SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AURICULARUM, powder and solvent for suspension for ear instillation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxytetracycline hydrochloride ..... 100.0 mg
Polymyxin B sulphate ..... 12.3 mg
Dexamethasone sodium phosphate ..... 10.0 mg
Nystatin ..... 1,000,000 IU
Per bottle

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for suspension for ear instillation.

4. CLINICAL DATA

4.1. Therapeutic indications

Local treatment:

- of external otitis of bacterial and/or fungal origin;
- chronic otitis:
  - pre-operatively to dry out,
  - post-operatively for petromastoid radical cavities with or without tympanoplasty.

Take into account the official recommendations relating to the appropriate use of antibiotics.

4.2. Dosage and method of administration

Auricular local route.

1/ *In powder form*:

. Hold the flexible bottle, head down; pack all of the powder into the neck;
. Press the bottle to obtain a dose of product;
. Insufflate the dose once or twice daily, or every 2 to 3 days.

2/ *In suspension form*:

In certain particular cases, it is possible to use the powder suspended in the contents of the ampoule of solvent.
From the suspension thus obtained, instill 5 to 10 drops into the auditory canal of the affected ear once or twice daily.
This auricular suspension prepared at the time of use retains its activity for 8 days **at between +2°C and +8°C (in the refrigerator).**
Warm the bottle at the time of use by holding it in the palm of the hand for several minutes in order to prevent the unpleasant contact of the cold solution with the ear. Shake vigorously before use.
With the head tilted, instill the drops into the affected ear pulling the outer ear several times. Keep the head tilted to one side for about 5 minutes to promote the penetration of the drops into the external auditory canal. If necessary, repeat for the other ear.
At the end of treatment, the remainder of the bottle is to be discarded and must not be retained for reuse.
Treatment duration:
The treatment duration is usually 7 days and may be up to 15 days at most in the treatment of fungal infection.

4.3. Contra-indications

This medicine is not to be used in the event of:

- hypersensitivity to oxytetracycline or another product of the cycline series,
- hypersensitivity to polymyxin B,
- hypersensitivity to nystatin,
- hypersensitivity to dexamethasone or any other ingredient of the solution,

- dry perforation of the eardrum (see section 4.4),
- viral infections of the external auditory canal, including varicella and *Herpes simplex* infections.

4.4. Special warnings and precautions for use

Check the state of the eardrum before any prescription.

This product contains oxytetracycline, a cycline antibiotic, which, after administration by the systemic route, is known for its toxicity to the teeth of children aged less than 8 years and for the risk of photosensitisation.

In the absence of data on the medicine administered in auricular powder or suspension form, these risks cannot be totally ruled out but are undoubtedly minimal given the quantity administered; the penetration of oxytetracycline into the systemic circulation is even more unlikely when the medicinal product is administered in powder form.

Local administration of antibiotics contributes to sensitisation to the active substances with, potentially, systemic reactions.

The presence of a corticosteroid does not prevent the manifestations of allergy to the antibiotic, but may modify their clinical presentation.

Discontinue treatment as of the first signs of emergence of skin rash or any other sign of local or systemic hypersensitivity.

The attention of sportsmen is drawn to the fact that this product contains an active substance (dexamethasone) which may lead to a positive reaction in tests carried out in the context of anti-doping controls.

The persistence of a deposit of brownish powder in the external auditory canal may necessitate cleaning.

Special attention is to be paid to patients with a hearing aid; indeed, the persistence of the deposit may interfere with hearing-aid operation.

Do not inject, do not swallow.

At the time of use, avoid contact between the nozzle and the ear or fingers in order to limit the risks of contamination.

It is advisable to not combine this medicine with another local treatment.

If, after 10 days, or after 15 days in the event of otomycosis, symptoms persist, the patient is to return for reevaluation of the disease and treatment.

4.5. Interactions with other medicinal products and other forms of interaction

Not applicable.

4.6. Pregnancy and lactation

This medicine is only to be used during pregnancy if necessary.

This medicine may be prescribed during lactation.

4.7. Effects on the ability to drive and use machines: Not applicable.

4.8. Adverse effects

- Exceptionally: hot sensation or itching at the start of treatment, local allergy, dizziness.
- Persistence of brownish residues in the auditory canal (see section 4.4.).
- Selection of resistant microorganisms.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Agence nationale de sécurité du medicament et des produits de santé (ANSM) in the network of the Regional Centres of Pharmacovigilance – Website: www.ansm.sante.fr

4.9 Overdose: Not applicable.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic class: **otologicals; corticosteroid and anti-infectives in combination; dexamethasone and anti-infectives**. ATC code: **S02CA06.**
Dexamethasone is a steroidal anti-inflammatory.
Oxytetracycline is an antibiotic in the cycline series.
Polymyxin B is an antibiotic in the polypeptide series.
Nystatin is an antifungal.
Antibiotic, antifungal and anti-inflammatory activity in otology due to the anti-inflammatory properties of dexamethasone, antifungal action of nystatin and antibacterial action of the two antibiotics with complementary activity.
The combination of the two antibiotics is justified by their good local tolerability and by the microorganisms encountered in middle-ear infections. Moreover, the combination of oxytetracycline and polymyxin B is synergistic. This property allows to widen the spectrum to include *Pseudomonas* and all *Proteus*.

ANTIBACTERIAL ACTIVITY SPECTRUM OF OXYTETRACYCLINE AND POLYMYXIN B.

OXYTETRACYCLINE

The critical concentrations separate sensitive strains from strains with intermediate sensitivity and the latter from resistant strains:

Category	**Frequency of acquired resistance in France (>10%) (range)**
SENSITIVE SPECIES	
Gram-positive aerobes	
Bacillus	
Enterococcus	40-80%
Methicillin-sensitive *Staphylococcus* *	
Methicillin-resistant *Staphylococcus* **	70-80%
Streptococcus A	20%
Streptococcus B	80-90%
Streptococcus pneumoniae	20-40%
Gram-negative aerobes	
Branhamella catarrhalis	
Brucella	
Escherichia coli	20-40%
Haemophilus influenzae	10%
Klebsiella	10-30%
Neisseria gonorrhoeae	
Pasteurella	
Vibrio cholerae	
Anaerobes	
Propionibacterium acnes	
Category	**Frequency of acquired resistance in France (>10%) (range)**
Other	
Borrelia burgdorferi	
Chlamydia	
Coxiella burnetii	
Leptospira	
Mycoplasma pneumoniae	
Rickettsia	
Treponema pallidum	
Ureaplasma urealyticum	

S $\leq$ 4 mg/l and R > 8 mg/l

The prevalence of acquired resistance may vary as a function of geography and time for certain species.

It is thus of value to have information on the prevalence of local resistance, particularly for the treatment of severe infections. These data can only orient the probability of sensitivity of a bacterial strain to the antibiotic.
When the variability of the prevalence of resistance in France is known for a given bacterial species, it is shown in the following table:

RESISTANT SPECIES
Gram-negative aerobes
Acinetobacter
Proteus mirabilis
Proteus vulgaris
Pseudomonas
Serratia

* Clinical efficacy demonstrated for the sensitive strains in the approved clinical indication in combination with polymyxin B.

** The frequency of methicillin-resistance is 30 to 50% for all Staphylococci and is mainly encountered in hospital environments.

Note: the spectrum is for the systemic form of the antibiotics belonging to the cyclines series. With local pharmaceutical presentations, the concentrations obtained *in situ* are markedly greater than the plasma concentrations. Some uncertainty persists with regard to concentration kinetics *in situ,* the local physicochemical conditions which may modify antibiotic activity and the stability of the product *in situ*.

POLYMYXIN B
The critical concentrations separate sensitive strains from strains with intermediate sensitivity and the latter from resistant strains:
S ≤ 2 mg/l and R > 2 mg/l

The prevalence of acquired resistance may vary as a function of geography and time for certain species. It is thus of value to have information on the prevalence of local resistance, particularly for the treatment of severe infections. These data can only orient the probability of sensitivity of a bacterial strain to the antibiotic.
When the variability of the prevalence of resistance in France is known for a given bacterial species, it is shown in the following table:

Category	**Frequency of acquired resistance in France (>10%) (range)**
SENSITIVE SPECIES **Gram-negative aerobes** *Acinetobacter* *Aeromonas* *Alcaligenes* *Citrobacter freundii* *Citrobacter koseri* *Enterobacter* *Escherichia coli* *Klebsiella* *Moraxella* *Pseudomonas aeruginosa** *Salmonella* *Shigella* *Stenotrophomonas maltophilia*	0-30%

RESISTANT SPECIES

Gram-positive aerobes
Cocci and bacilli

Gram-negative aerobes
Branhamella catarrhalis
Brucella
Burkholderia cepacia
Burkholderia pseudomallei
Campylobacter
Chryseobacterium meningosepticum
Legionella
Morganella
Neisseria
Proteus
Providencia
Serratia
Vibrio cholerae El Tor

Anaerobes
Cocci and bacilli

Other
Mycobacterium

* Clinical efficacy demonstrated for the sensitive strains in the approved clinical indication in combination with oxytetracycline.

Note: the spectrum is for the systemic form of the antibiotics belonging to the polypeptides series. With local pharmaceutical presentations, the concentrations obtained *in situ* are markedly greater than the plasma concentrations. Some uncertainty persists with regard to concentration kinetics *in situ,* the local physicochemical conditions which may modify antibiotic activity and the stability of the product *in situ*.

NYSTATIN
Contact antifungal of the polyene series, extracted from *Streptomyces noursei* culture.
Nystatin would act by binding to the sterol fraction of the fungal membrane, inducing changes in membrane permeability.
Antifungal action spectrum: nystatin is active on a wide variety of yeasts and filamentous fungi, including the main causal agents for otomycosis (*Candida, Aspergillus*)

5.2. Pharmacokinetic properties:
In the event of a perforated eardrum, there is no systemic absorption.

5.3. Preclinical safety data:
Not applicable.

6. PHARMACEUTICAL DATA

6.1. List of excipients
Sodium laurylsulphate
Solvent composition: sodium chloride, purified water.

6.2. Incompatibilities:
Not applicable.

6.3. Shelf life

Before reconstitution: 2 years.
After reconstitution: the suspension for ear instillation may be stored for at most 8 days.

6.4. Special precautions for storage

Before reconstitution: store at a temperature not exceeding +25°C.
After reconstitution: the suspension for ear instillation is to be stored at between +2°C and +8°C (in the refrigerator).

6.5. Nature and contents of container:
Bottle (PE) of powder and 10 ml of solvent in an ampoule (LDPE); box of 1.

6.6. Special precautions for disposal and handling:
No special requirements.

7. MARKETING AUTHORISATION HOLDER: LABORATOIRES GRIMBERG - 19, rue Poliveau - 75005 Paris - France

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT: 27th January 2011.

PRESCRIBING AND DISPENSING CONDITIONS

Medicinal product subject to medical prescription