SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Minims Dexamethasone sodium phosphate 0.1% w/v Eye drops, solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Dexamethasone sodium phosphate Ph Eur 0.1% w/v.

Excipients with known effect
Sodium dihydrogen phosphate dihydrate and
disodium phosphate
(0.16 mg phosphates in each drop equivalent to 3.95 mg/ml)

3 PHARMACEUTICAL FORM

Single-use, sterile eye drops.
A colourless solution when examined under suitable conditions of visibility, practically clear and practically free from particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-infected, steroid responsive, inflammatory conditions of the eye.

4.2 Posology and method of administration

Posology

Adults and the elderly

One or two drops should be applied topically to the eye up to six times a day. *Note:* In severe conditions the treatment may be initiated with 1 or 2 drops every hour, the dosage should then be gradually reduced as the inflammation subsides.

Paediatric population

At the discretion of the physician.

Method of administration

For ocular use.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Eye infections not controlled by appropriate anti-infectious treatment, such as: herpes simplex and other viral diseases of the cornea and conjunctiva, ocular fungal disease, ocular bacterial infections, ocular tuberculosis, untreated purulent infections,
- corneal damage or ulcerous processes of the cornea,

Patients with a pre-existing eye infection should only receive dexamethasone eye drops while using simultaneously specific anti-infective therapy.

In children, long-term, continuous corticosteroid therapy should be avoided due to possible adrenal suppression.

4.4 Special warnings and precautions for use

Care should be taken to ensure that the eye is not infected before Minims Dexamethasone sodium phosphate 0.1% w/v Eye Drops, solution is used.

These drops should be used cautiously in patients with glaucoma and should be considered carefully in patients with a family history of this disease.

This medicinal product contains phosphates which may lead to corneal deposits or corneal opacity when topically administered. It should be used with caution in patients presenting with compromised cornea and in instances where the patient is receiving polypharmacy with other phosphate containing eye medications *(see section 4.5).*

Topical corticosteroids should not be used for longer than 10 days except under ophthalmic supervision, as prolonged application to the eye of preparations containing corticosteroids has caused increased intraocular pressure and corneal damage. The dose of anti-glaucoma medication may need to be adjusted in these patients. Prolonged use may also increase the hazard of secondary ocular infections.

Cushing's syndrome and/or adrenal suppression associated with systemic absorption of ocular 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). In these cases, treatment should be progressively discontinued.

Fungal infections of the cornea may occur under long-term local corticosteroid treatment. Therefore, in case of persistent corneal ulcers, the possibility of a fungal infection under corticoid treatment should be considered. If suspicion is present, samples should be taken. If symptoms do not improve within 2 days, a discontinuation of corticosteroid therapy should be considered.

Contact lenses should not be worn during treatment with corticosteroid eye drops due to increased risk of infection.

Systemic absorption may be reduced by compressing the lacrimal sac at the medial canthus for a minute during and following the instillation of the drops. (This blocks the passage of drops via the naso-lacrimal duct to the wide absorptive area of the nasal and pharyngeal mucosa. It is especially advisable in children.)

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.

As any other corticosteroid, dexamethasone may affect the body's immune defence due to its protein catabolic nature and thus increase the hazard of secondary ocular infections. In these cases, treatment with dexamethasone should be discontinued until the infection is controlled effectively by an antibiotic therapy unless inflammation has been so violent that an anti-inflammatory treatment is mandatory.

4.5 Interaction with other medicinal products and other forms of interaction

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

The risk of increased intraocular pressure associated with prolonged corticosteroid therapy may be more likely to occur with concomitant use of anticholinergics, especially atropine and related compounds, in patients predisposed to acute angle closure.

The risk of corneal deposits or corneal opacity may be more likely to occur in patients presenting with compromised cornea and receiving polypharmacy with other phosphate containing eye medications.

Concomitant use of topical steroids and topical NSAIDs may increase the potential for corneal healing problems.

The following drug interactions are possible, but are unlikely to be of clinical significance, following the use of Minims Dexamethasone sodium phosphate 0.1% w/v Eye Drops, solution in the eye:

The therapeutic efficacy of dexamethasone may be reduced by phenytoin, phenobarbitone, ephedrine and rifampicin.

Glucocorticoids may increase the need for salicylates as plasma salicylate clearance is increased.

CYP3A4 inhibitors (including ritonavir and cobicistat): may decrease dexamethasone clearance resulting in increased effects and adrenal suppression/Cushing's syndrome. 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 Fertility, pregnancy and lactation

Fertility
Studies have not been performed to evaluate the effect of topical administration of dexamethasone on human fertility. There is limited clinical data to evaluate the effect of dexamethasone on male or female fertility.

Pregnancy
There are no adequate or well-controlled studies in pregnant women.

Synthetic glucocorticoids such as dexamethasone are generally less inactivated in the placenta than endogenous cortisol (=hydrocortisone) and therefore might pose a risk to the foetus.

Long-term treatment with glucocorticoids during pregnancy may retard intrauterine growth of the foetus.

If glucocorticoids are administered at the end of a pregnancy, there is a risk of atrophy of the foetal adrenal cortex which may require a gradual replacement therapy in the newborn.

Studies in animals have shown reproductive toxicity including formation of cleft palates (*see section 5.3 Preclinical safety data*).

Furthermore, epidemiological studies in connection with animal experiments indicated an association between prenatal exposure to glucocorticoids and an increased risk of metabolic and cardiovascular diseases during adulthood.

Topically applied steroids can be absorbed systemically and have been shown to cause abnormalities of foetal development in pregnant animals. The relevance of this finding to human beings has however not been established.

Since a relevant systemic exposure cannot be excluded even after use of glucocorticoids in the eye, the use of dexamethasone should be avoided during pregnancy.

Minims Dexamethasone sodium phosphate 0.1% w/v Eye Drops, solution should not be used during pregnancy unless the clinical condition of the woman requires treatment with dexamethasone. If administration of dexamethasone is clearly necessary, it should be applied at the lowest possible dose for the shortest time period.

Breastfeeding

There is insufficient information on the excretion of dexamethasone/metabolites in human milk. A risk to the suckling newborns/infants cannot be excluded.

Topically applied dexamethasone is not recommended in breastfeeding mothers, as it is possible that traces of dexamethasone may enter the breast milk.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Minims Dexamethasone sodium phosphate 0.1% w/v Eye Drops, solution therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

It should only be used during lactation if clearly necessary. If higher doses are required for severe inflammation, breastfeeding must be stopped.

4.7 Effects on ability to drive and use machines

As with any topical ophthalmic medicinal product, instillation of this eye drop may cause transient blurring of vision or other visual disturbances which may affect the ability to drive or use machines. If blurred vision occurs upon instillation, the patient must wait until vision is clear before driving or using machinery.

4.8 Undesirable effects

Tabulated list of adverse reactions

Adverse reactions are listed by system organ class and frequency. The following convention has been used for the classification of frequencies: 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); Not known (cannot be estimated from the available data).

MedDRA SOC	Adverse reaction (s)	Frequency
Infections and infestations	Infection masked	Not known
	Secondary infection	Not known
Immune system disorders	Hypersensitivity	Not known
Endocrine disorders	Adrenal suppression	Not known
	Cushing's syndrome	Not known
Eye disorders	Cataract (with long-term use)	Not known
	Cataract subcapsular	Rare
	Eye irritation	Not known
	Eyelid ptosis	Not known
	Eye pain	Not known
	Keratitis	Not known

	Lacrimation increased	Rare
	Mydriasis	Not known
	Ocular hyperaemia	Rare
	Ulcerative keratitis	Not known
	Vision blurred	Not known
	Visual acuity reduced	Not known
	Eye stinging	Rare
	Eye burning	Rare
General disorders and administration site complications	Impaired healing	Not known
Investigations	Blood glucose increased (in diabetics)	Not known
	Intraocular pressure increased (with long term use)	Not known
Injury, poisoning and procedural complications	Open globe injury	Not known
	Optic nerve injury	Not known

Note: Fungal infections of the cornea may occur under long-term topical corticosteroid treatment. Therefore, in case of persistent corneal ulcers, the possibility of a fungal infection under corticoid treatment should be considered. If suspicion is present, samples should be taken. If symptoms do not improve within 2 days, a discontinuation of corticosteroid therapy should be considered.

Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

As Minims are single-dose units, overdose is unlikely to occur. There is no information regarding overdose from case reports.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Corticosteroids/ antiinfectives/ mydriatics in combination, ATC code: S01CB01

Mechanism of action

Dexamethasone is a highly potent and long-acting glucocorticoid. It has an approximately 7 times greater anti-inflammatory potency than prednisolone, another commonly prescribed corticosteroid.

The actions of corticosteroids are mediated by the binding of the corticosteroid molecules to receptor molecules located within sensitive cells. Corticosteroid receptors are present in human trabecular meshwork cells and in rabbit iris ciliary body tissue.

Corticosteroids will inhibit phospholipase A2 thereby preventing the generation of substances which mediate inflammation, for example, prostaglandins. Corticosteroids also produce a marked, though transient, lymphocytopenia. This depletion is due to redistribution of the cells, the T lymphocytes being affected to a greater degree than the B lymphocytes. Lymphokine production is reduced, as is the sensitivity of macrophages to activation by lymphokines. Corticosteroids also retard epithelial regeneration, diminish post-inflammatory neo-vascularisation and reduce towards normal levels the excessive permeability of inflamed capillaries.

The actions of corticosteroids described above are exhibited by Minims Dexamethasone sodium phosphate 0.1% w/v Eye Drops, solution and they all contribute to its anti-inflammatory effect.

5.2 Pharmacokinetic properties

Absorption

When given topically to the eye, dexamethasone is absorbed into the aqueous humour, cornea, iris, choroid, ciliary body and retina. Systemic absorption occurs but may be significant only at higher dosages or in extended paediatric therapy. Up to 90% of dexamethasone is absorbed when given by mouth; peak plasma levels are reached between 1 and 2 hours after ingestion and show wide individual variations.

Biotransformation

Dexamethasone sodium phosphate is rapidly converted to dexamethasone within the circulation. Up to 77% of dexamethasone is bound to plasma proteins, mainly albumin. This percentage, unlike cortisol, remains practically unchanged with increasing steroid concentrations. The mean plasma half life of dexamethasone is 3.6 ± 0.9h.

Distribution

Tissue distribution studies in animals show a high uptake of dexamethasone by the liver, kidney and adrenal glands; a volume of distribution has been quoted as 0.58 l/kg.

In man, over 60% of circulating steroids are excreted in the urine within 24 hours, largely as unconjugated steroid.

Elimination
Dexamethasone also appears to be cleared more rapidly from the circulation of the foetus and neonate than in the mother; plasma dexamethasone levels in the foetus and the mother have been found in the ratio of 0.32:1.

5.3 Preclinical safety data

The use of corticosteroids, including Minims Dexamethasone sodium phosphate 0.1% w/v Eye Drops, solution and its derivatives, in ophthalmology is well established. Little relevant toxicology has been reported, however, the breadth of clinical experience confirms its suitability as a topical ophthalmic agent. Studies in animals have shown reproductive toxicity including formation of cleft palates.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous disodium hydrogen phosphate
Sodium dihydrogen phosphate ($2H_2O$)
Disodium edetate
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

15 months.

6.4 Special precautions for storage

Store below 25°C. Do not freeze. Protect from light.

6.5 Nature and contents of container

A sealed conical shaped polypropylene container fitted with a twist and pull-off cap. Each Minims unit contains approximately 0.5 ml of solution. Each unit is overwrapped in a sachet. 20 units are packed into a suitable carton.

6.6 Special precautions for disposal

Each Minims unit should be discarded after a single use.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Bausch & Lomb UK Limited
Bausch & Lomb House
106 London Road
Kingston-Upon-Thames
Surrey, UK
KT2 6TN

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