Otiflox™ Ear drops
Sterile New

1. Composition

Neomycin	0.5% w/v
Beclomethasone	0.025%
Clotrimazole	1%w/v
Lignocaine	2%w/v

2. Dosage form and strength

Otiflox new Ear Drops is available in 5 ml bottle with in-built dropper

3. Clinical particulars

3.1 Therapeutic indication

Indication Otiflox new ear drops are indicated for treatment:

- Mixed Ear Infections
- Otitis Externa
- Chronic suppurative otitis media

3.2 Posology and method of administration

Instil two drops of Otiflox new Ear Drops in affected ear 2-3 times a day.

3.3 Contraindication

Otiflox ear drops are contraindicated in patients with:

- Hypersensitivity to any of the ingredients
- Psychiatric illnesses and in patients with epilepsy or other seizure disorders.
- Severe systemic infections

3.4 Special warnings and precautions for use

None.

3.5 Drug interactions

No specific drug interactions noted.

3.6 Use in special population

- Pediatric: Not recommended in children.
- Geriatric: Safety and effectiveness of Otiflox ear drops in geriatric patients have not been established.
- Liver impairment: Use with caution.
- Renal failure: Use with caution.
- Pregnancy and lactation: Use with caution.

3.7 Effects on ability to drive and use machine

Patients should be cautioned against engaging in activities requiring complete mental alertness, and motor coordination such as operating machinery until their response to Otiflox new Ear Drops is known.

3.8 Undesirable effects

Otiflox new ear drops can give mild irritation, burning or stinging sensation in the ear after application.

3.9 Overdose

There is limited experience of overdose with Otiflox new Ear Drops. Initiate general symptomatic and supportive measures in all cases of overdosages where necessary.

4. Pharmacological properties

4.1 Mechanism of action

Aminoglycosides like neomycin "irreversibly" bind to specific 30S-subunit proteins and 16S rRNA. Specifically neomycin binds to four nucleotides of 16S rRNA and a single amino acid of protein S12. This interferes with decoding site in the vicinity of nucleotide 1400 in 16S rRNA of 30S subunit. This region interacts with the wobble base in the anticodon of tRNA. This leads to interference with the initiation complex, misreading of mRNA so incorrect amino acids are inserted into the polypeptide leading to non-functional or toxic peptides and the breakup of polysomes into non-functional monosomes.

Beclomethasone is a steroid which promptly blocks inflammation & allergy.

Clotrimazole works to kill individual Candida or fungal cells by altering the permeability of the fungal cell wall. It binds to phospholipids in the cell membrane and inhibits the biosynthesis of ergosterol and other sterols required for cell membrane production. This leads to the cell's death via loss of intracellular elements.

Lignocaine HCl blocks sensation of pain.

4.2 Pharmacodynamic properties

Neomycin is an aminoglycoside antibiotic. Aminoglycosides are useful primarily in infections involving aerobic, Gram-negative bacteria, such as Pseudomonas, Acinetobacter, and Enterobacter. In addition, some mycobacteria, including the bacteria that cause tuberculosis, are susceptible to aminoglycosides. Infections caused by Gram-positive bacteria can also be treated with aminoglycosides, but other types of antibiotics are more potent and less damaging to the host. In the past the aminoglycosides have been used in conjunction with penicillin-related antibiotics in streptococcal infections for their synergistic effects, particularly in endocarditis. Aminoglycosides are mostly ineffective against anaerobic bacteria, fungi and viruses.

Beclomethasone dipropionate works by attenuating the inflammatory responses associated with asthma, allergic rhinitis, nasal polyps, and corticosteroid-responsive dermatoses. It suppresses the actions of inflammatory cells, such as mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils. It also inhibits the release of inflammatory mediators, such as histamine, eicosanoids, leukotrienes, and cytokines. Beclomethasone dipropionate is reported to exhibit potent topical activity while possessing low systemic effects. Beclomethasone dipropionate is a corticosteroid drug with anti-inflammatory and vasoconstrictive effects used to treat chronic inflammatory processes such as asthma, allergic rhinitis, and corticosteroid-responsive dermatoses. When inhaled, it improves lung function, decreases airway hyper-reactivity, and reduces the severity of asthmatic symptoms. Although inhaled corticosteroids, including beclomethasone dipropionate, are reported to mainly act locally in the lungs, systemic effects such as disruption of hypothalamic-pituitary-adrenal (HPA) axis function, bone turnover, osteoporosis, and growth suppression may still be observed with chronic use or high dose administration. There were varying findings from clinical studies examining the effect of beclomethasone dipropionate on growth suppression in pediatric patients. It was shown to suppress the hypothalamo-pituitary-adrenal (HPA) axis in a dose-dependent manner. HPA axis is a central hormonal response system to stress and activation of HPA axis leads to the production of endogenous steroid hormone production. Long-term use of high-dose systemic corticosteroids, including those inhaled, was often associated with signs and symptoms of adrenal insufficiency when exposed to stress conditions, such as trauma, surgery, or infections. As corticosteroids work by suppressing the immune system, there may be an increased risk for developing infections. Cases of *Candida albicans* infection of the mouth and throat have been reported with inhaled beclomethasone dipropionate therapy.

Clotrimazole is a broad-spectrum antifungal agent that inhibits the growth of pathogenic yeasts by changing the permeability of cell membranes. The action of Clotrimazole is fungistatic at concentrations of drug up to 20 mcg/mL and may be fungicidal *in vitro* against Candida albicans and other species of the genus Candida at higher concentrations. Unfortunately, resistance to Clotrimazole, which was rare in the past, is now common in various patient populations. Clotrimazole is generally considered to be a fungistatic, and not a fungicidal drug, although this contrast is not absolute, as Clotrimazole shows fungicidal properties at higher concentrations.

Excessive blood levels of lidocaine can cause changes in cardiac output, total peripheral resistance, and mean arterial pressure . With central neural blockade these changes may be

attributable to the block of autonomic fibers, a direct depressant effect of the local anesthetic agent on various components of the cardiovascular system, and/or the beta-adrenergic receptor stimulating action of epinephrine when present. The net effect is normally a modest hypotension when the recommended dosages are not exceeded.

In particular, such cardiac effects are likely associated with the principal effect that lidocaine elicits when it binds and blocks sodium channels, inhibiting the ionic fluxes required for the initiation and conduction of electrical action potential impulses necessary to facilitate muscle contraction . Subsequently, in cardiac myocytes, lidocaine can potentially block or otherwise slow the rise of cardiac action potentials and their associated cardiac myocyte contractions, resulting in possible effects like hypotension, bradycardia, myocardial depression, cardiac arrhythmias, and perhaps cardiac arrest or circulatory collapse.

Moreover, lidocaine possesses a dissociation constant (pKa) of 7.7 and is considered a weak base. As a result, about 25% of lidocaine molecules will be un-ionized and available at the physiological pH of 7.4 to translocate inside nerve cells, which means lidocaine elicits an onset of action more rapidly than other local anesthetics that have higher pKa values. This rapid onset of action is demonstrated in about one minute following intravenous injection and fifteen minutes following intramuscular injection. The administered lidocaine subsequently spreads rapidly through the surrounding tissues and the anesthetic effect lasts approximately ten to twenty minutes when given intravenously and about sixty to ninety minutes after intramuscular injection.

4.3 Pharmacokinetic properties

Neomycin is poorly absorbed from the gastrointestinal tract, about 97% of an oral dose being excreted unchanged in the faeces. Doses of 3 g orally produce peak plasma concentrations of up to 4 micrograms/mL and absorption is similar after an enema. Absorption may be increased in conditions which damage or inflame the mucosa. Absorption has also been reported to occur from the peritoneum, respiratory tract, bladder, wounds, and inflamed skin. Once neomycin is absorbed it is rapidly excreted by the kidneys in active form. It has been reported to have a half-life of 2 to 3 hours

Beclomethasone is stated to be readily absorbed from sites of local application, and rapidly distributed to all body tissues. It is metabolised principally in the liver, but also in other tissues including gastrointestinal tract and lung; enzymatic hydrolysis rapidly produces the monopropionate (which has some glucocorticoid activity), and, more slowly, the free alcohol, which is virtually devoid of activity. Only a small proportion of an absorbed dose is excreted in urine, the remainder being excreted in the faeces mainly as metabolites.

When applied topically Clotrimazole penetrates the epidermis but there is little if any systemic absorption. Absorption of 3 to 10% of a dose has been reported after vaginal use. Clotrimazole is metabolised in the liver to inactive compounds and excreted in the faeces and urine.

Lidocaine is readily absorbed across mucous membranes and damaged skin but poorly through intact skin. The agent is quickly absorbed from the upper airway, tracheobronchial tree, and alveoli into the bloodstream. And although lidocaine is also well absorbed across the gastrointestinal tract the oral bioavailability is only about 35% as a result of a high degree of first-pass metabolism. After injection into tissues, lidocaine is also rapidly absorbed and the absorption rate is affected by both vascularity and the presence of tissue and fat capable of binding lidocaine in the particular tissues. The protein binding recorded for lidocaine is about 60 to 80% and is dependent upon the plasma concentration of alpha-1-acid glycoprotein. Lidocaine is metabolized predominantly and rapidly by the liver, and metabolites and unchanged drug are excreted by the kidneys.

5. Nonclinical properties

5.1 Animal Toxicology or Pharmacology

Not required.

6. Description

Already mentioned and covered in the above points.

7. Pharmaceutical particulars

7.1 Incompatibilities

There are no known incompatibilities.

7.2 Shelf-life

18 months.

7.3 Storage and handling instructions

Store in a dry, well-ventilated place at a temperature not exceeding 30^{o}C. Do not freeze.