial origins. Ear infections caused by such mixed pathogens increase the morbidity and mortality associated with the ear infections. Thus the therapy with antimicrobials should cover these multiple pathogens which cause these infections, warranting the use of antibacterial with antifungal together<sup>4</sup>.

Neomycin, an aminoglycoside is active against most gram negative bacilli and some gram-positive cocci. Neomycin exerts antibacterial action by inhibition of protein synthesis. Neomycin is often used in the ear for the treatment of ear infection. Clotrimazole 1% solution is used to treat fungal infections in the ear. Clotrimazole

works to kill individual Candida or fungal cells by altering the permeability of the fungal cell wall<sup>8</sup>. A combination of Neomycin with that of Clotrimazole would cover most of the mixed pathogens including the bacteria and fungi infecting the ear.

The infection of mixed origin is also accompanied by inflammation of the skin and mucosa of the external and middle ear respectively. This inflammation results in redness and swelling of the ear tissues. Studies have shown steroids mixed with an antibiotic lead to a hasty resolution of Otitis Media and Otitis Externa. Beclomethasone is a potent corticosteroid producing anti-inflammatory & vasoconstrictor effects. Addition of the Beclomethasone to the antibiotic regimen improved the results of treatment with respect to the otoscopic and tympanometric findings, increasing the resolution of symptoms and quality of hearing<sup>9</sup>.

Due to abundant nerve supply to the ear tissues, ear infections and inflammation leads to excruciating pain. The pain is also associated instillation of ear drops on inflamed skin/mucosa. Lignocaine is a widely accessible local anaesthetic with rapid onset (peak effect in 2–5 minutes). It has low lipid solubility it is poorly absorbed through the ear, thus not absorbed systemically. Lignocaine is used commonly in the ear for myringotomy-related local anaesthesia<sup>10</sup>. Anecdotally, topical aqueous lignocaine does provide relief for pain of Otitis Media / Externa and is recommended by the clinical practitioners. Karen Koch et al.<sup>11</sup>, mention Otitis Externa can be topically treated by antibiotics (Fluoroquinolones- Ofloxacin or Ciprofloxacin), antifungal agents (Clotrimazole has greatest zone of inhibition for common fungi), anti-inflammatory agents (Glucocorticoid) and any agent for pain management can be used as a treatment option. Topical therapy in the form of ear drops will be

applicable in case of Otitis Media only in case the barrier of tympanic membrane is ruptured / perforated.

The combination of Neomycin (0.5% w/v) + Beclomethasone Dipropionate (0.025 % w/v) + Clotrimazole (1% w/v) + Lignocaine Hydrochloride (2% w/v) per ml is available in the Indian market for the topical treatment of Otitis Media with perforations and Otitis Externa. We explored a striking dearth of clinical data in regard to this combination. Thus, this study was conducted to assess the safety and efficacy of this combination on patients to generate clinical data in the said indication.

### **Materials and Methods**

This Phase IV clinical trial enrolled 12 ENT centres in various cities in India for the study. This study was conducted from February 2017 to April 2017. Total 196 patients were recruited for the study out of which 160 patients completed the study. 36 patients were lost to follow-up.

### **Inclusion and exclusion study**

Patients with confirmed diagnosis of ear inflammation and infection, either due to Otitis Externa or Otitis Media with perforation were included in the study. The study subsumed patients of both gender between the ages of 18 to 75 years. Only the patients who would strictly cohere to the protocol were recruited for the study. Patients with hypersensitivity to the individual study drug or to any of its ingredients were excluded from the study.

### **Study intervention**

A combination of Neomycin (0.5% w/v) + Beclomethasone Dipropionate (0.025 % w/v) + Clotrimazole (1% w/v) + Lignocaine Hydrochloride (2% w/v) in the form of ear drops was provided by the sponsor free of cost to the patients enrolled in the study. Study dosage and administration – Patients were asked to instil

two drops of Ear Drops thrice a day at 8 hrs interval for a study period of 5 days.

### **Study procedure**

The study stretch was decided to be 5 days to test safety and efficacy of the combination. Patients of Otitis media with perforation and Otitis externa satisfying the inclusion and exclusion criteria were recruited for the study. Medical history was taken and physical examination (including respiratory rate, blood pressure in the sitting position, oral temperature and pulse rate) was conducted by the investigators. Investigators holding post-graduate degree in ENT speciality were involved in conduction of this study. Patients were given free samples in the dose of 4 ml to instil one to two drop thrice a day for a study period of 5 days with 8 hrs interval. Patients were asked to maintain a symptoms diary and note any adverse events occurring during the study duration. Three visits were outlined for all the patients recruited in this study – V<sub>1</sub> (baseline visit) on day 1 before treating patient with the study medication, V<sub>2</sub> (reevaluation visit) on day 3 and V<sub>3</sub> (last or conclusion visit) on day 5. Total Symptom Score (TSS) and adverse events occurring were noted at each visit along with physical examination and medical history. Patients were instructed to keep a diary of daily symptoms. Investigators were asked to discontinue the study drug in case of severe adverse event and with discretion, clinical experience contingent upon mild or moderate adverse events.

### **Concomitant therapy**

No topical concomitant pharmacological therapy was allowed during the trial duration. Systemic therapy with antibiotic/anti-inflammatory/analgesic was as per clinical discretion. Non-Pharmacotherapy of Hot Fomentation for the ear Pinna externally was advocated. Patients were strictly instructed not to use ear buds or Q-tips as they are harmful.

### Efficacy assessment

The primary assessment was done to evaluate the reduction in the Total Symptom Score (TSS) score for the Ear pain, Ear discharge and Ear itching related to Otitis media and Otitis Externa on an eleven-point scale (0 to 10) where 0 means no symptoms i.e. patients who are completely cured and 10 means patient maximum tolerated symptoms. The secondary assessment was done to analyse the percentage reduction in TSS score of ear pain, ear discharge and ear discharge at visit 2 and visit 3 as compared to baseline.

### Safety assessment

Patients were questioned about any adverse event at each visit and if present were noted in the case record form (CRF) during each visit. These adverse events were classified into serious and non-serious adverse events. Patients with any adverse events if present were recorded in the case report form after thorough investigation. 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 and Ethical matters

This combination is available in India and classified under the category of schedule 'H' drug, which means that it should be sold only if prescription of registered medical practitioners is present with the patient. All the participated patients in the study have read and voluntarily signed the informed consent form (ICF). This study was conducted by following all the rules and guidelines as per schedule Y. The ICF, protocol, CRF, investigators CV, investigators undertaking, ethics committee registration certificates and investigators medical registration certificates (including post-graduation certificates) were submitted to the office of DCGI (Drug Controller General

of India), Central Drugs Standard Control Organization (CDSCO) and are registered under ref. no. 2514/17.

### Result

The baseline demographic characteristics are given in Table 1.

Mean Age	29.6 years
Males / Females	89 / 71
Mean BMI	22.7

Mean of TSS score of ear pain, ear itching and ear discharge at each visit was calculated and separately plotted graphically as shown in figure no. 1, 2 and 3 respectively.. At baseline mean TSS score for ear pain, ear itching and ear discharge was 5.73, 4.84 and 5.63 respectively. On day 3 (2<sup>nd</sup> visit) after taking study drug combination, Mean TSS score for ear pain, ear discharge and ear itching was reduced to 2.19, 1.48 and 1.73 respectively .On day 5 (3<sup>rd</sup> visit) after taking drug combination Mean TSS score for ear pain, ear itching and ear discharge was 0.22, 0.13 and 0.15 respectively i.e. there was a reduction of in mean TSS score of 96.37%, 97.9% and 97.35% for Ear Pain, Ear Itching and Ear Discharge Respectively. The reduction of TSS every visit for ear pain, ear itching and ear discharge has been shown in Figure 1, 2 and 3.

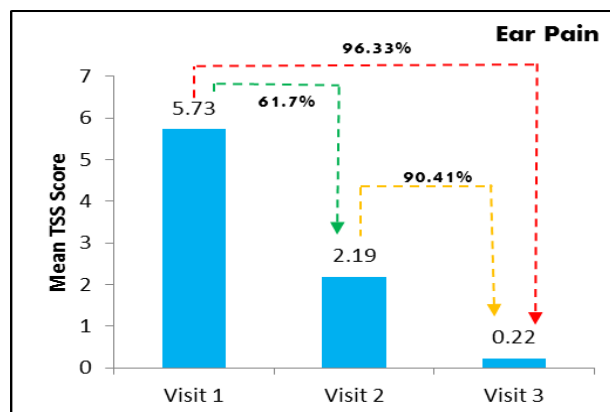


Figure 1: Reduction in mean and percent reduction in mean TSS score in ear pain.

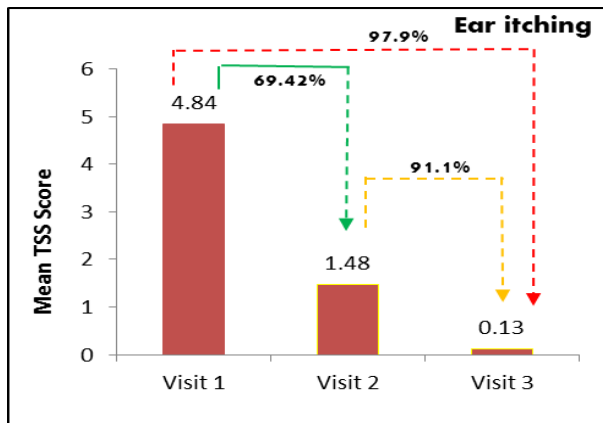


Figure 2: Reduction in mean and Percent reduction in mean TSS score in ear itching.

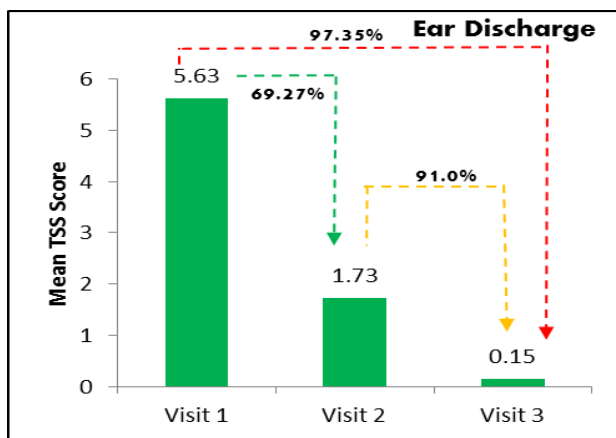


Figure 3: Reduction in mean and Percent reduction in mean TSS score in ear discharge.

### Safety analysis

The overall drug related adverse effects incidences were 21 seen in 15 patients i.e. in 9.37% of total population. The list of adverse events with the number of patients is mentioned in the Table 2 as below.

Adverse events	No. of episodes	No. of patients	% of total population
Severe burning sensation	15	11	6.87%
Mild vertigo	6	4	2.5%
Total	21	15	9.37%

### Discussion

About 65-330 million people suffer from ear infection worldwide and 60% of them had significant hearing impairment<sup>9</sup>. It is weighed out to be the most frequent disease for patients to visit clinicians and take antibiotics. Ear infection is a common problem for both children and adults but the magnitude is different in different countries, more common in developing countries<sup>10</sup>. In addition to the distress that it brings on the patient and the family, it also causes an enormous economic burden to the society in terms of physician visits, medications, surgical procedures, and absences from work, school, or day care. Application of topical preparation is generally the treatment of choice because high concentration of active agents can be delivered to the site of infection with minimal side effects<sup>11</sup>.

In author's knowledge this was the first clinical trial conducted to study the efficacy and safety of a combination of Neomycin, Beclomethasone, Clotrimazole and Lignocaine in mixed infection of external or middle ear with perforation. Strong arm of this clinical study is that Total Symptom score (TSS) is used as a criterion for efficacy reckoning. What makes TSS more impressionable is that it has 11 grades for symptom assessment, thus increasing the sensitivity of the study. In visit 1 before treating patient, mean TSS score of ear pain, ear itching and ear discharge was 5.73, 4.84 and 5.63 respectively. After treatment with the study medication at day 3 ear pain, ear itching and ear discharge was reduced to 2.19, 1.48 and 1.73 respectively. On 3<sup>rd</sup> visit after taking drug combination Mean TSS score for ear pain, ear itching and ear discharge was 0.21, 0.13 and 0.15 respectively i.e. there was a reduction of in mean TSS score of 96.37%,97.9% and 97.35% for Ear Pain, Ear Itching and Ear Discharge respectively. There was a reduction in Total Symptom Score (TSS) in all the patients in the phase IV post market surveillance study. This implies that the study

medication was efficacious in treating mixed ear infections.

Twenty one adverse events incidences were observed in 15 patients i.e. in 9.37% of patients. The adverse events observed were of mild intensity including burning sensation (in 6.87% of patients) and mild vertigo (in 2.5% of patients) which need not to be treated separately or patients were not needed to be withdrawn from the study.

Abelardo et al.<sup>12</sup> conducted a double-blind controlled trial of combination of Betamethasone and Neomycin to determine if the addition of topical antibiotic increases the efficacy of topical steroid in controlled otitis externa. Safety and efficacy of the combination were gauged in 45 adults with otitis externa based on the presence of oedema, discharge or debris in the outer ear canal. Efficacy assessment was done by Visual analogue symptom scores with mean symptom score of 19.2 for beclomethasone group and 28.7 for beclomethasone-neomycin group. The mean symptom score change in response to treatment with betamethasone-neomycin was 82.8%. All patients in the betamethasone-neomycin group showed symptom improvement showing Topical antibiotic-steroid combination therapy is paramount for symptomatic control of otitis externa.

Behrooz Barati et al.<sup>13</sup> concluded in a single blinded randomized clinical trial that the administration of Beclomethasone as an adjuvant for the treatment of Otitis Media with Effusion not only reduced the local inflammation around the eustachian tube but also increased the resolution of symptoms and the patients' quality of hearing in 92 patients. Efficacy assessment, improvement in the symptoms or the quality of hearing was made by curtailment in chi-square test which was from (76.1%) to 22(47.8%). Thus, the study ceased that the administration of Beclomethasone not only improves the results of treatment with the otoscopic and tympanometric findings, but also

increases the resolution of symptoms and the patients' quality of hearing.

Karen Koch et al.<sup>8</sup>, theorize the rationale for bringing together multiple topical therapy including antibiotics (Aminoglycosides, Neomycin, Tobramycin, Gentamycin), antifungal agents (Clotrimazole, Miconazole) anti-inflammatory (Glucocorticoids) and any agent for management of pain delivering high concentration of medication to the infected and inflamed tissue, with minimal side effects for the treatment of Otitis Externa.

Prasanna V et al.<sup>13</sup> escorted a clinical study of 1% Clotrimazole otic solution on 75 patients diagnosed with otomycosis (superficial fungal infection in deeper ear canal skin and tympanic membrane). 83 ears were treated by 1% Clotrimazole ear drops after ingrained clearance of ear canal by suction. All the patients were reckoned clinically at the end of 4 weeks. 80 out of 83 (i.e. 98.36%) ears were healed at the end of study. Which ceases that 1% Clotrimazole is effective in achieving complete mycological cure in otomycosis.

Rowbotham MC et al.<sup>14</sup> conducted a study on 47 subjects for testing topical pain relief efficacy of Lidocaine. It was found that in 39 out of 47 patients intensity of pain was reduced. So it was concluded that local topical application of lidocaine is efficacious in reducing the topical pain intensity.

The only limitation of this study is lesser enrolment of patients and children younger than ----- of age, which is the age group that is most prone to ear infections.

### **Conclusion**

A combination of Neomycin (0.5% w/v) + Beclomethasone Dipropionate (0.025 % w/v) + Clotrimazole (1% w/v) + Lignocaine Hydrochloride (2% w/v) topically as ear drops is safe and efficacious in the treatment of Mixed infection of the external and middle ear (with perforation).

## Acknowledgement

We would like to acknowledge the co-investigators in this study Dr. Shrinivas Kishore Sistla (Hyderabad), Dr. S. Chaitanya Kumar (Kodad), Dr. Rajnikanth (Stanpalli), Dr. Vijay. K. Jagasia (Ulhasnagar), Dr. Mansuk P. Rangani (Rajkot), Dr. Vaishali Sangole (Navi Mumbai), Dr. S.S. Mishra (Odisha), Dr. Nilamadhab Prusty (Odisha), Dr. Santosh Kumar Sahu (Odisha), Dr. K.V. Doshi (Mumbai), Dr. Dinesh P. Dabha (Karnataka), Dr. Sandeep Agrawal (Aurangabad), Dr. Bhanukant M. Patel (Gujarat).

## Disclosure

Authors are employees of Centaur Pharmaceuticals Pvt. Ltd. This study was conducted as a part of Pharmacovigilance activity for Otiflox New Ear drops manufactured and marketed by Centaur Pharmaceuticals Pvt. Ltd. In accordance with Pharmacovigilance Program of India (PvPI).

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