Neomycin
Triamcinolone acetonide
Gramicidin
Nystatin

Combiz

2.5 mg/1 mg/0.25 mg/100,000 units per mL

OTIC SOLUTION

Antibacterial / Antifungal / Corticosteroid

FOR EXTERNAL USE ONLY

DESCRIPTION:
COMBIZ Otic Solution is a yellowish-brown suspension filled in dropper-tipped bottles

FORMULATION:
Each mL contains:
Neomycin (as Sulfate) ..... 2.5 mg
Triamcinolone acetonide ..... 1 mg
Gramicidin ..... 0.25 mg
Nystatin ..... 100,000 units

PHARMACOLOGY:
Pharmacodynamics

Mechanism of Action
COMBIZ Otic Solution is intended for application to the external auditory canal.

Triamcinolone acetonide, a topical corticosteroid has anti-inflammatory, antipruritic, and vasoconstrictive actions.

Neomycin and Gramicidin provide antibacterial activity against microorganisms likely to be responsible for bacterial infections of the external auditory canal.

Neomycin exerts it antibacterial activity against a number of gram-negative organisms by inhibiting protein synthesis. It is not active against Pseudomonas aeruginosa, and resistant strains of gram-negative bacteria may develop.

Gramicidin exerts its antibacterial activity against many gram-positive organisms by altering cell membrane permeability.

Nystatin, an antifungal antibiotic, is included for the prevention or treatment of Candida albicans infections. Nystatin acts by binding to steroids in the cell membrane of susceptible species resulting in a change in membrane permeability and the subsequent leakage of intracellular components. On repeated sub-culturing with increasing levels of nystatin, Candida albicans does not develop resistance to nystatin. Generally, resistance to nystatin does not develop during therapy. Nystatin exhibits no activity against bacteria, protozoa, or viruses.

These ingredients give symptomatic relief of the pain, burning and itching of infected otitis externa, while combatting the relevant bacterial and/or monilial infection.

The mechanism of anti-inflammatory activity of topical corticosteroids is unclear. Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and/or clinical efficacies of the topical corticosteroids. There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man.

Pharmacokinetics:

Absorption
The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressing.

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption.

Once absorbed through the skin, topical corticosteroids are handled through the same pharmacokinetic pathways as systemically administered corticosteroid.

Nystatin and gramicidin are not absorbed from intact skin or mucous membranes. Neomycin can be absorbed through inflamed skin.

Distribution
Corticosteroids are bound to plasma proteins in varying degrees.

Metabolism and Excretion
Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

Once absorbed, Neomycin is rapidly excreted unchanged through the kidneys. the half-life is approximately 2 to 3 hours.

INDICATIONS:
COMBIZ is intended for the treatment of otitis externa (acute and chronic) when a topical corticosteroid is required and active infections with susceptible organisms are either present or likely to supervene. It is recommended for short term use

DOSAGE AND ADMINISTRATION:
Prior to administration of any COMBIZ Otic preparation, all wax and epithelial debris should be removed and the tympanic membrane inspected. Two or three drops should be instilled into the ear two or three times daily or as prescribed by the physician

CONTRAINDICATIONS:
Tuberculous lesions and topical or systemic viral infections such as Herpes Simplex, but particularly in vaccinia and varicella.
In the treatment of otitis media or in the presence of a perforate tympanic membrane.
Known hypersensitivity to Triamcinolone acetonide, Neomycin, Nystatin, Gramicidin or any other component of the preparation.

WARNINGS and PRECAUTIONS:

General
If sensitivity or irritation develops, use of this medication should be discontinued and appropriate therapy instituted. Hypersensitivity reactions to the anti-infective components may be masked by the presence of a corticosteroids.

This medication is not for ophthalmic use.

Because of the potential hazard of nephrotoxicity and ototoxicity, this medication should not be used in patients with extensive skin damage where absorption of Neomycin is possible. The risk of hypersensitivity to Neomycin is increased with prolonged or repeated use.

As with any antibiotic preparation, prolonged use may result in overgrowth of non-susceptible organisms, including fungi other than Candida. Corticosteroids, furthermore, can enhance microbial infections. Therefore, constant observation of the patient is essential. Should superinfection due to non-susceptible organisms occur, suitable concomitant antimicrobial therapy must be administered. If a favorable response does not occur promptly, application should be discontinued until the infection is adequately controlled by other anti-infective measures.

Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia and glucosuria in some patients.

Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, and prolonged use. Therefore, patients receiving a large dose of any potent topical steroid under any condition(s) which may enhance systemic absorption should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests, and for impairment of thermal homeostasis. If any of these conditions occur, an attempt should be made to withdraw the drug, to reduce the frequency of application, or substitute a less potent steroid.

Recovery of HPA axis function and thermal homeostasis are generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Visual Disturbance
Visual disturbance may be reported with systemic and topical corticosteroids use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for

referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids

Information for Patients
Patients administering these preparations should receive the following information and instructions.

1. This medication is to be used as directed by the physician
2. Avoid contact with eyes
3. Patients should be advised not to use this medication for any disorder other than for which it was prescribed
4. Even if symptomatic relief occurs within the first few day of treatment, the patient should be advised not to interrupt or discontinue the therapy until the prescribed course of treatment is completed
5. Patients should report any signs of adverse reactions
6. Exercise special care when introducing the cannula tip into the ear

Use in Elderly
No data available

Pediatric Use
Use of this medication for prolonged periods in pediatric patients could result in sufficient systemic absorption to produce systemic effects. Pediatric patients may demonstrate greater susceptibility to HPA axis suppression and Cushing's syndrome than mature patients

HPA axis suppression, Cushing's syndrome and intracranial hypertension have been reported in children receiving topical corticosteroids. When applied to pediatric patients, this medication should be limited to the least amount for the shortest duration compatible with an effective therapeutic regimen. Pediatric patients should be closely monitored for signs and symptoms of systemic effects.

Effects on Laboratory Test
I there is a lack of therapeutic response, KOH smears, cultures or other diagnostic methods should be repeated. A urinary free cortisol test and ACTH stimulation test may be helpful in evaluating hypothalamic-pituitary-adrenal (HPA) axis suppression due to corticosteroid.

PREGNANCY and LACTATION:

Use in Pregnancy (Pregnancy Category D)
Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after skin application in laboratory animals. Gentamicin and other aminoglycosides cross the placenta. There is evidence of selective uptake of Gentamicin by the foetal kidney resulting in damage (probably reversible) to immature nephrons. Eight cranial nerve damage has also been report following in-utero exposure to some of the aminoglycosides. Because of their chemical similarity, all aminoglycosides must be considered potentially nephrotoxic and ototoxic to the fetus.

There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied components in this medication.

It should also be noted that therapeutic blood levels in the mother do not equate with safety for the fetus.

Use in Lactation
It is not known whether topical administration of this medication could result in sufficient systemic absorption of the components to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk quantities not likely to have a deleterious effect on the infant. Nevertheless, caution should be executed when this medication is administered to a nursing woman.

DRUG INTERACTIONS:
No data available

ADVERSE DRUG REACTIONS:
COMBIZ Otic Solution is usually well tolerated. The reactions listed, while uncommon, may occur.
The following local adverse reactions are reported infrequently with topical corticosteroids (reactions are listed in an approximate decreasing order of occurrence); burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.

Corticosteroids may cause damage to collagen which constitutes a middle layer of the tympanic membrane. They may also delay healing, and may exert systemic effects including adrenal suppression if absorbed in appreciable amounts.

Nystatin is well tolerated even with prolonged therapy. Irritation and cases of contact dermatitis have been reported.

Delayed type hypersensitivity reactions have been reported during use of Neomycin; sensitization has been reported following prolonged use. Ototoxicity and nephrotoxicity have been reported when applied to damaged skin. This antibiotic in itself may cause an allergic otitis externa.

Sensitivity reactions to Gramicidin have been reported. While no reports of Gramicidin absorption following topical administration have been reported, haemolysis may occur should be the drug enter the blood. If Gramicidin is allowed to come in close proximity to the subarachnoid space, a chemical arachnoiditis may occur.

Adverse Effects – Pediatric Patients
Manifestations of adrenal suppression in pediatric patients include linear growth retardation, delayed weight gain, low plasma cortisol levels and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches and bilateral papiloedema.

Post Marketing Adverse Effects
Eye disorders: blurred vision

OVERDOSE and TREATMENT:
Topically applied corticosteroids and Neomycin can be absorbed in sufficient amounts to produce systemic effects.

Treatment: No specific antidote available, and treatment should be sypmtomatic

STORAGE CONDITIONS:
Store at temperatures not exceeding 30oC

PACKAGING AVAILABILITY:
10 mL LDPE Plastic Dropper-Tipped Bottle x 5 mL (box of 1's)

Marketing Authorization Holder:

PHARMABIZ SOLUTIONS, INC.
Unit 3, 3rd Floor, 317 Roosevelt Ave., Brgy. San Antonio, Quezon City, Metro Manila

Manufactured by:

Ashford Pharmaceutical Laboratories, Inc.
145 P. Oliveros St., Antipolo City

CAUTION:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription

ADR REPORTING:
For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

INSTRUCTION TO PATIENT: seek medical attention immediately at the first sign of any adverse drug reaction shall appear

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