SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DEKORT 5 mg/5 mL Eye and Ear Drops, Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL drop:
Active substance:
Dexamethasone 21-phosphate (as dexamethasone 21-phosphate disodium) 1 mg
Excipients:
Benzalkonium chloride 0.2 mg
For the full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Eye and ear drops.
Almost colorless to very light yellow, characteristic odor (phenylethyl-alcohol), clear solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Indicated for treatment of steroid responsive inflammatory conditions of the conjunctiva, cornea and anterior segment of the eye, such as, anterior uveitis, iritis, cyclitis, allergic and vernal conjunctivitis, herpes zoster keratitis, superficial punctate keratitis and non-specific superficial keratitis.

Also indicated for the treatment of corneal injury from chemical, radiation or thermal burns or following penetration by foreign bodies. Indicated for post-operative use to reduce inflammatory reactions and suppress graft reaction.

4.2 Posology and method of administration

For ocular and auricular use.

Posology/frequency and duration of administration
Instill 1-2 drops topically into the conjunctival sac.

Severe or acute inflammations require 1-2 drops instilled into the conjunctival sacs of the affected eye(s) every 30-60 minutes.

After a satisfactory response to the treatment is obtained, the frequency of instillation should be reduced to 1-2 drops in the conjunctival sacs of the affected eye(s) every 2-4 hours.

When the inflammation is adequately controlled, the dose can be reduced to one drop 3-4 times a day.

If there is no favorable response within 3-4 days, systemic or subconjunctival therapy should be considered.
In chronic inflammation, the dose is 1-2 drops into the conjunctival sacs of the affected eye(s) every

3-6 hours or as often as needed.

In allergy or minor inflammation, the dose is 1-2 drops instilled into the conjunctival sacs of the affected eye(s) every 3-4 hours until the desired response is achieved.

Care should be taken to ensure that the treatment is not discontinued before it is completed.

Regular measurement of intraocular pressure is recommended.

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.

In case of concomitant therapy with other topical ocular medicines, an interval of at least 5 minutes should be allowed between two applications. Eye ointments must be applied last.

For auricular administration, after the ear is thoroughly cleaned and dried, 3-4 drops are instilled into the ear canal 2-3 times a day. The dose is gradually reduced after response to treatment.

Method of administration
Shake the bottle well before use.

Do not let the dropper tip of the bottle touch the eyelids, surrounding areas, inside the ear or other surfaces to avoid contamination of the dropper tip or solution.

Additional information on special populations
Renal/Hepatic impairment
Dexamethasone has not been studied in these patient groups. However, after topical use of this product, no dose adjustment is required due to the low systemic absorption of dexamethasone.

Pediatric population
The safety and efficacy of DEKORT in pediatric patients have not been established.

It is not recommended to use DEKORT in infants and young children unless it is necessary.

Geriatric population
No special dose adjustment is required. Dosing in the elderly is the same as in adults.

4.3 Contraindications

It is contraindicated in:

- Patients with hypersensitivity to dexamethasone or any of the other excipients,
- Acute, untreated bacterial infections,
- Herpes simplex keratitis
- Ocular diseases caused by acid-fast bacilli such as *Mycobacterium tuberculosis*, *Mycobacterium leprae* or *Mycobacterium avium*, and other mycobacteria,
- Vaccinia, varicella, or other viral infections of cornea and conjunctiva (except herpes zoster keratitis)
- Fungal diseases of the eye and ear, or untreated parasitic eye infections
- Tympanic membrane perforation

- Acute purulent infections of the eye which may be masked or exacerbated by the use of corticosteroids, as in other diseases caused by microorganisms.

4.4 Special warnings and precautions for use

DEKORT eye and ear drops are for ocular and otological administration. It is not applied orally or by injection.

The use of corticosteroids in the treatment of herpes simplex requires special attention.

Prolonged use or increased frequency of use of corticosteroids may result in ocular hypertension and/or glaucoma, with damage to the optic nerve, reduced visual acuity, visual field defects and posterior subcapsular cataract formation. In susceptible patients, intraocular pressure may occur even at usual doses. Intraocular pressure and lenses should be checked routinely and frequently, in patients receiving prolonged ophthalmic corticosteroid therapy, particularly in those with a history of glaucoma.

In patients with glaucoma, treatment should be limited to two weeks, and intraocular pressure should be monitored regularly, unless longer-term treatment is required. This is particularly important in pediatric patients, as the risk of corticosteroid-induced ocular hypertension may be greater in children and may occur earlier than in adults. DEKORT is not approved for use in pediatric patients. The risk of corticosteroid-induced raised intraocular pressure and/or cataract formation is increased in predisposed patients (e.g. diabetes).

Topical corticosteroids should not be used for longer than one week except under ophthalmic supervision, with regular checks of intraocular pressure.

Cushing's syndrome and/or adrenal suppression associated with systemic absorption of ocular dexamethasone may occur after intensive or long-term therapy in predisposed patients, including children and patients treated with ritonavir (see section 4.5). In these cases, treatment should be progressively discontinued.

Corneal fungal infections sometimes tend to develop with prolonged administration of steroids. The possibility of fungal growth should be taken into account in persistent corneal ulceration where steroid treatments are applied. Secondary bacterial ocular infections may occur due to suppression of patient responses. Corticosteroids may reduce resistance to bacterial, viral, fungal infections and mask the clinical signs of infections. In such cases antibiotic therapy is mandatory. Fungal infection should be suspected in patients with persistent corneal ulceration and corticosteroids therapy should be discontinued if fungal infection occurs.

Untimely interruption of the therapy should be avoided. Unexpected interruption of the therapy while taking high doses of steroids results in rebound inflammatory ocular conditions.

Topical ophthalmic corticosteroids may slow corneal wound healing. Topical non-steroidal anti-inflammatory drugs (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.

Contact lens wear is not advised in the presence of an ocular infection. DEKORT eye and ear drops contain benzalkonium chloride as preservative, which may cause eye irritation and is known to discolor soft contact lenses. Therefore, patients must be instructed to remove their contact lenses prior to application of DEKORT and wait at least 15 minutes before reinsertion.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Concomitant use of topical steroids and topical NSAIDs may increase the potential for corneal healing problems.

Plasma concentrations of dexamethasone may be increased in patients treated with ritonavir (see section 4.4).

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.

Additional information on special populations

Pediatric population

No interaction studies have been performed in the pediatric population.

4.6 Fertility, pregnancy and lactation

General advice: Pregnancy category is C.

Potential risk to humans is unknown. DEKORT should be used during pregnancy, only if the potential benefit outweighs the potential risk to the fetus.

Women with child-bearing potential/Birth control (Contraception)

No studies have been conducted to evaluate the effect of topical ocular application of dexamethasone on childbearing potential. Limited clinical data are available to evaluate the effect of dexamethasone on male and female fertility.

Dexamethasone did not show adverse effects on fertility in the rat model given chorionic gonadotropin.

Pregnancy

There are no adequate data on the use of dexamethasone in pregnant women. Potential risk to humans is unknown. Prolonged or repeated corticoid use during pregnancy has been associated with an increased risk of intra-uterine growth retardation. DEKORT should be used during pregnancy only if the potential benefit outweighs the potential fetal risk. 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. Ocular administration of 0.1% dexamethasone also resulted in fetal anomalies in rabbits (see section 5.3).

The maximum daily dose following topical administration (2x 30 microliter drops x 4 times daily = approximately 0.240 mg/day dexamethasone) is well below the standard daily systemic anti-inflammatory dose of approximately 0.5 to 10 mg.

DEKORT is not recommended during pregnancy unless the clinical condition of the woman requires treatment with DEKORT.

Lactation
Systemically administered corticosteroids are excreted in human milk in quantities that may affect the breastfed child and may cause growth arrest, inhibition of physiological corticosteroid production, or undesirable effects.

It is unknown whether topical administration of dexamethasone results in systemic absorption and is excreted in human milk. The systemic exposure is low when instilled topically, but this should be taken into account when the drug is administered to lactating women.

The benefit of breastfeeding for the child and the benefit of DEKORT therapy for the nursing mother should be taken into account when deciding whether to stop breastfeeding or to stop/avoid the treatment with DEKORT.

Fertility
Animal studies have shown reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

As with any topical ophthalmic medicinal product, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines.
If blurred vision occurs upon instillation, the patient must wait until the vision clears before driving or using machinery.

4.8 Undesirable effects

Treatment-related undesirable effects include: glaucoma with optic nerve damage, visual acuity and visual field deficiency, cataract formation, secondary bacterial ocular infections followed by suppressed patient responses, globe (eyeball) perforation, local irritation, and allergic reactions.

The following undesirable effects are listed as: 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).

The following undesirable effects were reported in clinical trials with dexamethasone:

Immune system disorders
Not known: Hypersensitivity

Endocrine disorders
Not known: Cushing's syndrome, adrenal suppression

Nervous system disorders
Uncommon: Dysgeusia
Not known: Dizziness, headache

Eye disorders
Common: Ocular discomfort
Uncommon: Keratitis, conjunctivitis, keratoconjunctivitis sicca (dry eye syndrome), corneal damage, photophobia, vision, blurred, eye pruritus, foreign body sensation in eyes, lacrimation increased, abnormal sensation in eyes, eyelid margin crusting, eye irritation, ocular hyperemia
Not known: Intraocular pressure increased, visual acuity reduced, corneal erosion, eye pain,

mydriasis, eyelid ptosis

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).

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 authorization 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 to Turkey Pharmacovigilance Center (TÜFAM) (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; phone number: +90 800 314 00 08; fax: +90 312 218 35 99).

4.9 Overdose
Long-term intensive topical use may lead to systemic effects. Oral ingestion of the contents of the bottle (up to 10 milliliters) is unlikely to lead to any serious adverse effects.

A topical overdose of DEKORT can be flushed from the eye(s) with lukewarm water.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Ophthalmologics, otological preparations, corticosteroids.
ATC code: S03BA01

Dexamethasone has been demonstrated by animal and human studies based on oral application to possess approximately 6-7 times the potency of prednisolone and at least 30 times the potency of cortisone. The potency of the compound is accomplished by the addition of a methyl radical and a fluorine atom to the prednisolone radical.

5.2 Pharmacokinetic properties
General Properties
Dexamethasone is absorbed rapidly after oral administration with a half-life of about 190 minutes. Sufficient absorption may occur after topical application to the skin and eye to produce systemic effects. In plasma dexamethasone protein binding is less than for most other corticosteroids.

Corticosteroids diffuse into tissue fluids and cerebrospinal fluid but transplacental diffusion in significant amounts has not been demonstrated. Corticosteroids are metabolized in the liver the kidney and excrete in the urine. Metabolism is similar to other corticosteroids.

Intraocular penetration occurs in significant amounts and contributes to the effectiveness of

dexamethasone in anterior segment inflammatory disease.

Absorption:
After topical ocular administration, dexamethasone is detectable in the eye fluid after 30 minutes and peaks in 90 to 120 minutes with a mean concentration of 31 ng/mL. After 12 hours, low but detectable concentrations are found in the eye fluid. In normal volunteers and patients, oral bioavailability of dexamethasone ranges from 70-80%.

Distribution:
After intravenous administration, the steady-state volume of distribution is 0.58 L/kg. *In vitro*, no change in human plasma protein binding (with a mean plasma protein binding of 77.4%) was observed with dexamethasone concentrations ranging from 0.04 to 4 mcg/mL.

Biotransformation:
After oral administration, dexamethasone was converted to two major metabolites (6β-hydroxydexamethasone obtained from 60% of the dose, and 6β-hydroxy-20-dihydrodexamethasone up to 10% of the dose).

Elimination:
After intravenous administration, systemic clearance is 0.125 L/hour/kg. After oral administration, 2.6% of unchanged parent drug is excreted in the urine, and up to 70% of the dose excreted as identifiable metabolites. Although the half-life after systemic dosing has been reported to be 3-4 hours, it has been observed to be slightly longer in men. This difference was not associated with changes in systemic clearance, but was associated with a difference in volume of distribution and body weight.

Linearity/Non-linearity:
Non-linear pharmacokinetics were observed at doses between 0.5 and 1.5 mg (at doses less than proportionality of AUC to oral dose).

Pharmacokinetic/Pharmacodynamic Relationships:
No pharmacokinetic/pharmacodynamic relationship has been established following topical ocular administration.

Characteristics in patients
Renal/hepatic failure:
The pharmacokinetics of systemic dexamethasone were not significantly different in patients with renal impairment compared to normal volunteers.

Pediatric population:
Pediatric pharmacokinetics vary between age groups; wide inter-patient variability also has been observed.

5.3 Preclinical safety data
The systemic toxicity profile of the active substance has been thoroughly evaluated. Systemic exposure to dexamethasone may be due to the effects related to glucocorticosteroid imbalance. Repeated-dose toxicity studies with dexamethasone eye drop suspension in rabbits have shown systemic corticosteroid effects; however, the clinical relevance to human exposure is minimal. Such effects are considered to be unlikely when DEKORT is used as recommended.

Mutagenicity:
Dexamethasone was clastogenic in the in vitro human lymphocyte assay and in vivo in the mouse micronucleus assay at doses in excess of those obtained following topical application.

Teratogenicity:
Corticosteroids have been found to be teratogenic in animal studies. The ocular administration of 0.1% dexamethasone preparation in pregnant rabbits resulted in fetal anomalies and intra-uterine growth retardation. Deceleration of fetal growth and increased mortality rates have been observed in chronic dexamethasone treatment in mice.

No studies have been conducted to assess the carcinogenic potential of dexamethasone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Creatinine,
Celite 512
Tween 80,
Sodium citrate dihydrate,
Sodium bisulfite,
Sodium borate decahydrate,
E.D.T.A. disodium,
2-phenylethanol,
Benzalkonium chloride,
Purified water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
48 months.
After first opening, it should be used within 15 days.

6.4 Special precautions for storage
Store below 25°C at room temperature and protect from light.
Keep the bottle in an upright position with the cap tightly closed.

6.5 Nature and contents of container
Supplied in a sterile, opaque, low-density polyethylene (LDPE) bottle containing 5 mL solution. The bottle is also equipped with a white, safety ringed, capped, high-density polyethylene (HDPE) dropper which has a sterile inner stopper. All presented with a package leaflet in a cardboard box.

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No.: 1

34303 Küçükçekmece - ISTANBUL/TURKEY

8. MARKETING AUTHORIZATION NUMBER

19.12.1991 – 158/65

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 19.12.1991
Date of latest renewal : 19.12.2007

10. DATE OF REVISION OF THE TEXT