NOVARTIS

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).
- FOR SEVERE OR ACUTE INFLAMMATION: drops may be used every 30 to 60 minutes as initial therapy, being tapered to discontinuation as inflammation subsides.
- If favorable response is not obtained in 3 to 4 days, additional systemic or conjunctival therapy may be indicated.
- FOR CHRONIC INFLAMMATION: drops may be used every 3 to 6 hours, or as frequently as necessary. Being tapered to discontinuation as inflammation subsides.
- ALLERGIES OR MINOR INFLAMMATION: drops may be used 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 pediatric patients (below 18 years)

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

Use in patients with hepatic or renal impairment

No studies have been performed in patients with renal or hepatic impairment. *Use in geriatric patients (65 years of age or above)*

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

Method of administration

For ocular use only.

Shake the bottle well before use.

After cap is removed, if tamper evident snap collar is loose, it should be removed before using the 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(s) after administration is recommended. This may reduce the systemic absorption of medicinal products administered via 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 favorable response is observed, dosage may be reduced gradually to once a day application for several days.

Use in pediatric patients (below 18 years)

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

Use in patients with hepatic or renal impairment

No studies have been performed in patients with renal or hepatic impairment.

Use in geriatric patients (65 years of age or above)

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

Method of administration

For ocular use only.

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 disease of ocular structures or untreated parasitic eye infections.
- Mycobacterial ocular infections

4.4 Special warnings and precautions for use

- 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.

- Prolonged use of topical ophthalmic corticosteroid 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 CYP34A 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 or 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 may possibly discolour soft contact lenses. Contact lenses must be removed before administration of MAXIDEX Ophthalmic suspension and reinserted at least 15 minutes later.
- 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 of dexamethasone 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 corticosteroid use during pregnancy has been associated with an increased risk of intrauterine 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 fetal anomalies in rabbits (see Section 5.3).

MAXIDEX is not recommended during pregnancy.

Lactation
It is not known if dexamethasone is transferred into human milk after administration of Maxidex. 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 or on milk production following maternal use of the product.

A risk to the breastfed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
There are no data regarding the effects of topical ocular administration of Maxidex on human or animal 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

Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs after instillation, 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 have been reported during clinical trials with MAXIDEX* Eye Drops/Ointment and are classified according to the subsequent 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). Adverse drug reactions from clinical trials are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. 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 Classification	**MedDRA Preferred Term**
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

The following adverse drug reactions have been derived from post-marketing surveillance include the following. Frequencies cannot be estimated from the available data. Within each System Organ Class, adverse drug reactions are presented in order of decreasing seriousness.

System Organ Classification	**MedDRA Preferred Term**
Immune system disorders	*Not known*: Hypersensitivity
Endocrine Disorders	*Not known:* Cushing's syndrome, adrenal insufficiency
Eye disorders	*Not known*: Glaucoma, ulcerative keratitis, intraocular pressure increased, visual acuity reduced, corneal erosion, eyelid ptosis, eye pain, mydriasis

4.9 Overdose

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: corticosteroids. ATC code: S01BA01

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

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.

5.2 Pharmacokinetic properties

Absorption

After topical ocular administration, dexamethasone is detectable after 30 minutes in the aqueous humor and peaks at 90-120 minutes with a mean concentration of 31 ng/mL. Low but detectable concentrations are observed in the aqueous humor 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 6βhydroxydexamethasone and up to 10% recovered as 6β-hydroxy-20-dihydrodexamethasone.

Elimination

After intravenous administration, the systemic clearance was 0.125 L/hr/kg. After oral administration, 2.6% of the unchanged parent drug was recovered in the urine while up to 70% of the dose 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

Non-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.

Pediatric pharmacokinetics varied between age groups but wide interpatient variabilities were observed. The safety and efficacy of dexamethasone suspension/ointment have not been studied in children.

5.3 Preclinical safety data

In comparison to clinically relevant doses, non-clinical data reveal no special hazard for humans, at the recommended clinical dose, based on conventional studies of repeated dose toxicity, genotoxicity or carcinogenic potential. For reproductive toxicity, see Section 4.6 Pregnancy and lactation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

MAXIDEX* ophthalmic suspension

Disodium phosphate, 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 eye drop 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

Novartis Pharma AG, Basel, Switzerland