Summary Product Characteristics for Pharmaceutical Product

1. NAME OF THE MEDICINAL PRODUCT

Dexa-G®, eye drops
Dexamethasone sodium phosphate 1.0 mg/ml and
Gentamicin sulfate 5.0 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substances:
1 ml of solution contains:
Dexamethasone sodium phosphate 1.0 mg
Gentamicin sulfate 5.0 mg
(equivalent to 3 mg gentamicin)

Contains benzalkonium chloride.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops

pH: 6.5-7.5
Osmolality: 250-290 mOsm/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Infections of the anterior eye including conjunctivitis, keratitis, blepharitis, and hordeolum, caused by gentamicin-sensitive pathogens; allergic inflammation of the anterior eye with bacterial superinfection.

4.2 Posology and method of administration

Posology

1 drop is administered 4-6 times daily into the conjunctival sac.

Method of administration

For ocular use.

The treatment with Dexa-G®, eye drops should normally not extend beyond a period of two weeks. Periodically, depending on the severity of the clinical picture, efficacy should be controlled and decided if the therapy should be continued or changed.
Generally, eye drops should be used avoiding contact of the bottle tip with the eye or the skin of the face.

Paediatric population
There is no experience in children.

4.3 Contraindications

Hypersensitivity to one of the active substances or to any of the excipients listed in section 6.1, herpes corneae superficialis, injuries and ulcerations of the cornea, narrow- and open-angle- glaucoma, tuberculosis of the eye, fungal infections of the eye as well as solely bacterial infections.

Contact lenses should not be worn during the treatment with Dexa-G® eye drops.

4.4 Special warnings and precautions for use

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.

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 chorioretinpathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Benzalkonium chloride may cause eye irritations. Avoid contact with soft contact lenses. Benzalkoniumchloride can cause discoloration of soft contact lenses. Remove contact lenses prior to application and wait at least 15 minutes before reinseration.

4.5 Interaction with other medicinal products and other forms of interaction

CYP3A4 inhibitors (including ritonavir and cobiscitat): 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.

No interaction studies were performed.

There are no clinical relevant interactions with gentamicin known.

Corticoid:
Atropine and other anticholinergic drugs: Additional increase of the intraocular pressure during concomitant use of anti-cholinergic drugs.

Advice:
In concomitant treatment with other topical ophthalmologic medicinal products, a 15 minutes interval between the applications should be considered.

See also section 6.2 Incompatibilities.

4.6 Fertility, pregnancy and lactation

There is no sufficient data concerning the use of dexamethasone sodium phosphate/ dexamethasone and gentamicin sulfate in pregnant women. Animal studies showed reproduction toxicity (also refer to section 5.3). The potential risk for humans is not known.

For that reason, Dexa-G® eye drops should not be applied in the first trimenon and during the further course of pregnancy only after a careful benefit-risk-assessment. Dexamethasone may be systemically absorbed in topical treatment of the eye and may also pass into breast milk during lactation. A harmful effect to the infant has not been reported until now.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

The assessment of undesirable effects is based on the following 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)
Unknown (Incidence cannot be estimated from the available data.)

Endocrine disorders
Not known: Cushing's syndrome, adrenal suppression (see section 4.4)

Eye Disorders
In very rare cases allergic reactions or the sensation of temporary light burning in the eye are possible. Very rarely hypersensitive reactions (contact allergies) with itching, oedema or eczema of the eye lids have been observed.

Furthermore: Elevation of the intraocular pressure (glaucoma), irreversible lens opacity (cataract), especially in children, herpes simplex keratitis, perforation of

the cornea in an existing keratitis, fungal infections (e.g. candida albicans), aggravation of bacterial infections of the cornea, ptosis, mydriasis. After injuries of the cornea the use of Dexa-G® eye drops may lead to disorders in wound healing.

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.

Not known: Vision, blurred (see also section 4.4)

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:

4.9 Overdose

No cases of overdosing have been reported.
Overdosing or intoxications are not to be expected after proper application of Dexa-G®, eye drops.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmics/corticosteroids and antiinfectives in combination, ATC code: S01CA01

Gentamicin is a bactericidal acting aminoglycoside-antibiotic. It is a mixture of the homologues gentamicin C1, C2 and C1a, which have a very similar chemical structure. Gentamicin's mechanism of action is based on a disturbance of the protein biosythesis at the bacterial ribosome by interaction with the rRNS and following inhibition of the translation. From this a bactericidic action results.

Relation between pharmacokinetics and pharmacodynamics

The efficacy is dependent on the relation of the local concentration of gentamicin at the point of infection and the minimum inhibitory concentration (MIC) of the germ.

Mechanism of resistance

Resistance against gentamicin may be based on the following mechanisms:

- Enzymatic inactivation: The enzymatic modification of the aminogycoside molecules is the most frequent mechanism of resistance. This is realised by acetyltransferases, phosphotransferases or nucleotiyltransferases which are mostly plasmid-coded.

- Reduced penetration and active efflux: This mechanism of resistance is found mainly with
  Pseudomonas aeruginosa.
- Change of target structure: Modification within the ribosome are uncommon as cause for a resistance.

There is an extensive cross-resistance of gentamicin with other aminoglycoside-antibiotics.

Limit values
The tests on gentamicin were carried out under the use of the common dilution series for gentamicin. The following minimal inhibition concentrations for sensitive, intermediate and resistant germs were assessed:

EUCAST (European Committee an Antimicrobial Susceptibility Testing) Thresholds

Germ	*Sensitive*	*Resistent*
Enterobacteriaceae	□ *2 mg/l*	*> 4 mg/l*
Pseudomonas spp.	□ *4 mg/l*	*> 4 mg/l*
Acinetobacter spp.	□ *4 mg/l*	*> 4 mg/l*
Staphylococcus spp.	□ *1 mg/l*	*> 1 mg/l*
*Non-specific thresholds**	□ *2 mg/l*	*> 4 mg/l*

** Mainly based on the serum pharmacokinetic*

Prevalence of acquired resistance in Germany
The prevalence of acquired resistances can vary locally and temporarily. Therefore it is preferable to have information concerning the situation of resistances in the local area, particularly for an adequate treatment of serious infections. If there is any reason that a treatment with gentamicin seems critical because of the local prevalence of a resistance, advice from an expert is recommended. Particularly in case of serious infections or therapy failure a microbiological diagnosis is aimed to detect the specific germ and its gentamicin sensitivity.

The information given below is mainly based on an updated resistance study with 1.391 ocular isolates (predominantly external smears) from 31 german centers conducted 2009 in Germany. These specifications underlie the above mentioned threshold for systemic administration. After ocular administration of gentamicin, (mostly) distinct higher local concentrations of the antibiotic are reached compared to systemic administration, so that a clinical efficacy for the authorized indications may be also given for germs that were defined resistant in in vitro resistance studies. That applies e.g. for the bacterial species Streptococcus and Enterococcus.

Usually sensitive species
Gram-positive aerobes
Bacillus spp.

Corynebacterium spp.
Staphylococcus aureus (Methicillin-sensitive)
Gram-negative aerobes
Acinetobacter baumannii
Acinetobacter lwoffi
Haemophilus influenzae
Haemophilus parainfluenzae
Enterobacter cloacae
Escherichia coli
Klebsiella oxytoca
Klebsiella pneumoniae
Moraxella catarrhalis
Proteus mirabilis
Pseudomonas aeruginosa
Serratia marcescens
Species where acquired resistances may be a problem
Gram-positive aerobes
Staphylococcus aureus (Methicillin-resistant)
Staphylococcus epidermidis
Naturally resistant species
Gram-positive aerobes
Enterococcus spp.
Streptococcus spp.
Gram-negative aerobes
Stenotrophomonas maltophilia

Corticoid:
Dexamethasone is a monofluoroglucocorticoid with marked anti-allergic, anti-phlogistic and membrane stabilising properties, combined with effects on carbohydrate-, protein- and lipid- metabolism.

The glucocorticoid effect of dexamethasone is about 7.5-fold higher than that of prednisolone and prednisone. It is about 30-fold more active than hydrocortisone. It lacks mineralocorticoid activity.

Glucocorticoids such as dexamethasone act by activating the transcription of corticoid sensitive genes. The anti-inflammatory, immunosuppressive and antiproliferative effects are in part due to the reduction of formation, release and activity of inflammatory mediators and to the inhibition of specific functions and the migration of cells involved in inflammation. In addition, it is possible that corticosteroids inhibit the activity of sensitised T-lymphocytes and macrophages on target cells.

5.2 Pharmacokinetic properties

Antibiotic:
After local administration of gentamicin, depending on the dosage frequency, bactericidal tissue concentrations are reached in conjunctiva and cornea. After frequent application to the inflamed eye, therapeutically active concentrations are also reached in the aqueous humour. No systemic absorption is to be expected

which could lead to levels above the detection limit for gentamicin in serum.

Corticoid:
Dexamethasone sodium phosphate is hardly absorbed over the intact epithelium. Dexamethasone itself is slightly absorbed. However, the ability of these compounds to penetrate is greatly increased if the mucous membrane is inflamed or damaged by epithelial lesions.

Dexamethasone is dose-dependently bound by plasma albumins. At very high doses, most of the dexamethasone circulates freely in blood. The proportion of unbound (active) corticoids increases in hypoalbuminaemia. After intravenous administration of radiolabelled dexamethasone to humans, maximal liquor concentrations were measured after four hours. These were about one sixth of the plasma concentrations measured at the same time.

The biological half-life of dexamethasone is over 36 hours, so that it can be regarded as a very long acting glucocorticoid. Because of the very long duration of action, continuous daily systemic administration of dexamethasone can cause accumulation and overdosage.
The mean (serum) elimination half-life of dexamethasone in adults is about 250 min (± 80 min). Dexamethasone is mainly eliminated renally as free dexamethasone alcohol. There is partial metabolism. The metabolites are also mainly eliminated through the kidneys as glucuronates or sulfates. The elimination of dexamethasone is hardly affected by disturbances in renal function. On the other hand, the elimination half-life is prolonged by severe liver disease.

5.3 Preclinical safety data

Acute Toxicity

Antibiotic:
Investigations of the acute toxicity in various species have found no particular sensitivity.

Corticoid:
The LD50 within the first 7 days for dexamethasone after a single oral dose is 16 g/kg body weight in the mouse and 3 g/kg body weight in the rat. After a single subcutaneous administration, the LD50 within 7 days in the mouse is greater than 700 mg/kg body weight and about 120 mg/kg body weight in the rat. The values are reduced gradually over a period of 21 days, which is regarded as the consequence of severe infectious disease, caused by hormone-linked immune suppression.

Chronic

Toxicity

Antibiotic:
Studies on chronic toxicity after intramuscular administration to various animal species showed

nephrotoxic and ototoxic effects at higher dosages.

Application to the eye:
Absorption is negligibly small after topical administration to the eye, so that systemic toxic effects can hardly be expected. Also refer to section 4.8 Undesirable Effects.

Corticoid:
There is no data on chronic human or animal toxicity. No corticoid-linked toxicity symptoms are known. Distinctive side effects can be expected after long-term therapy with doses in the range of or above the Cushing threshold (1.5 mg/day) (see Section 4.8).

Mutagenic and Carcinogenic

Potential Antibiotic:
No extensive mutagenicity tests are available for gentamicin. Previous investigations have been
negative. There are no long-term animal studies available on potential carcinogenicity.

Corticoid:
The available study results on glucocorticoids do not provide any evidence that these substances possess clinically relevant genotoxic properties.

Reproduction Toxicity

Antibiotic:
Gentamicin crosses the placenta and also passes into breast milk in low levels. Although there have been no reports about harmful effects of gentamicin, there is a potential danger of damage to the inner ear or kidneys of the foetus.

Corticoid:
In experiments in mice, rats, hamsters, rabbits and dogs, dexamethasone causes cleft palate and - to a slight extent - other malformations. Disturbances in intrauterine growth have been observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
1 ml solution contains
Benzalkonium chloride 0.05 mg/ml
Sodium chloride, potassium dihydrogen phosphate, dipotassium phosphate, water for injections

6.2 Incompatibilities

Gentamicin is incompatible with amphothericin B, heparin, sulfadiazin, cephalotin and cloxacillin. Concomitant local application of gentamicin and one of

these substances may cause visible precipitate in the conjunctival sac.

6.3 Shelf life

2 years

Dexa-G® eye drops can be used up to 4 weeks after the bottle has been opened.

Dexa-G® eye drops should not be used beyond the expiration date (imprinted on the folding carton or the label).

6.4 Special precautions for storage

Do not store above 25 °C.

Store the bottle in the folding carton to protect it from light.

6.5 Nature and contents of container

Dropping bottle with screw cap, both of polyethylen.
The following package sizes are available: Folding carton with 1 dropping bottle of 10 ml.

For production reasons, 5 ml of Dexa-G® eye drops are filled in 10 ml dropping bottles. The protection cap guarantees for the integrity of the product.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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14672

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