NOVARTIS

Drug Regulatory Affairs

SPERSADEX® Comp.

(chloramphenicol and dexamethasone sodium phosphate)

5 mg/mL chloramphenicol and 1 mg/mL dexamethasone, Eye drops

Basic Prescribing Information

NOTICE

The Basic Prescribing Information (BPI) is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

National Prescribing Information is based on the BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Package Insert or European SPCs) may differ in several respects, including but not limited to the characterisation of risks and benefits.

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GLC approval: 29 November 2005, amended 7 September 2010

Release date: 29 September 2010

Document status: Final

Number of pages:

1 Name of the medicinal product

SPERSADEX® Comp., 5 mg/mL chloramphenicol [7] and 1 mg/mL dexamethasone sodium phosphate [17], eye drops.

2 Qualitative and quantitative composition

Each mL contains 5 mg chloramphenicol and 1 mg dexamethasone sodium phosphate.

For a full list of excipients, see section 6.1. List of Excipients.

3 Pharmaceutical form

Eye drops.

Opalescent, colourless to slightly yellow solution.

Information might differ in some countries.

4 Clinical particulars

4.1 Therapeutic indications

Inflammation of the anterior segment of the eye in patients in whom corticosteroid therapy is indicated and there is either concurrent infection with bacteria susceptible to chloramphenicol (see section 5.1 Pharmacodynamic properties) or a high risk of such infection [6,9,11,14,15b,28,29].

4.2 Posology and method of administration

1 drop, instilled into the conjunctival sac 3 to 5 times daily for up to 10 days [5,6,9,19,29].

In acute cases: up to 1 drop per hour.

Elderly: There is no indication that dosage needs to be modified for the elderly.

Paediatric use: Studies in the paediatric population have not been performed. Due to the possibility of adverse systemic effects, caution is required when administering the product to infants (28 days to 3 months old), and children under 2 years of age (see section 4.4 Special warning and precautions for use). Spersadex® Comp. must not be used in newborn infants (0 to 27 days old), (see section 4.3 Contraindications).

Following instillation of the eye drops nasolacrimal occlusion or closing the eyelids for 3 minutes may reduce systemic absorption. This may result in a decrease in systemic side effects and an increase in local activity.

The dispenser remains sterile until the original closure is broken. Patients must be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures as this may contaminate the solution.

If more than one medication needs to be instilled in the eye an interval of at least 5 minutes between application of the different medicinal products must be allowed.

4.3 Contraindications

- Known hypersensitivity to the active substances or to any of the excipients.
- Corneal lesions due to non-bacterial infections and ulcerative processes. Herpes simplex and other viral infections. Mycosis and other fungal infections.
- Severe blood disorders due to bone marrow depression and hepatic dysfunction.
- Family history of bone marrow depression.
- Newborn infants (0 to 27 days old).

4.4 Special warnings and precautions for use

Long-term treatment with chloramphenicol, also when applied topically to the eye, may in very rare occasions lead to bone marrow aplasia [1,12,15,20,22,31,32,34]. The irreversible form may occur following a latent period of weeks or months.

Prolonged use may result in secondary ocular infections or may support growth of non-susceptible bacteria. Corticosteroids may mask, activate or exacerbate an eye infection [17].

The prolonged use of corticosteroids may cause a pathological increase in intraocular pressure. In predisposed individuals and those known to have glaucoma, intraocular pressure must be monitored regularly, especially in cases of prolonged treatment [17].

Intensive, long-term therapy may possibly contribute to the formation or exacerbation of posterior sub-capsular cataracts [17].

The preparation should not be used for more than a maximum of 10 days.

In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with chronic use of topical steroids [17]. Caution should also be exercised when topical steroids such as dexamethasone are used concomitantly with topical NSAIDs (see section 4.5 Interactions with other medicinal products and other forms of interaction) [36].

If there is no improvement after 3 days of treatment, other therapeutic measures should be considered.

The use of steroids immediately after cataract surgery may delay healing and increase the incidence of bleb formation [17].

Caution should be exercised in patients with diabetes mellitus. These patients may be predisposed toward increases in intraocular pressure and/or cataract formation [17].

In general, caution is required when administering corticosteroids to infants (28 days to 3 months old) and children under 2 years of age [17].

The use of contact lenses with eye infections is not recommended as they may spread micro-organisms. Benzalkonium chloride may cause eye irritation and is known to discolour soft contact lenses.

Eye drops are not for injection. They should never be injected subconjunctivally nor should they be directly introduced into the anterior chamber of the eye.

4.5 Interaction with other medicinal products and other forms of interaction

Spersadex Comp. should not be used concurrently with topical bactericidal substances (penicillins, cephalosporins, gentamicin, tetracyclines, polymixin B, vancomycin, sulfadiazine) because bacteriostatic antibiotics can inhibit those with a bactericidal action [1].

As a precaution, Spersadex Comp. should not be used during systemic treatment with drugs that cause haemopoietic damage such as sulphonylureas, coumarin derivatives, hydantoins and methotrexate [20,34].

Concomitant use of topical steroids such as dexamethasone and topical NSAIDs in patients with significant pre-existing corneal inflammation may increase the risk of developing corneal complications, therefore caution should be used.(see section 4.4 Special warnings and precautions for use) [36].

4.6 Pregnancy and lactation

Animal studies with chloramphenicol have demonstrated undesirable effects on the foetus (see section 5.3 Preclinical safety data) [23]. Administration of chloramphenicol during pregnancy can cause neonatal ‘grey’ syndrome [1,26].

Dexamethasone has been shown to be teratogenic in mice and rabbits following topical ophthalmic application in multiples of the therapeutic dose (see section 5.3 Preclinical safety data) [1,18,26]. No controlled trials in pregnant women are available.

Chloramphenicol is excreted in breast milk [1] and may cause bone marrow toxicity in infants [4].

Spersadex Comp. should not be used during pregnancy or by breast feeding mothers.

4.7 Effects on ability to drive and use machines

Any patient who experiences blurred vision or visual impairment should not drive or operate machines until vision returns to normal.

4.8 Undesirable effects [4b]

As Spersadex Comp. contains a combination of dexamethasone and chloramphenicol adverse reactions observed with each active substance may be expected. There is no evidence from post marketing experience of added toxicity following concurrent administration of the two compounds [24,24b].

Blood and lymphatic system disorders

Rare cases of sometimes irreversible blood dyscrasias (aplastic anaemia, pancytopenia, leucopenia, thrombocytopenia and agranulocytosis) with a fatal outcome have been reported

in the literature following the use of ophthalmic preparations containing chloramphenicol [1,12,15,20,22,31,32,34].

Immune system disorders

Anaphylactic reactions [2,21] to topical chloramphenicol have been published in the literature. Rarely, allergic reactions in the form of eczema of the lid margins have been reported.

Nervous system disorder

In rare cases, reversible optic neuritis has been observed following administration of chloramphenicol [30].

Eye disorders

The most frequently reported adverse reactions are those indicative of irritation or hypersensitivity reactions (itching, redness, swelling, foreign body sensation, or other sign of irritation not present before therapy). Ocular burning or stinging upon drug instillation and blurred vision have also been reported [2].

Adverse reactions associated with topical steroid therapy include elevation of intraocular pressure with possible development of glaucoma (optic nerve damage; visual acuity and field defects), posterior subcapsular cataract formation, secondary ocular infection following suppression of host response; delayed wound healing and corneal thinning and/or perforation of the globe may occur [17].

Ptosis and mydriasis have also been related to the use of ophthalmic steroids [17].

Gastrointestinal disorder

The patient may experience a bitter taste (dysgeusia) shortly after application of chloramphenicol [1].

Although systemic effects are uncommon, there have been some cases of systemic corticosteroid effects after topical administration of corticosteroids [17].

4.9 Overdose

There have been no known cases of overdose involving topical use. Oral ingestion of the contents of one 5 mL bottle would be equivalent to 25 mg of chloramphenicol and 5 mg dexamethasone which is 1 % (usual dose 50 mg/kg daily) and within the range (usual dose 0.5 to 10 mg daily) respectively of the recommended oral daily dose for an adult [4].

Measures should be taken to delay absorption in case of inadvertent oral ingestion. There is no specific antidote.

5 Pharmacological properties

5.1 Pharmacodynamic properties [1,3,17,22,32]

Pharmacotherapeutic group: Corticosteroids and anti-infectives in combination. ATC code: S01CA01.

Dexamethasone

The anti-inflammatory effect of dexamethasone is about 25 times greater than that of hydrocortisone. Like all anti-inflammatory glucocorticoids, dexamethasone inhibits phospholipase A2, the first step in prostaglandin synthesis, and thus prevents subsequent formation of inflammatory mediators such as prostaglandins and leukotrienes. In addition, dexamethasone inhibits the chemotactic migration of neutrophils into the focus of inflammation and reduces the numbers and activity of lymphocytes [17].

Chloramphenicol

Chloramphenicol is a low-molecular weight, bacteriostatic antibiotic, with a broad spectrum of activity against gram-positive and gram-negative bacteria, Rickettsia and Mycoplasma. [1,22]. The mechanism of action has been shown to be selective inhibition of bacterial protein synthesis.

Chloramphenicol is active against the following common bacterial eye pathogens: *Staphylococcus aureus, Streptococci* including *Streptococcus pneumoniae*, *Escherichia coli, Haemophilus influenzae, Klebsiella/Enterobacter* species, *Moraxella lacunata* (Morax-Axenfeld bacillus) and the *Neisseria* species. It does not provide adequate coverage against *Pseudomonas aeruginosa* and *Serratia marcescens.*

Chloramphenicol-resistance has been demonstrated in vitro and in vivo in strains of *Staphylococci, Salmonella, Shigella, E. coli,* and *Pseudomonas aeruginosa*. Resistance to chloramphenicol is due, in part, to a plasmid-mediated resistance factor. In vitro susceptibility tests of bacteria isolated from the surface of clinically symptomatic eyes and using various topical antibiotics showed that chloramphenicol had the highest in vitro activity of the antibiotics tested and chloramphenicol-resistance was minimal [13].

5.2 Pharmacokinetic properties [8,10]

Dexamethasone

In rabbit eyes, peak concentrations of 15 micrograms/g in the cornea (7.5 minutes after instillation) and 1 microgram/g in the aqueous humour (40 to 45 minutes after instillation) were measured after a single 50 microlitres application of a 0.1 % radioactively labelled ^{14}C-dexamethasone sodium phosphate solution. Iris concentrations of dexamethasone varied greatly with time [27]. Another study in rabbits confirmed the rapid (2 micrograms/g in the cornea and 0.2 micrograms/mL in the aqueous humour, 10 minutes after instillation of 50 microlitres of 1 mg/mL dexamethasone) and lasting (radioactivity detected up to 24 hours after instillation) intraocular absorption of ophthalmic dexamethasone [25].

Chloramphenicol

Following topical application of 50 microlitres of 5 mg/mL chloramphenicol to the eye, chloramphenicol rapidly penetrates the human cornea (aqueous humor concentrations ranged from 3.5 to 6.7 micrograms/mL 1 to 2 hours after instillation) and can be found in the aqueous humour for up to 5 hours after instillation [7]. Another study confirmed the rapid penetration of chloramphenicol 0.5 % ophthalmic solution but concluded that chloramphenicol 1 % ointment achieved more lasting intraocular concentrations of chloramphenicol [16]. Systemic levels of chloramphenicol were not detected using High Pressure Liquid Chromatography (HPLC) after ophthalmic administration of 5 mg/ml of chloramphenicol, one drop 4 times daily, for 2 weeks [34] although the possibility of systemic absorption cannot be ruled out [3,34]. In another study, urine samples from 5 children receiving 2-hourly ophthalmic chloramphenicol (concentration of 5 mg/mL) drops for 5 to 7 days were assayed by Gas Liquid Chromatography (GLC) and no chloramphenicol was detected [33].

5.3 Preclinical safety data

Preclinical safety data with chloramphenicol and corticosteroids relevant for ocular use include reproductive toxicity studies [18,23,26].

Chloramphenicol, given systemically in high doses to rats, has been shown to have significant embryotoxic effects (foetal growth retardation) accompanied by weak teratogenic effects [23].

Dexamethasone has been shown to be teratogenic in mice and rabbits following topical ophthalmic application in multiples of the therapeutic dose. In the mouse, corticosteroids produce foetal resorptions and cleft palate. In the rabbit, corticosteroids have produced foetal resorptions and multiple abnormalities involving the head, ears, limbs and palate [18,26].

6 Pharmaceutical particulars

6.1 List of excipients

Macrogol 400; Macrogolglycerol ricinoleate; Disodium edentate; Sodium hydroxide; Benzalkonium chloride; Water for injections.

Information might differ in some countries.

6.2 Incompatibilities

None known for Spersadex Comp.

6.3 Shelf life

Unopened container: 1 year. Once the bottle has been opened, do not use for more than 1 month.

Information might differ in some countries.

6.4 Special precautions for storage

The eye drops should be stored in a refrigerator (2 to 8°C) prior to initial use.

Spersadex Comp. must be kept out of reach and sight of children.

6.5 Nature and contents of container

White coloured low-density polyethylene bottles of 5 mL with low-density polyethylene droppers, and closed with white coloured high-density polyethylene caps.

6.6 Instructions for use and handling, and disposal

No special requirements.

This is a non-referenced document.