SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<Product name> 1.315 mg/ml eye drops single-dose container

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml eye drops contains 1.315 mg of dexamethasone sodium phosphate (Ph.Eur.) equivalent to 1 mg of dexamethasone (1.2 mg of dexamethasone phosphate).

Excipients with known effect:
This medicine contains 4.36 mg phosphates in each 1 ml eye drops.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.
Clear and colourless to slightly yellow solution (pH 6.9 – 7.5; 275 – 315 mOsmol/kg).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For steroid treatment of non-infectious inflammatory diseases affecting the conjunctiva, cornea and anterior part of the eye including allergies, irritations, burns and chemical burns.

4.2 Posology and method of administration

Ocular use.

Apply 1 drop 2-5 times daily to the conjunctival sac of the affected eye during the first 2 days, subsequently 1 drop three 3 times daily. In particularly severe cases initially 1 drop up to every hour. The treatment duration should not exceed 2 weeks.

Nasolacrimal occlusion or gently closing the eyelid following application is recommended. This may decrease the systemic uptake of medicinal products administered via the eyes and reduce systemic adverse effects.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Acute, untreated, bacterial infections
- Herpes simplex keratitis
- Vaccinia, chicken pox, and other viral infections of the cornea or conjunctiva
- Fungal diseases of ocular structures or untreated parasitic eye infections
- Mycobacterial infections of the eye
- Injuries or ulcerous processes of the cornea
- Glaucoma.

In case of infection application of <product name> is only indicated with simultaneous specific anti-infective therapy.

4.4 Special warnings and precautions for use

Only for use in the eye.

Prolonged application of topical, ophthalmological corticosteroids may result in ocular hypertension and/or glaucoma in conjunction with damage to the optic disc, reduced visual acuity, visual field defects, and posterior, subcapsular cataract. Intraocular pressure, the cornea and the lens should be routinely and closely monitored in patients receiving long-term corticoid therapy. This is especially important in paediatric patients because the risk of corticoid-induced, ocular hypertension in children is higher and may occur earlier than in adults. In the case of predisposed patients (e.g. diabetics), the risk of a corticoid-induced increase in intraocular pressure and/or cataract formation is elevated. 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.

Corticosteroids may weaken resistance and increase susceptibility to bacterial, viral, fungal or parasitic infections and may mask clinical signs of an infection.

Fungal infections should be considered in patients with persistent corneal ulcer. If a fungal infection occurs, corticosteroid treatment should be discontinued.

Topical ophthalmic corticosteroids may delay the healing of corneal wounds. Topical NSAIDs are also known to slow or delay wound healing. Simultaneous administration of topical NSAIDs and topical steroids increases the potential for wound healing issues (see section 4.5).

In the case of diseases that cause a thinning of the cornea (e.g. keratitis) or sclera, the application of topical corticosteroids may result in perforation.

Note for contact lens users
The wearing of contact lenses is not advised during treatment of ocular inflammations. If the physician allows the patient to wear contact lenses, then the patient should be instructed to remove them before applying <product name> and to wait at least 15 minutes following application before reinserting the contact lenses.

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.

4.5 Interaction with other medicinal products and other forms of interactions

No studies have been conducted concerning interactions.

Simultaneous administration of topical NSAIDs and topical steroids increases the potential for wound healing issues.

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.

With simultaneous administration of <product name> and eye drops containing atropine or other anticholinergics an additional increase in the inner eye pressure in predisposed patients cannot be ruled out.

A minimum interval of 5 minutes between applications should be observed when applying more than one topical medicinal product to the eye. Eye ointments should be the last product to be applied.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is no or only very limited experience with the use of dexamethasone in pregnant women. Prolonged or repeated systemic application of glucocorticoids during pregnancy has been associated with an increased risk of intrauterine growth restriction and low birth weight of the foetus and an increased risk of high blood pressure, vascular diseases, and insulin resistance in adulthood. The administration of high systemic doses of glucocorticoids at the end of pregnancy also increases the risk of atrophy of the foetal adrenal cortex.
Studies in animal models have demonstrated reproductive toxicity including oral cleft formation (see section 5.3).
Due to the fact that relevant systemic exposure is also unable to be ruled following application of glucocorticoids in the eye, the use of <product name> during pregnancy is not recommended.

Lactation
Systemically administered glucocorticoids pass into the breast milk and may suppress growth and endogenous glucocorticoid production or cause other adverse effects. It is not known whether significant quantities of <product name> pass into human breast milk. However, a risk to the breast-feeding child is unable to be ruled out. It must be decided whether to stop breast-feeding or to discontinue or forego treatment with <product name>. Here, the benefits of breast-feeding the infant and the benefits of treating the mother must be considered.

Fertility
Systemically administered glucocorticoids may influence hormonal secretion from the hypothalamus and pituitary gland and gametogenesis in the testes and ovaries, thus influencing fertility. However, it is unknown whether dexamethasone also influences fertility following ophthalmological use.

4.7 Effects on ability to drive and use machines

<Product name> has no effects or negligible influence on the 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 or visual disturbances occur at instillation, the patient must wait until the vision clears before driving or using machines.

4.8 Undesirable effects

System organ classes	**Undesirable effects**		
	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	not known (cannot be estimated from the available data)
Immune system disorders			Hypersensitivity
Endocrine disorders			Adrenal insufficiency, Cushing's syndrome, adrenal suppression (see section 4.4)
Nervous system disorders		Dysgeusia	Dizziness, headache

Eye disorders	Ocular discomfort	Keratitis, conjunctivitis, dry eye, photophobia, blurred vision (see also section 4.4), eye pruritus, foreign body sensation in the eye, increased lacrimation, abnormal sensory perception of the eye, eyelid margin crusting, eye irritation, ocular hyperaemia	Glaucoma, ulcerative keratitis, increased intraocular pressure, reduced visual acuity, corneal erosion, ptosis, eye pain, mydriasis, cataract

Description of selected adverse reactions
Prolonged application of topical, ophthalmic corticosteroids may result in elevated intraocular pressure with damage to the optic disc, reduced visual acuity, visual field defects and posterior, subcapsular cataract (see section 4.4).

In the case of diseases that cause a thinning of the cornea or sclera, there is an increased risk of perforation based on the corticosteroid components especially following prolonged application (see section 4.4).

Corticosteroids may weaken resistance and increase susceptibility to infections (see section 4.4).

Without simultaneous causal therapy, existing corneal infections may worsen due to the application of <product name> or there is an increased risk of secondary infection, such as a fungal (Candida albicans) or viral infection (Herpes simplex keratitis).

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 national reporting system listed in Appendix V*.

4.9 Overdose

An overdose is virtually ruled out based on the physiological conditions of the eye (capacity of the conjunctival sac). Based on the properties of this product, no additional toxic effects are to be expected in the case of an acute, ocular overdose or inadvertent ingestion of the content of one single-dose container.
A topical overdose of <product name> may be rinsed from the eye(s) with lukewarm tap water.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals; anti-inflammatory agents; corticosteroids, plain
ATC code: S01BA01

Dexamethasone is a 11-hydroxy-16-methyl-glucocorticoid with a fluorine atom at the 9-α-position, used in <product name> in its phosphate ester form.
Therapeutic use of dexamethasone sodium phosphate is based on its strongly anti-inflammatory effect, which is 25-30 times stronger than that of cortisol, whereas systemic side effects such as sodium and

water retention, loss of potassium and disturbed glucose metabolism are minimal in comparison to cortisol.
The mechanism of action of synthetic steroids is similar to that of cortisol. They bind to specific intracellular receptor proteins. The specific mechanism of action which suppresses inflammatory and allergic reactions is not fully known. The inhibition of the synthesis of specific proteins important for chemotoxic and immunologic reactions as well as other changes in the function of leukocytes and macrophages seem to play a role in this effect.

Topical use of steroids in the eye has proven to be effective in the treatment of non-infectious inflammatory and allergy-related diseases affecting the conjunctiva, cornea and anterior part of the eye. Dexamethasone and other steroids are used for post-surgery prophylaxis and management of inflammations. However, for treating diseases of the posterior part of the eye, systemic administration of a steroid is required.

5.2 Pharmacokinetic properties

The ocular availability of dexamethasone after topical ocular instillation was determined in patients during a cataract extraction. Maximum aqueous humor levels were reached within 2 hours. The subsequent drop in levels displayed a half-life of 3 hours.

Passing the placenta
Like all corticoids dexamethasone is able to pass the placenta. Prophylactic administration of corticoids during pregnancy in order to enhance the growth of the unborn child’s lungs if a preterm birth is suspected is based on this fact.

Passing into mother’s milk
No data are available for dexamethasone. Glucocorticoids pass into mother’s milk in small amounts. Usually, the nursing infant absorbs less than 1/100 of the dose which is systemically available in the nursing mother. Nonetheless, lactation should be discontinued when using higher doses or during long-term treatment.

5.3 Preclinical safety data

Based on conventional studies on the acute toxic potential of dexamethasone, the preclinical data do not indicate any particular risks for humans related to dexamethasone eye drops.
Studies on toxicity with repeated administration of dexamethasone found typical symptoms of a glucocorticoid overdose (e.g. elevated serum glucose and cholesterol values, decrease in lymphocytes in the peripheral blood, bone marrow suppression, atrophic changes to the spleen, thymus, and adrenal gland, and reduced body weight gain). Available study findings for glucocorticoids provide no evidence of clinically relevant, genotoxic properties. Long-term studies on tumorigenic potential are not available.

In studies on reproductive toxicity, dexamethasone induced cleft palate formation and, to a smaller extent, other deformities in mice, rats, hamsters, rabbits, and dogs. Based on the small number of human cases, a risk during clinical application is unable to be ruled out.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Disodium phosphate anhydrous
Sodium dihydrogen phosphate dihydrate
Disodium edetate
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 3 years.
The eye drops should be used immediately after opening. Single-dose containers are intended for single use only. Any remaining quantities after single use must be discarded.

6.4 Special precautions for storage

Store in the original package in order to protect from light.
After opening the protective foil pouches, use within 6 months.

6.5 Nature and contents of container

Pack sizes: 10, 20, 30 or 50 single-dose containers (LD-PE) à 0.4 ml eye drops solution.
Five single-dose containers each are sealed in foil (PETP/ALU/LD-PE) to protect against evaporation.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

<[to be completed nationally]>
{Name and address}
<{tel:}>
<{fax:}>

8. MARKETING AUTHORISATION NUMBER(S)

<[to be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

<{DD Month YYYY}>

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>