SUMMARY OF PRODUCT CHARACTERISTICS

Summary of Product Characteristics

MAXIDEX® 1 mg/ml eye drops, suspension.

MAXIDEX® 1 mg/g eye ointment.

1. NAME OF THE MEDICINAL PRODUCT

MAXIDEX® 0.1% sterile ophthalmic suspension

MAXIDEX® 0.1% sterile ophthalmic ointment

(dexamethasone)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MAXIDEX ophthalmic suspension
1 ml of suspension contains 1 mg dexamethasone.
Preservative: 1 ml of suspension contains 0.1 mg benzalkonium chloride.

For the full list of excipients, see section 6.1.

MAXIDEX ophthalmic ointment
1 g of ointment contains 1 mg dexamethasone.
Preservative: 1 g of ointment contains 0.5 mg methylparaben and 0.1 mg propylparaben.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

MAXIDEX ophthalmic suspension

Sterile ophthalmic suspension.

Opaque, white to pale yellow suspension, no agglomerates.

MAXIDEX ophthalmic ointment

Sterile ophthalmic ointment.

A greasy, translucent, white to off-white, homogeneous ointment.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MAXIDEX contains dexamethasone, a synthetic corticosteroid.

MAXIDEX is indicated in the management of conditions generally responsive to corticosteroids such as:

- Certain inflammatory eye conditions of the anterior segment: acute and chronic anterior uveitis, iridocyclitis, iritis and cyclitis, herpes zoster ophthalmicus.
- Certain external diseases such as phlyctenular kerato-conjunctivitis, nonpurulent conjunctivitis, including vernal, allergic, catarrhal. It is very effective where allergy is a main factor.
- Recurrent marginal ulceration of toxic or allergic etiology.
- Thermal and chemical burns.
- Post-operatively to reduce inflammatory reactions.

4.2 Posology and method of administration

MAXIDEX ophthalmic suspension

Posology

Topical application (1 or 2 drops in the conjunctival sac).

SEVERE OR ACUTE INFLAMMATION: Every 30 to 60 minutes as initial therapy, being tapered to discontinuation as inflammation subsides. If favourable response is not obtained in 3 to 4 days, additional systemic or conjunctival therapy may be indicated.

CHRONIC INFLAMMATION: Every 3 to 6 hours, or as frequently as necessary, being tapered to discontinuation as inflammation subsides.

ALLERGIES OR MINOR INFLAMMATION: Every 3 to 4 hours until the desired response is obtained, being tapered to discontinuation as inflammation subsides.

Prolonged treatment over several days should only be carried out under medical supervision.

Use in children

The safety and efficacy of MAXIDEX ophthalmic suspension in children have not been established.

Use in patients with hepatic or renal impairment

MAXIDEX ophthalmic suspension has not been studied in patients with hepatic or renal disease.

Use in geriatric patients

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

Method of administration

For ocular use.

Shake well before use.

After cap is removed, if tamper evident snap collar is loose, remove before using product.

To prevent contamination of the dropper tip and suspension, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip. Keep the bottle tightly closed when not in use.

Nasolacrimal occlusion or gently closing the eyelid after administration is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route and result in a decrease in systemic adverse reactions.

If more than one topical ophthalmic product is being used, the products must be administered at least 5 minutes apart. Eye ointments should be administered last.

MAXIDEX ophthalmic ointment

Posology

Apply ribbon of ointment into the conjunctival sac(s) up to 4 times daily. When a favourable response is observed, dosage may be reduced gradually to once a day application for several days.

Use in children

The safety and efficacy of MAXIDEX ophthalmic ointment in children have not been established.

Use in patients with hepatic or renal impairment

MAXIDEX ophthalmic ointment has not been studied in patients with hepatic or renal disease.

Use in geriatric patients

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

Method of administration

For ocular use.

To prevent contamination of the tube tip and ointment, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the tube tip. Keep the tube tightly closed when not in use.

If more than one topical ophthalmic product is being used, the products must be administered at least 5 minutes apart. Eye ointments should be administered last.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Acute, untreated bacterial infections which like other diseases caused by micro-organisms, may be masked or enhanced by the presence of the steroid.
- Herpes simplex keratitis.
- Vaccinia, varicella, and other viral infections of cornea or conjunctiva.
- Fungal diseases of ocular structures or untreated parasitic eye infections.
- Mycobacterial ocular infections.

4.4 Special warnings and precautions for use

- Prolonged use of topical ophthalmic corticosteroids may result in ocular hypertension and/or glaucoma, with damage to the optic nerve, reduced visual acuity and visual field defects, and posterior subcapsular cataract formation. In patients receiving prolonged ophthalmic corticosteroid therapy, intraocular pressure should be checked routinely and frequently. This is especially important in paediatric patients, as the risk of corticosteroid-induced ocular hypertension may be greater in children and may occur earlier than in adults.
- The risk of corticosteroid-induced raised intraocular pressure and/or cataract formation is increased in predisposed patients (e.g. diabetes).
- Cushing's syndrome and/or adrenal suppression associated with systemic absorption of ophthalmic dexamethasone may occur after intensive or long-term continuous therapy in predisposed patients, including children and patients treated with CYP3A4 inhibitors (including ritonavir and cobicistat). (See section 4.5). In these cases, treatment should not be discontinued abruptly, but progressively tapered.
- Corticosteroids may reduce resistance to and aid in the establishment of bacterial, viral, fungal or parasitic infections and mask the clinical signs of infection.
- Fungal infection should be suspected in patients with persistent corneal ulceration. Corticosteroids therapy should be discontinued if fungal infection occurs.
- Topical ophthalmic corticosteroids may slow corneal wound healing. Topical NSAIDs are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems (see section 4.5).
- In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical corticosteroids.
- During the course of therapy, if the inflammatory reaction does not respond within a reasonable period, other forms of therapy should be instituted.
- A few individuals may be sensitive to one or more of the components of this product. If any reaction indicating sensitivity is observed, discontinue use.
- The wearing of contact lenses is discouraged during treatment of an ocular inflammation. MAXIDEX ophthalmic suspension contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. Avoid contact with soft contact lenses. In case patients are allowed to wear contact lenses, they must be instructed to remove contact lenses prior to application of MAXIDEX ophthalmic suspension and wait at least 15 minutes before reinsertion.

- MAXIDEX ophthalmic ointment contains methylparaben and propylparaben which may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

- Concomitant use of topical steroids and topical NSAIDs may increase the potential for corneal healing problems.
- CYP3A4 inhibitors including ritonavir and cobicistat may increase systemic exposure resulting in increased risk of adrenal suppression/Cushing's syndrome. (See Section 4.4). The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side effects, in which case patients should be monitored for systemic corticosteroid effects.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate or well-controlled studies evaluating MAXIDEX in pregnant women. Prolonged or repeated corticoid use during pregnancy has been associated with an increased risk of intra-uterine growth retardation. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be observed carefully for signs of hypoadrenalism (see section 4.4).

Studies in animals have shown reproductive toxicity after systemic administration. The ocular administration of 0.1% dexamethasone also resulted in foetal anomalies in rabbits (see section 5.3).

MAXIDEX is not recommended during pregnancy.

Breast-feeding

It is unknown whether MAXIDEX is excreted in human milk. No data is available on the passage of dexamethasone into human breast milk. It is not likely that the amount of dexamethasone would be detectable in human milk or be capable of producing clinical effects in the infant following maternal use of the product. A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue or abstain from MAXIDEX therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Studies have not been performed to evaluate the effect of topical ocular administration of dexamethasone on fertility. There is limited clinical data to evaluate the effect of dexamethasone on male or female fertility. Dexamethasone was free of adverse effects on fertility in a chorionic gonadotropin primed rat model.

4.7 Effects on ability to drive and use machines

MAXIDEX has no or negligible influence on the ability to drive and use machines.

However, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs after administration, the patient must wait until the vision clears before driving or using machinery.

4.8 Undesirable effects

Tabulated summary of adverse reactions

The following adverse reactions are 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; data from post-marketing surveillance). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness. The adverse reactions have been reported during clinical trials and identified from post-marketing surveillance.

System Organ Class	**Adverse reactions**
Immune system disorders	*Not known:* hypersensitivity
Endocrine disorders	*Not known:* Cushing's syndrome, adrenal insufficiency
Nervous system disorders	*Uncommon*: dysgeusia *Not known*: dizziness, headache
Eye disorders	*Common*: ocular discomfort *Uncommon*: keratitis, conjunctivitis, dry eye, vital dye staining cornea present, photophobia, vision blurred, eye pruritus, foreign body sensation in eyes, lacrimation increased, abnormal sensation in eye, eyelid margin crusting, eye irritation, ocular hyperaemia *Not known*: glaucoma, ulcerative keratitis, intraocular pressure increased, visual acuity reduced, corneal erosion, eyelid ptosis, eye pain, mydriasis

Description of selected adverse reactions

- Prolonged topical ophthalmic corticosteroids may result in increased intraocular pressure with damage to the optic nerve, reduced visual acuity and visual field defects, and to posterior subcapsular cataract formation (see section 4.4).
- Due to the corticosteroid component, in diseases causing thinning of the cornea or sclera there is a higher risk for perforation especially after long treatments (see section 4.4).

- Corticosteroids may reduce resistance to and aid in the establishment of infections (see section 4.4).

4.9 Overdose

An ocular overdose of MAXIDEX may be flushed from the eye(s) with lukewarm water.

Due to the characteristics of this preparation, no additional toxic effects are to be expected with an acute ocular overdose of this product or in the event of accidental ingestion of the contents of one bottle or tube.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-inflammatory agents, corticosteroids. ATC code: S01BA01.

Topical corticosteroids exert an anti-inflammatory action and have been used for the treatment of inflammation of the anterior chamber of the eye since the 1950s. Aspects of the inflammatory process such as edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, deposition of collagen, scar formation and fibroblastic proliferation are suppressed. Topical corticosteroids are effective in acute inflammatory conditions of the conjunctiva, sclera, cornea, lids, iris and anterior segment of the globe as well as in ocular allergic conditions.

Mechanism of action

The exact mechanism of anti-inflammatory action of dexamethasone is unknown. It inhibits multiple inflammatory cytokines and produces multiple glucocorticoid and mineralocorticoid effects.

Pharmacodynamic effects

Dexamethasone is one of the most potent corticosteroids; with a relative anti-inflammatory potency greater than prednisolone or hydrocortisone.

The potency of this compound is accomplished by the addition of a methyl radical and a fluorine atom to the prednisolone radical. Of paramount importance with regard to local therapy is the fact that dexamethasone is over 2000 times more soluble than hydrocortisone or prednisolone.

Dexamethasone suspension/ointment is metabolized primarily in the liver (CYP450: 3A4 substrate; 3A4 inducer) with minimal systemic absorption and excreted primarily in urine with a half-life 1.8 to 3.5h, 36 to 54h (biological half-life).

Clinical efficacy and safety

The safety and efficacy of dexamethasone suspension/ointment have been established in adult clinical trials, published literature, and post-marketing surveillance.

Paediatric population

The safety and efficacy of dexamethasone suspension/ointment have not been studied in children; however, dexamethasone is reportedly safe for paediatric use, in general.

5.2 Pharmacokinetic properties

Absorption

After topical ocular administration, dexamethasone is detectable after 30 minutes in the aqueous humour and peaks at 90-120 minutes with a mean concentration of 31 ng/ml. Low but detectable concentrations are observed in the aqueous humour after 12 hours. Oral bioavailability of dexamethasone ranged from 70-80% in normal subjects and patients.

Distribution

After intravenous administration, the volume of distribution at steady state was 0.58 l/kg. *In vitro*, no change in human plasma protein binding was observed with dexamethasone concentrations from 0.04 to 4 µg/ml, with a mean plasma protein binding of 77.4%.

Biotransformation

After oral administration, two major metabolites were recovered which 60% of the dose was recovered as 6β-hydroxydexamethasone and up to 10% recovered as 6β-hydroxy-20-dihydrodexamethasone.

Elimination

After intravenous administration, the systemic clearance was 0.125 l/hr/kg. After i.v. bolus administration, 2.6% of the unchanged parent drug was recovered in the urine while up to 70% was recovered as identified metabolites. After systemic dosing, the half-life has been reported as 3-4 hours but was found to be slightly longer in males. This observed difference was not attributed to changes in systemic clearance but to differences in volume of distribution and body weight.

Linearity/non-linearity

Linear pharmacokinetics was observed after oral administration with doses between 0.5 to 1.5 mg where the AUC was less than proportional to the oral dose.

Pharmacokinetic/pharmacodynamic relationship(s)

A pharmacodynamic/pharmacokinetic relationship after topical ocular administration has not been established.

Special population pharmacokinetics

Pharmacokinetics of systemic dexamethasone did not significantly differ in renal-impaired patients when compared to normal subjects. Paediatric pharmacokinetics varied between age groups but wide interpatient variabilities were observed.

5.3 Preclinical safety data

In comparison to clinically relevant doses, non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity or toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

MAXIDEX ophthalmic suspension

Disodium phosphate anhydrous, polysorbate 80, disodium edetate, sodium chloride, citric acid monohydrate and/or sodium hydroxide (to adjust pH), benzalkonium chloride, hydroxypropyl methylcellulose and purified water.

MAXIDEX ophthalmic ointment

Methylparaben, propylparaben, anhydrous liquid lanolin and white petrolatum.

6.2 Incompatibilities

Not applicable.

6.3 Special precautions for storage

MAXIDEX ophthalmic suspension

Do not use this medicine after the expiry date which is stated on the packaging.

Discard 4 weeks after first opening.

Keep this medicine out of the sight and reach of children.

MAXIDEX ophthalmic ointment:

Do not use this medicine after the expiry date which is stated on the packaging.

Discard 4 weeks after first opening.

Keep this medicine out of the sight and reach of children.

6.4 Nature and contents of container

MAXIDEX ophthalmic suspension:

Sterile DROP-TAINER® dispenser containing 5 ml.

MAXIDEX ophthalmic ointment:

Tube containing 3.5 g ointment.

6.5 Special precautions for disposal and other handling

No special requirements.

Manufactured by:

ALCON-COUVREUR

B-2870 Puurs (Belgium) for Novartis Pharma AG, Basel, Switzerland