SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin/Dexamethasone 3 mg/ml / 1 mg/ml ear drops, suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of suspension contains 3 mg ciprofloxacin (as hydrochloride) and 1 mg dexamethasone.

Excipients with known effect:
This medicine contains 0.004 mg benzalkonium chloride in each drop which is equivalent to 0.1 mg per millilitre suspension.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Ear drops, suspension.

White to off-white uniform suspension (pH 4.3-4.8).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ciprofloxacin/Dexamethasone is indicated for the treatment of the following infections in adults and children (see section 4.2). See section 5.1 for commonly susceptible species.

- Acute otitis media in patients with tympanostomy tubes (AOMT)
- Acute otitis externa (AOE)

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology
Adults and elderly population

Instil four drops in the affected ear(s) twice a day for 7 days according to the different instillation instructions for patients with acute otitis media with typanostomy tubes and patients with acute otitis externa.

No overall differences in safety and effectiveness have been observed between elderly and other adult patients.

Paediatric population
This medicine has been shown to be safe and effective in paediatric patients 6 months of age and older for the treatment of AOMT and 1 year of age and older for the treatment of AOE (see Section 4.4 for use in children younger than 6 months for AOMT and in children younger than 1 year for AOE). Ciprofloxacin/Dexamethasone can be used at the same dose as in adults (see Section 5.2).

Patients with hepatic and renal impairment
Hepatic or renal impairment (mild to moderate) does not alter the pharmacokinetics of ciprofloxacin or dexamethasone following systemic administration.

Following topical otic administration of Ciprofloxacin/Dexamethasone ear drops, small increases in ciprofloxacin and dexamethasone plasma concentrations may be observed in patients with severe renal or hepatic impairment. However, since systemic exposure to ciprofloxacin or dexamethasone is low after topical otic administration, any increase in systemic concentrations due to renal or hepatic dysfunction would still be well below plasma concentrations that are well tolerated in children or adults following oral or intravenous recommended doses.

Dose adjustment of this medication in patients with renal or hepatic dysfunction is not necessary.

Method of administration
For otic use only.

Instruct the patients to shake the bottle well before use. The suspension should be warmed by holding the bottle in the hand for several minutes to avoid dizziness, which may result from the instillation of a cold suspension. The patient should lie with the affected ear upward, and then the drops should be instilled pulling several times on the aurical. For patients with acute otitis media with tympanostomy tubes, the tragus should be pumped 5 times by pushing inward to facilitate penetration of the drops into the middle ear. This position should be maintained for around 5 minutes to facilitate penetration of the drops in the ear. Repeat, if necessary, for the opposite ear.

To prevent contamination of the dropper tip in order to limit bacterial risks, care should be taken not to touch the auricle or the external ear canal and surrounding areas, or other surfaces with the dropper tip of the bottle. Keep the bottle tightly closed when not in use. Keep the bottle until the completion of the treatment.

4.3 Contraindications

Hypersensitivity to ciprofloxacin, to other quinolones, to dexamethasone or to any of the excipients listed in section 6.1.

Viral (i.e., varicella, herpes simplex) and fungal otic infections.

4.4 Special warnings and precautions for use

This medicinal product is for otic use only, not for ophthalmic use, inhalation or injection.

If otorrhea persists after a full course of therapy, or if two or more episodes of otorrhea occur within six months, further evaluation is recommended to exclude an underlying condition such as cholesteatoma, foreign body, or a tumour.

As with other antibacterial preparations, prolonged use of this product may result in overgrowth of non-susceptible organisms, including bacterial strains, yeast and fungi. If superinfection occurs, discontinue use and appropriate therapy should be initiated. If after one week of therapy some signs and symptoms persist, further evaluation is recommended to reassess the disease and the treatment.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolones. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial edema), airway obstruction, dyspnea, urticaria and itching. This product should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management should be administered as clinically indicated.

Tendon inflammation and rupture may occur with systemic fluoroquinolone therapy including ciprofloxacin, particularly in elderly patients and in those treated currently with corticosteroids. Therefore treatment with Ciprofloxacin/Dexamethasone should be discontinued at the first sign of tendon inflammation.

Corticosteroids may reduce resistance to, and aid in, the establishment of bacterial, viral, or fungal infections and mask the clinical signs of an infection, preventing recognition of ineffectiveness of the antibiotic, or may suppress hypersensitivity reactions to substances in the product.

Visual disturbance
Visual disturbance may be reported with systemic and topical corticosteroid 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.

Benzalkonium chloride may irritate the skin.

<u>Paediatric population</u>
Safety and efficacy of Ciprofloxacin/Dexamethasone have not been established in children younger than 6 months in acute otitis media in patients with tympanostomy tubes and in children younger than 1 year in acute otitis externa. Under exceptional circumstances, Ciprofloxacin/Dexamethasone treatment could be used in this sub-paediatric population after a very careful benefit-risk evaluation by the prescribing physician taking into account that although there are no known safety concerns or differences in disease process to preclude use in these children, clinical experience is insufficient in these specific subgroups of paediatric population.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Following topical otic administration in paediatric patients with patent tympanostomy tubes, low plasma concentrations were observed for ciprofloxacin (≥ 0.50 ng/ml in only 4 of 25 patients) and for dexamethasone (≥ 0.05 ng/ml in 14 of 24 patients) at 6 hours post-dose. It is concluded that clinically relevant drug-drug pharmacokinetic interactions for ciprofloxacin or dexamethasone through protein binding, or involving P450 metabolism with concomitant medications, would be unlikely for both compounds following topical otic administration.

However, the systemic administration of some quinolones has been shown to enhance the effects of the oral anticoagulant, warfarin, and its derivatives, and has been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.

Oral administration of ciprofloxacin has been shown to inhibit cytochrome P450 CYP1A2 and CYP3A4 isozymes, and alter the metabolism of methylxanthine compounds (caffeine, theophylline). Following topical otic administration of Ciprofloxacin/Dexamethasone, ciprofloxacin plasma concentrations are low, and it is unlikely that an interaction involving P450 metabolism with concomitant medications would result in clinically relevant changes in plasma levels of methylxanthine compounds.

4.6 Fertility, pregnancy and lactation

Pregnancy
Since no animal reproduction studies and no adequate or well controlled studies in pregnant women have been conducted with the combination of ciprofloxacin and dexamethasone, Ciprofloxacin/Dexamethasone should not be used during pregnancy unless clearly necessary and only if the potential benefit justifies the potential risk to the foetus (see section 5.3).

Breast-feeding
Ciprofloxacin and corticosteroids, as a class, appear in milk following oral administration. It is not known whether topical administration to humans could result in sufficient systemic absorption to produce detectable quantities in breast milk. A risk to the suckling child cannot be excluded. Caution should be exercised if this medicine is administered during lactation.

Fertility
No human data on the effect of Ciprofloxacin/Dexamethasone on fertility are available (see also section 5.3). Topical dermal studies in animals have shown effects on male sex organs following long-term use of dexamethasone at high doses. Reproduction studies performed in rats and mice at doses up to six-times the usual daily human oral dose revealed no evidence of impaired fertility.

4.7 Effects on ability to drive and use machines

Ciprofloxacin/Dexamethasone has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

In 5 clinical studies involving 976 patients, Ciprofloxacin/Dexamethasone was administered twice daily. This included 439 patients participating in 3 clinical studies with acute otitis media with tympanostomy tubes and 537 patients participating in 2 clinical studies with acute otitis externa. No serious otic or systemic undesirable effects related to Ciprofloxacin/Dexamethasone were reported in any of the clinical studies. In clinical trials, the most common adverse drug reactions were ear pain and ear discomfort, occurring approximately 1% to 1.5% patients.

Tabulated summary of adverse events

The following adverse reactions listed in the table below were observed in clinical studies or with post-marketing experience. They are ranked according to system organ class and classified according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), or not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Classification	**Adverse reactions**
Eye disorders	*Not known:* vision blurred (see section 4.4.)
Infections and Infestations	*Uncommon:* candidiasis
Immune system disorders	*Not known:* hypersensitivity
Nervous System Disorders	*Uncommon:* paraesthesia (tingling in ears), crying *Rare:* dizziness, headache
Ear and Labyrinth Disorders	*Common:* ear pain *Uncommon:* otorrhoea, ear congestion, ear discomfort, ear pruritus, ear infection fungal, *Rare:* hypoacusis, tinnitus, medication residue present *Not known:* auricular swelling
Vascular Disorders	*Uncommon:* flushing
Gastrointestinal Disorders	*Uncommon:* vomiting, dysgeusia
Skin and Subcutaneous Tissue Disorders	*Uncommon:* skin exfoliation *Rare:* rash erythematous
General Disorders and Administration Site Conditions	*Uncommon:* device occlusion (tympanostomy tube obstruction), irritability, fatigue

Description of selected adverse reactions

The most frequently reported adverse reactions reported in the 439 patients with acute otitis media with tympanostomy tubes were ear pain (2.5%), ear discomfort (2.5%), and dysgeusia (characterised as tasting the medicine) (1.1%). Of these events, only 1 patient discontinued therapy with that being due to an occurrence of ear discomfort.

The most frequently reported adverse reaction reported in the 537 patients with acute otitis externa was ear pruritus (1.5%). No patient discontinued therapy due to an occurrence of ear pruritus.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial oedema), airway obstruction, dyspnoea, urticaria, and itching.

The development of secondary infections has occurred after the use of combinations containing corticosteroids or antimicrobials.

Ruptures of the shoulder, hand, Achilles, or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving systemic fluoroquinolones. Studies and post marketing experience with systemic fluoroquinolones indicate that the risk of these ruptures may be increased in patients receiving corticosteroids, especially geriatric patients and in tendons under high stress, including the Achilles tendon. To date, clinical and post marketing data have not demonstrated a clear association between otic administration of ciprofloxacin and these musculoskeletal and connective tissue adverse reactions.

Paediatric population
Ciprofloxacin/Dexamethasone has been shown to be safe in paediatric patients 6 months of age or older for the treatment of AOMT and 1 year of age or older for the treatment of AOE. The frequency, type and severity of adverse reactions in paediatric patients are expected to be the same as in adults.

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 the national reporting system:

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

The limited holding capacity of the ear canal for topical otic products practically precludes overdosing via the ototopical route. However, oral ingestion of Ciprofloxacin/Dexamethasone resulting in overdose or long-term ototopical therapy may produce suppression of the Hypothalamic-Pituitary-Adrenal (HPA) Axis. Although decreases in paediatric growth velocity and/or suppression of cortisol plasma concentrations may be more pronounced after substantial overdose or prolonged treatment (e.g. several months) with Ciprofloxacin/Dexamethasone, the effect is expected to be transient (days to weeks) and easily reversible with no long-term sequelae.

Treatment of acute overdosage is generally by supportive and systemic therapy, and may initially include emesis and gastric lavage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Classification:
Pharmacotherapeutic group: OTOLOGICALS, Corticosteroids and anti-infectives in combination.

ATC-Code: S02CA06.

Mechanisms of Action:

These ear drops contain the fluoroquinolone, ciprofloxacin as the antibacterial agent. The bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

The mechanism of action of dexamethasone, a corticosteroid is not fully understood. However, it is known that corticosteroids bind to receptors in the cytoplasm, translocate to the nucleus, with subsequent binding to corticosteroid responsive elements on corticosteroid responsive genes. Corticosteroids are known to increase the transcription of anti-inflammatory proteins as well as inhibiting the expression of multiple inflammatory genes. Dexamethasone has an anti-inflammatory activity that is approximately 25 times more potent than hydrocortisone.

Mechanism of Resistance:

In-vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutation in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.

Impermeability and/or active substance of efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All in-vitro mechanisms of resistance are commonly observed in clinical isolates. Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may affect susceptibility to ciprofloxacin. Plasmid-mediated resistance encoded by qnr-genes has been reported.

Susceptibility testing breakpoints:

- Currently, minimal inhibitory concentration (MIC) breakpoints as established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) take into consideration drug concentrations achievable systemically following oral or intravenous administration of the antibiotic. These Susceptible/Resistant (S/R in mg/L) breakpoints are used in every day clinical laboratory practice to predict clinical efficacy. However, when ciprofloxacin is used by ototopical administration, higher concentrations could be achieved in the ear and the drug activity influenced by the physiochemical characteristics at this site of administration. EUCAST breakpoints are not adequate for a topical antibiotic but these recommendations that follow are consistent for a general use.

EUCAST S/R Recommended Breakpoints for Ciprofloxacin (version 10.0-2020.01.01)

Microorganisms	Susceptible (S)	Resistant (R)
Staphylococcus species	S ≤ 0.001 mg/L	R > 1 mg/L
Haemophilus influenzae	S ≤ 0.06 mg/L	R > 0.06 mg/L
Moraxella catarrhalis	S ≤ 0.125 mg/L	R > 0.125 mg/L
Pseudomonas aeruginosa	S ≤ 0.001 mg/L	R > 0.5 mg/L

- The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of

resistance is such that the utility of the agent in at least some types of infections is questionable.

Acute Otitis Media with Tympanostomy Tubes (AOMT)

Commonly susceptible species
Aerobic Gram-positive microorganisms: *Staphylococcus aureus* (methicillin-susceptible) *Streptococcus pneumoniae*
Aerobic Gram-negative microorganisms: *Haemophilus influenzae* *Moraxella catarrhalis* *Pseudomonas aeruginosa*
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms: *Staphylococcus aureus* (methicillin-resistant)

Acute Otitis Externa (AOE)

Commonly susceptible species
Aerobic Gram-positive microorganisms: *Staphylococcus aureus (methicillin- susceptible)* Aerobic Gram-negative microorganisms: *Pseudomonas aeruginosa*
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms: *Staphylococcus aureus* (methicillin-resistant)

The above information is based on microbiological surveillance studies performed at various sites in Europe and data obtained in the U.S.A. and Canadian clinical studies.

5.2 Pharmacokinetic properties

Ciprofloxacin

Absorption

Ciprofloxacin plasma levels are very low following topical otic doses of Ciprofloxacin/Dexamethasone to human paediatric patients. Following 4-drops in each ear (equivalent to 0.84 mg ciprofloxacin total dose), peak ciprofloxacin concentrations (C_{max}) were achieved within one hour and ranged from less than 0.50 ng/mL to 3.45 ng/mL with a mean C_{max} of 1.33 ng/mL. After C_{max} ciprofloxacin is eliminated from plasma with a half-life of approximately 3 hours similar to adult subjects following oral doses.

Distribution

Tissue distribution studies in animals show that ciprofloxacin distributes to all major organs and tissues. The highest concentrations are typically found in liver and kidney. Low concentrations are found in brain, fat and bone. Increases in dose result in proportional increases in tissue concentrations. The distribution and elimination of radioactivity is similar after single and repeated doses. Ciprofloxacin is not extensively bound to plasma proteins. In

rats and monkeys, the percent-bound is about 20 % to 40 % and is constant over a concentration range of 0.02 to 2.0 μg/mL.

Ciprofloxacin distributes into milk of lactating rats. Radioactivity in the milk is primarily associated with unchanged parent drug. In pregnant rats administered ^{14}C-ciprofloxacin, radioactivity distributes to the fetus but at lower levels than observed in maternal plasma.

Biotransformation
The metabolism of ciprofloxacin is similar in rats, monkeys and humans. Ciprofloxacin is not extensively metabolized and is eliminated primarily as unchanged drug in urine. Metabolism leads to metabolites with substantially less microbiological activity than parent drug. In *in vitro* studies with rat and human liver microsomes, ciprofloxacin inhibits biotransformation by the CYP1A and CYP3A families of P450. Drug-drug interactions have been demonstrated for a few specific drugs following coadministration with ciprofloxacin by the intravenous and oral routes. Some of these interactions have been linked to the ability of ciprofloxacin to inhibit CYP1A and CYP3A P450 isozyme mediated biotransformation.

Elimination
Ciprofloxacin is excreted in urine, feces and bile. In rats, following an intravenous dose, 51 % is recovered in the urine and 47 % is recovered in the feces. In monkeys and humans, urinary excretion is the major route of elimination. There is no indication of relevant enterohepatic circulation in the rat.

Paediatric population
Following a single bilateral 4-drop per ear (8 drops per administration) dose of Ciprofloxacin/Dexamethasone in 25 paediatric patients, the mean plasma ciprofloxacin C_{max} was 1.33 ± 0.96 ng/ml. Thereafter, ciprofloxacin concentrations decreased and were not quantifiable (< 0.50 ng/ml) in 21 patients at 6 hours post-dose, indicating low systemic exposure. The mean ciprofloxacin C_{max} (1.33 ng/ml) was ~570-fold lower than the mean C_{max} of 760 ng/ml reported after a therapeutic 250-mg ciprofloxacin oral dose in adult subjects. The mean ciprofloxacin $t_{1/2}$ was approximately 3 hours and was similar to that reported in adult subjects after oral administration. The systemic exposure to ciprofloxacin observed in clinical studies following topical otic administration of Ciprofloxacin/Dexamethasone represents the maximum in paediatric AOMT patients because of the presence of patent tympanostomy tubes without otorrhea. The systemic exposure to ciprofloxacin in AOE patients following topical otic administration of Ciprofloxacin/Dexamethasone would not be expected to be as high as those seen in paediatric patients with tympanostomy tubes due to lower bioavailability of topical drugs through an intact tympanic membrane.

Dexamethasone

Absorption
Dexamethasone plasma levels are very low following topical otic doses of Ciprofloxacin/Dexamethasone to human paediatric patients. Following 4-drops in each ear (equivalent to 0.28 mg dexamethasone total dose), peak dexamethasone concentrations (C_{max}) were achieved within one hour with a mean C_{max} of 0.09 ng/mL. After C_{max} dexamethasone is eliminated from plasma with a half-life of approximately 4 hours similar to adult subjects following oral doses.

Distribution
The mean volume of distribution in man has been reported as 0.576 to 1.15 L/kg. In animals, corticosteroids, as a class, distribute to muscles, liver, skin, intestine and kidneys. In pregnant rats, dexamethasone crosses the placenta, but fetal plasma levels are below maternal levels.

Dexamethasone also distributes into breast milk, but to a small extent. Binding to serum albumin is approximately 77 % to 84 %.

Biotranformation
The major elimination route for dexamethasone is liver metabolism. Approximately 60 % of the dose in man is found in the urine as 6-(beta)-hydroxydexamethasone, with 6-(beta)-hydroxy-20-dihydrodexamethasone also identified as a significant urinary metabolite. Parent dexamethasone is not found in the urine. The primary P450 isozyme responsible for the biotransformation of dexamethasone is CYP3A4. Clearance of dexamethasone in man is 0.111 to 0.225 L/hr/kg. The elimination half-life is about 3 to 4.7 hours in man. Dexamethasone metabolism is induced by anticonvulsants and inhibited by isoniazid and the potent P450 CYP3A4 inhibitor itraconazole.

Paediatric population
Following a single bilateral 4-drop per ear (8 drops per administration) dose of Ciprofloxacin/Dexamethasone in 24 paediatric patients, the mean plasma dexamethasone C_{max} was 0.90 ± 1.04 ng/ml. Thereafter, dexamethasone concentrations decreased and were not quantifiable (<0.05 ng/ml) in 10 patients at 6 hours post-dose, indicating low systemic exposure. The mean dexamethasone C_{max} (0.90 ng/ml) was ~8.8-fold lower than the mean C_{max} of 7.9 ng/ml reported after a 0.5-mg oral dose of dexamethasone in adult subjects. The mean dexamethasone $t_{1/2}$ was approximately 4 hours and was similar to that reported in adult subjects after oral administration. The systemic exposure to dexamethasone observed in clinical studies following topical otic administration of Ciprofloxacin/Dexamethasone represents the maximum in paediatric AOMT patients because of the presence of patent tympanostomy tubes without otorrhea. The systemic exposure to dexamethasone in AOE patients following topical otic administration of Ciprofloxacin/Dexamethasone would not be expected to be as high as those seen in paediatric patients with tympanostomy tubes due to lower bioavailability of topical drugs through an intact tympanic membrane.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of repeated dose toxicity.

There is no evidence that the topical otic administration of Ciprofloxacin/Dexamethasone has any effect on weight bearing joints, even though oral administration of some quinolones has been shown to cause arthropathy in immature animals.

Guinea pigs dosed in the middle ear with Ciprofloxacin/Dexamethasone ear drops for one month exhibited no drug-related structural or functional changes of the cochlear hair cells and no lesions in the ossicles.

Mutagenic and Carcinogenic potential
Available data of genetic toxicology tests with ciprofloxacin and dexamethasone did not show evidence for a biologically relevant mutagenic potential for the topical otic application of Ciprofloxacin/Dexamethasone.

No long-term studies of Ciprofloxacin/Dexamethasone have been performed to evaluate carcinogenic potential.

Reproduction Toxicity
Topical dermal studies in animals have shown effects on male sex organs following long-term use of dexamethasone at doses much higher than those resulting from the use of Ciprofloxacin/Dexamethasone. Reproduction studies performed in rats and mice at doses up

to six-times the usual daily human oral dose revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin.

After intravenous administration of doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed. Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Hydroxyethyl cellulose

Sodium acetate, trihydrate

Acetic acid

Sodium chloride

Disodium edetate

Tyloxapol

Boric acid

Hydrochloride acid / sodium hydroxide (for pH adjustment)

Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

After first opening: 4 weeks

6.4 Special precautions for storage

Do not freeze. Keep the bottle in the outer carton in order to protect from light.

6.5 Nature and contents of container

5 ml DROP-TAINER LDPE bottle and plug with polypropylene closure, containing 5 ml of suspension.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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10 DATE OF REVISION OF THE TEXT

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