Decentralised Procedure

Public Assessment Report

Dexafluid sine

Dexamethasone sodium phosphate

DE/H/5049/001/DC

Applicant: mibe GmbH Arzneimittel, Germany

Reference Member State	DE

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product(s) in the RMS	Dexafluid sine
Name of the drug substance (INN name):	Dexamethasone sodium phosphate
Pharmaco-therapeutic group (ATC Code):	S01BA01
Pharmaceutical form(s) and strength(s):	Eye drops, solution 1.315 mg/ml
Reference Number(s) for the Decentralised Procedure	DE/H/5049/001/DC
Reference Member State:	DE
Member States concerned:	HR, PL
Applicant (name and address)	mibe GmbH Arzneimittel Münchener Str. 15 D-06796 Brehna Germany

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for *"Dexafluid sine"* indicated 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, is approved.

II. EXECUTIVE SUMMARY

II.1 Problem statement

N/A

II.2 About the product

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

Mode of action:
Dexamethasone is an 11-hydroxy-16-methyl-glucocorticoid with a fluorine atom at the 9-α-position, used in Dexafluid sine 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 inflammatory and allergic diseases affecting the anterior part of the eye, cornea and conjunctiva. 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.

Pharmacological classification:
Dexamethasone sodium phosphate 1.315 mg/ml eye drops contains as active substance the dexamethasone derivative dexamethasone 21-(dihydrogen phosphate) disodium salt, 1.315 mg/ml, commonly designated as dexamethasone sodium phosphate (DMSP).

Claimed indication:
Dexafluid is indicated 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.

II.3 General comments on the submitted dossier

This application is made according to Art. 10(3) of Dir. 2001/83/EC (so called *"hybrid application"*), which is acceptable. The originator product is *"Dexa-Sine 1 mg/ml eye drops"* by Alcon Pharma GmbH, registered since 21st July 1993 in Germany. As part of the same global marketing authorisation, the same MAH subsequently gained a German MA for *"Dexa-sine SE 1.315 mg/ml eye drops"* on 14th February 2005, which contains 1.315 mg/ml dexamethasone dihydrogen phosphate corresponding also to 1 mg/ml dexamethasone.
Reference product of this generic application is Dexa-Sine SE eye drops, solution from Alcon Pharma GmbH.
A scientific advice meeting was held at the BfArM.
No paediatric development programme is available, which is acceptable and not required for a generic application.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug Substance

Dexamethasone sodium phosphate is a well-known active substance and described in the Ph. Eur. A Certificate of Suitability to the Monograph of the European Pharmacopoeia (CEP) has been granted. A retest period of 60 months has been certified by the EDQM when stored at a temperature between 2°C and 8°C in an air tight container protected from light.

Drug product

The drug product Dexamethasone sodium phosphate 1.315 mg/ml eye drops, single dose, containing 1.315 mg/ml dexamethason dihydrogen-phosphat - disodium as drug substances comprises a sterile, unpreserved solution contained in 0.4 ml single-dose optioles. For protection against light and evaporation of water five primary containers are sealed in a three layer foil pouch.

Development of the drug product has been described and the choice of active substance and excipients is considered justified. Novel excipients are not used.

The manufacturing process includes sterile filtration and aseptic processing including filling in a blow-fill-seal machine. Validation of the manufacturing process has been successfully finalised with three recent full scale production batches.

The drug product specifications are considered appropriate for the quality control of the present dosage form. Analytical methods have been described and validated. Batch analysis results of three recent full production batches demonstrate compliance with the specification. The specifications for related substances comply with Q3B (R2), qualification threshold for impurities, and are justified by batch results.

Satisfactory ICH stability study results have been provided. Duration of studies was 24 months at long term conditions (25°C/60%RH), 12 months at intermediate conditions (30°C/65%RH) and 6 months at accelerated conditions (40°C/75%RH). Stability study results available demonstrate compliance with the updated specifications especially in terms of impurity levels.

A shelf life of 36 months is accepted on the basis of 24 months stability study results, together with the storage precaution: “store in the original package to protect content from light”. An in-use stability after opening of foil pouches of 6 month is accepted.

III.2 Non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of dexamethasone sodium phosphate are well known for more than 30 years. Consequently, the Applicant complemented the rather old scientific references with more recently published relevant literature. This approach is acknowledged.

The applied medicinal product contains the same amount of active substance and excipients as the reference product, i.e. 1 mg/ml dexamethasone. In addition, the API including its impurities is controlled according to the limits proposed in the current Ph. Eur. monograph.

The instructions on use of the compound during pregnancy and lactation and the preclinical safety data contained in the proposed SmPC and PL, respectively, essentially reflect the characteristics of the active substance and were meanwhile substantially revised in line with prevailing European requirements to improve comprehensibility for prescribing physician and patient, which is endorsed.

Environmental Risk Assessment (ERA)
A final conclusion on the environmental risk assessment cannot be drawn. The applicant provided an environmental risk assessment for the active ingredient dexamethasone being not in line with the respective guidelines and which is considered not acceptable. However, the applicant committed to provide a tailored ERA for the active ingredient dexamethasone.

III.3 Clinical aspects
In this generic application no clinical studies are conducted. This is applicable as bioequivalence cannot be demonstrated through bioavailability studies such as for products for local use intended to act without systemic absorption after (e.g. oral, nasal, inhalation, ocular, dermal administration). The applicant claims essentially similarity to the reference product based on the contents of the product and does not submit bioequivalence studies and clinical studies. According to Guideline on The Investigation of Bioequivalence CPMP/QWP/EWP/1401/98 Rev.1: In the case of solutions for topical use, e.g. eye drops or cutaneous solutions, and if the test product is of the same type of solution (aqueous or oily), contains the same concentration of the same active substance and the same excipients in the same amounts as the medicinal product currently approved, a biowaiver is acceptable. The indications for use claimed by the applicant are well established for this class of drugs, e.g. in [HSDB 2014, Brayfield, A. 2014, DRUGDEX Evaluations 2009].

Pharmacokinetics
Following topical instillation of corticosteroids into the conjunctival sac, the drugs are absorbed into the aqueous humour, and systemic absorption occurs. However, because topical ophthalmic corticosteroid dosage is less than when the drugs are given systemically, clinical evidence of systemic absorption usually does not occur [AHFS DI 2014b]. Topical preparations distribute throughout the area of application; ophthalmic preparations distribute into the local tissues [Clinical Pharmacology 2014]. Systemic bioavailability of dexamethasone after topical application depends on the state of the skin at the application site. In general, absorption of topical preparations is increased in areas of skin damage, inflammation and occlusion or where the stratum corneum is thin such as the eyelids, and face [Clinical Pharmacology 2014, Brayfield, A. 2014]. Serum concentrations for dexamethasone are available only if the drug was administered intravitreally: After the insertion of the dexamethasone intravitreal implant (0.35 mg or 0.7 mg) in 21 patients, plasma concentrations were obtained on days 7, 30, 60, and 90. Overall, the majority of dexamethasone plasma concentration measurements were below the lower limit of quantitation (LLOQ = 50 pg/ml). Ten of the 73 samples in the patients receiving the 0.7 mg dose and 2 of the 42 samples in the patients receiving the 0.35 mg dose were above the LLOQ (range, 52-94 pg/ml). The highest plasma concentration (94 pg/ml) was observed in one patient who had received the 0.7 mg dose. Age, body weight, and gender did not affect the plasma dexamethasone concentrations [Clinical Pharmacology 2014]. Systemic dexamethasone is quickly distributed into the kidneys, intestines, skin, liver, and muscle [Clinical Pharmacology 2014]. The volume of distribution is about 1 l/kg [Moffat, A. C. 2014]. Its biological half-life in plasma is about 190 minutes. Binding of dexamethasone to plasma proteins is about 67 - 77%, which is less than for most other corticosteroids [Brayfield, A. 2014, Moffat, A. C. 2014]. According to other sources, the plasma elimination half-life of dexamethasone is approximately 1.8-3.5 hours (or 2-5 h [Moffat, A. C. 2014]) whereas the biological half-life is 36-54 hours [Clinical Pharmacology 2014]. Corticosteroids distribute into breast milk and cross the placenta [Clinical Pharmacology 2014]. Ophthalmic doses of dexamethasone are metabolized locally, and systemic dexamethasone is metabolized by the liver to inactive metabolites. The inactive metabolites, as well as a small portion of unchanged drug, are excreted in the urine [Clinical Pharmacology 2014]. After systemic use, up to 65% of a dose is excreted in urine within 24 hours. Clearance in premature neonates is reported to be proportional to gestational age, with a reduced elimination rate in the most premature. It readily crosses the placenta with minimal in-activation [Brayfield, A. 2014].

Pharmacodynamics
Following topical application to the conjunctiva of the eye, corticosteroids inhibit the inflammatory response to mechanical, chemical, or immunologic agents [AHFS DI 2014b]. Corticosteroids inhibit oedema, fibrin deposition, capillary dilatation, and migration of leukocytes and phagocytes in the acute inflammatory response. The drugs also reduce capillary proliferation, fibroblast proliferation,

deposition of collagen, and scar formation [AHFS DI 2014b]. Based on these properties, corticosteroids and dexamethasone eye drops in particular are widely used in ophthalmology. Corticosteroids are applied topically to the conjunctiva for the symptomatic relief of corticosteroid-responsive allergic and inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic or vernal conjunctivitis, acne rosacea keratitis, superficial punctate keratitis, herpes zoster keratitis, uveitis, iritis, and cyclitis. The drugs also are used topically as anti-inflammatory agents in corneal, conjunctival, and scleral injuries from chemical, radiation, or thermal burns or penetration of foreign bodies and, during the acute phase, may help prevent fibrosis and scarring and resultant visual impairment. Topical ophthalmic corticosteroids also are used prophylactically after ocular surgery (e.g., cataract extraction, glaucoma surgery, corneal transplant) to prevent inflammation, pain, and scarring, but the drugs may possibly delay wound healing. The drugs should not be used for minor abrasions or wounds [AHFS DI 2014b]. Application of corticosteroids to the eye may reduce the facility of aqueous outflow, thereby increasing intraocular pressure (IOP) and inducing or aggravating open-angle (simple) glaucoma [AHFS DI 2014b]. Results of various studies indicate that, on a weight basis, the anti-inflammatory activity of ophthalmic corticosteroids in decreasing order is: fluorometholone, dexamethasone, prednisolone, loteprednol etabonate, rimexolone, medrysone, and hydrocortisone [AHFS DI 2014b].

Clinical efficacy

No clinical studies have been conducted to support the application. Essential similarity with the reference originator product is claimed based on the comparative quality attributes of the product.

According to Guideline on The Investigation of Bioequivalence CPMP/QWP/EWP/1401/98 Rev.1: "In the case of solutions for topical use, e.g. eye drops or cutaneous solutions, and if the test product is of the same type of solution (aqueous or oily), contains the same concentration of the same active substance and the same excipients in the same amounts as the medicinal product currently approved, a biowaiver is acceptable. In certain cases quantitative differences in excipients may be acceptable for these products, if adequately justified".

The generic medicinal product indicated in the application comes in same type of solution for topical use (eye drops), contains the same concentrations of the active substance, the same concentration of the excipient critical for appropriate absorption of the active substance and the same excipients as the reference medicinal product currently approved. Also the intended posology and indications are the same.

The omission of in vivo equivalence studies is based on the CPMP/EWP/239/95 final Note for Guidance on the Clinical Requirements for Locally Applied, Locally Acting Products Containing Known Constituents.

Anti-inflammatory effects assessed by course of clinical symptoms:

Controlled clinical studies demonstrated that Dexamethasone and its derivatives 0.1% Eye Drops have clearly superior anti-inflammatory activity in comparison to placebo. Active controlled studies showed that the medicinal product under investigation provides higher or similar anti-infective effects compared with topical diclofenac and indomethacin.

Anti-infective effects assesses by using the Tyndall effect and cell counts:

In active controlled studies where the Tyndall effect and cell counts were used for assessment of outcome was shown that dexamethasone and its derivatives is at least comparable with alternative topical anti-inflammatory therapies. A number of additional active-controlled clinical studies with topical dexamethasone and its derivatives primarily used after different ocular surgical procedures support the already established beneficial anti-inflammatory effects of the medicinal product under discussion.

Clinical safety
A summary of dexamethasone-associated adverse events/reactions based on 11 clinical studies with 724 patients is comprised in the following Table:

System organ class	
Nervous system disorders	*uncommon:* headache
Eye disorders	*Common*: Eye pain, Conjunctival hyperaemia, Punctate keratitis, Conjunctival oedema, Hyphaema, Eyelid oedema *uncommon*: Eye inflammation, Anterior chamber fibrin, Anterior chamber inflammation, Posterior capsule rupture, Corneal oedema, Conjunctivitis, Ulcerative keratitis
General disorders and administration site conditions	*uncommon*: face oedema

Based on this relatively small pool of patients, common eye disorders were reported as the most frequently adverse events/adverse reactions: Eye pain, Conjunctival hyperaemia, Punctate keratitis, Conjunctival oedema, Hyphaema, Eyelid oedema.
Uncommon eye disorders include the followings: Eye inflammation, Anterior chamber fibrin, Anterior chamber inflammation, Posterior capsule rupture, Corneal oedema, Conjunctivitis, Ulcerative keratitis.

None of the reported adverse events pertaining to the 'Eye disorders' can be assigned to dexamethasone-associated adverse reactions. Each of these complaints is more or less associated with the inflammatory conditions of the diseased eye.
Other uncommon adverse events include 'headache' (Nervous system disorder) and 'face oedema' (General disorders and administration site conditions). A causal association of these events with the topical dexamethasone is at least questionable.
It appears that none of these effects were classified as serious. Moreover, regarding the prior operative measures in the majority of clinical studies, dexamethasone and its derivatives cannot be considered as the cause of the reported adverse effects. This conclusion is supported by a comparison of adverse events reported with placebo- and reference-medication treated. Eye inflammation and hyphaema are the most frequent adverse events in the placebo group. The most frequently reported adverse event in patients treated with reference therapy was eye inflammation, conjunctivitis, eye pain, hyphaema, and ocular hypertension.
The safety profile of dexamethasone, and dexamethasone and its derivatives eye drops in particular, was evaluated repeatedly in commercial scientific databases, e.g. [DRUGDEX Evaluations 2009, AHFS DI 2014a, Clinical Pharmacology 2014].
The most comprehensive compilations available in the Hazardous Data Base [HSDB 2014], and the 'Gold Standard Monographs'[Clinical Pharmacology 2014] will be quoted.
The most frequent adverse reactions to ophthalmic dexamethasone and its derivatives are visual impairment (i.e., visual acuity and field defects), secondary ocular infection (including viral and fungal infections) exacerbation, and perforation of the globe [Clinical Pharmacology 2014].
Rarely, ocular irritation consisting of burning and stinging may occur with ophthalmic administration. Temporary or permanent visual impairment, including blindness, has been reported with corticosteroid administration by several routes of administration including intranasal and ophthalmic administration. Ophthalmic preparations of dexamethasone and its derivatives can cause an increased intraocular pressure, the magnitude of which depends on the frequency and duration of dosing. Ocular hypertension can occur after 1-6 weeks of topical ophthalmic therapy, and it usually is reversible upon discontinuance of the drug. Prolonged use of ophthalmic dexamethasone and its derivatives therapy can result in ocular hypertension, optic nerve damage, and visual defects. Although systemic corticosteroids are used to treat Graves' ophthalmopathy, ocular effects, such as exophthalmos, posterior subcapsular cataracts, retinopathy, or ocular hypertension, can result from prolonged use of corticosteroids and could result in glaucoma, or ocular nerve damage including optic neuritis [Clinical Pharmacology 2014].

Because some systemic absorption may occur following topical application or intravitreal implantation of corticosteroids to the eye, the possibility of adverse systemic effects exists. Headache, hypotension, rhinitis, pharyngitis, and taste perversion have been reported in patients following topical instillation of ophthalmic corticosteroids. Other adverse systemic effects associated with systemic corticosteroids are uncommon with topical ophthalmic corticosteroids, even with extended use, but the risk may be increased with frequent topical ophthalmic administration of potent steroids [HSDB 2014].
Rare instances of anaphylactoid reactions, such as anaphylactic shock and angioedema have occurred in patients during corticosteroid therapy [Clinical Pharmacology 2014].

Legal Status
Subject to medicinal prescription.

User Testing
In Round 1 all success criteria were fulfilled, no modification of the PL was necessary. Round 2 was therefore carried out with the same PL-version. In Round 2 also all success criteria were fulfilled. In conclusion the patient leaflet for the product has been user tested and achieved a satisfactory result.

Summary Pharmacovigilance system
The Applicant/Proposed Future MAH has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Dexafluid sine.

The MAH submitted a RMP. The summary of safety concerns is as follows:

Summary of safety concerns	
Important identified risks	- Ocular infections - Keratopathy - Impaired healing - Intraocular pressure increase - Lenticular opacity and cataract
Important potential risks	- Adrenal suppression - Cushing`s syndrome
Missing information	- Safety during pregnancy and lactation - Use in the paediatric population

The routine pharmacovigilance and routine risk minimisation measures are considered as sufficient.

Periodic Safety Update Report (PSUR)
Medicinal products authorised in accordance with Article 10(3) of Directive 2001/83/EC (hybrid application) are not exempted from the obligation to submit PSUR. Therefore PSUR submissions are required for hybrid medicinal products. The PSUR submission of this product should follow the EURD list.

IV. BENEFIT RISK ASSESSMENT

Benefits:

1. Dexamethasone sodium phosphate has got an established place in the treatment of open of non-infectious inflammatory diseases affecting the conjunctiva, cornea and anterior part of the eye including allergies, irritations, burns and chemical burns.
2. There is sufficient evidence on benefits of Dexamethasone sodium phosphate from clinical trials.
3. The safety profiles of Dexamethasone sodium phosphate and the contained excipients are well characterised.
4. Essential similarity with the reference originator product is claimed based on the comparative quality attributes of the product.
5. The properties of the product at issue and innovator product show similar characteristics.
6. The results provided by the applicant are considered sufficient for demonstrating that the physico-chemical properties of the reference product and the test product are similar.
7. The claim for pharmaceutical equivalence is accepted.

Risks:

1. This product contains phosphate buffer as an excipient. The CHMP decided that a thorough scientific discussion was necessary in order to establish the value and safe use of phosphates buffers in topical ophthalmic medicinal products for human use, because of the risk of corneal calcification.
2. Blurred vision may temporarily occur immediately after administration of Dexamethasone sodium phosphate 1.315 mg/ml eye drops single-dose. Patients should not take part in road traffic, work without secure fixation or operate machines before this impairment has worn off.
3. Corticosteroids may reduce resistance to and aid in the establishment of bacterial, viral, or fungal infections and mask the clinical signs of infection, preventing recognition of ineffectiveness of the antibiotic, or may suppress hypersensitivity reactions to substances in the product. Fungal infection should be suspected in patients with persistent corneal ulceration who have been or are receiving these drugs, and corticosteroid therapy should be discontinued if fungal infection occurs [AHFS DI 2014b].
4. In genetically predisposed patients, long-term treatment with corticosteroids may cause a more or less pronounced increase in intraocular pressure reversible after termination of medication (cortisone glaucoma). Regular controls of intraocular pressure, cornea and lens are recommended due to possible side effects.
5. Eye drops containing corticosteroids may slow down wound healing especially after prolonged use and at higher concentrations.
6. Various ocular diseases and long-term use of topical corticosteroids have been known to cause corneal or scleral thinning with a risk for perforation.
7. Cushing syndrome following use of ocular administration of steroids (eye drops) has not been reported, while single cases of this conditions were known after topical corticosteroid use, e.g. after intranasal uses [Dutta, D. 2012].

Conclusion on risk/benefit:

The application for the topical medicinal product Dexamethasone sodium phosphate 1.315 mg/ml eye drops single-dose indicated for steroid treatment of non-infectious inflammatory diseases affecting the conjunctiva, cornea and anterior part of the eye including allergies, irritations, burns and cauterizations is approved. The legal basis of the application is Article 10.3 of Directive 2001/83/EC (Hybrid Application). From pharmacological, toxicological and clinical view, Dexamethasone sodium phosphate 1.315 mg/ml eye drops single-dose will not act differently as compared to the reference product (Dexa-sine SE). The applicant demonstrates that the proposed medicinal product will not lead to any different systemic absorption in comparison to the reference product. As consequence the clinical studies on efficacy and tolerability can be waived. Extensive evaluation of all of the clinical literature data accessible by the experts allows the conclusion that the medicinal product under discussion, Dexamethasone sodium phosphate 1.315 mg/ml eye drops single-dose has a favourable risk-benefit ratio. The beneficial effects clearly outweigh any potential risk that could be

attributed to its use. This conclusion regards the latest limitations in use, precautions, and warnings to be included in the current product label.
Based on a critical review of the extensive documentation relating to the clinical pharmacology, efficacy, and safety of Dexamethasone sodium phosphate 1.315 mg/ml eye drops single-dose, the application for Dexamethasone sodium phosphate 1.315 mg/ml eye drops single-dose is approved.
For intermediate amendments see current product information.