LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Ultracortenol
(prednisolone pivalate)

SE/H/1794/01/MR

This module reflects the scientific discussion for the approval of Ultracortenol. The procedure was finalised on 2020-10-22. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Ultracortenol, 5 mg/g, eye ointment.

The active substance is prednisolone pivalate. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Ultracortenol, 5 mg/g, eye ointment, is submitted according to Article 10a of Directive 2001/83/EC. The applicant, Agepha Pharma s.r.o., applies for a marketing authorisation in CMS through this mutual recognition procedure with Sweden acting as reference member state (RMS). The product was first approved through a National Procedure.

For an application according to Article 10a, WEU, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use for the claimed therapeutic indication within the Union for at least ten years, with recognised efficacy and an acceptable level of safety.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology

Corticosteroids are a class of chemicals that includes steroid hormones naturally produced in the adrenal cortex of vertebrates and analogues of these hormones that are synthesized in laboratories. Corticosteroids are involved in a wide range of physiologic processes, including stress response, immune response, and regulation of inflammation, carbohydrate metabolism, protein catabolism, blood electrolyte levels, and behaviour.

Endogenous glucocorticoids such as cortisol control carbohydrate, fat and protein metabolism and are anti-inflammatory by preventing phospholipid release, decreasing eosinophil action and a number of other mechanisms. Mineralcorticoids such as aldosterone control electrolyte and water levels, mainly by promoting sodium retention in the kidney.

Anti-inflammatory effects result from decreased formation, release and activity of the mediators of inflammation (eg, kinins, histamine, liposomal enzymes, prostaglandins, leukotrienes) which reduced the initial manifestations of the inflammatory process. The immunosuppressive properties decrease the response to delayed and immediate hypersensitivity reactions (eg, type III and type IV). Moreover, nearly all immune cell types are influenced such as macrophages, monocytes, lymphocytes, mastcells and eosinophils by inhibiting chemotaxis, ahesion and phagocytosis activity.

On a molecular level, glucocorticoids excerpt their anti-inflammatory and immunosuppressive properties by binding to its corresponding receptors, the glucocorticoid receptor and the mineralocortocoid receptor. They are located intracellularly and upon activation, inhibit pro-inflammatory pathways by either altering gene transcription or protein function. With regard to the first point, ligand-bound glucocorticoid receptors bind nuclear factor-κ B (NF-κB) and AP-1, major transcription factors involved in the propagation of immune responses. This causes inhibition of gene transcription of pro-inflammatory genes such as IL-1, COX-2 as well as activation of anti-inflammatory genes such as IL-10, IL-1RA and IκBα. Corticosteroids affect early inflammatory events such as edema, vascular dilatation, fibrin deposition and leucocyte migration as well as late inflammatory events suchas capillary proliferation, fibroblast proliferation and collagen deposition.

Prednisolone is a synthetic glucocorticoid with anti-inflammatory and anti-allergic properties. The anti-inflammatory activity of prednisolone per weight unit is 4-5 times higher than for hydrocortisone. The efficacy of prednisolone in ophthalmic preparations as an anti-inflammatory agent is well-established.

Pharmacokinetics

The maximum concentrations of prednisolone in the cornea and aqueous humor after application of 1% prednisolone were about 20 μg/g corneal tissue and 1.7 μg/ ml aqueous humor when the cornea was intact and ocular inflammation present. An in vivo study using a 0.5% prednisolone gel formulation has indicated that bioavailability is not completely similar to a suspension after instillation into the conjunctival sac. In corneal washings, the AUC of the gel was higher than that of the suspension. This seems to reflect the prolonged retention time of the gel on the ocular surface. However, prednisolone levels in aqueous humor and plasma seem to reflect correctly the difference in the dose and can be regarded as indicative of linear bioavailability. In the plasma, glucocorticoids are partially bound to plasma corticosteroid-binding globulin and albumin.

Upon parenteral administration, prednisolone is widely distributed into all body tissues. When entering the circulation, all corticosteroids can distribute into all body tissues including the brain. Prednisolone can cross the placenta and distributed into breast milk.

Prednisolone is metabolized by the 11-beta hydroxysteroid dehydrogenase system. The half-life of prednisolone acetate in the cornea has been cited as being 17-89 minutes, that in aqueous humour 80-156 minutes.

Prednisolone is excreted in urine as free and conjugated metabolites with an appreciable proportion of unchanged prednisolone.

Toxicology

The acute toxicity of prednisolone has been investigated in mice and rats and is considered low.

Repeated dose toxicity studies in different species using high dermal and oral doses revealed reduced body weight gain and food consumption, reduced leukocyte counts, and decreased thymic, spleen and adrenal weights.

In a 6-month study (3 times daily one drop of 0.25% prednisolone into the cul-de-sac of the right eye of each animal) in rabbit, ocular toxicity was assessed upon chronic exposure. At termination of the study, signs of infection were noted in steroid-treated animals but not in control animals. No deaths occurred during the treatment period. Total body weight and the weight of liver, adrenals, and thyroid were reduced in prednisolone-treated animals. Spleen and kidneys were increased. Chronic pyelonephritis, of varying degrees, was observed in a large number of the animals. Major increases in IOP occurred during the first three weeks of treatment but were only transient. The IOP of the majority of eyes treated returned to a normal pressure after four of five weeks of continued corticosteroid treatment. Two out of 10 animals treated with prednisolone showed lenticular changes.

No mutagenic effect of prednisolone was observed in an in vitro mouse lymphoma assay for gene mutation in both presence and absence of metabolic activation. In a carcinogenicity study with prednisolone in rats it was shown that prednisolone did not increase the incidence of any tumor type.

Teratogenic effects are observed after high doses of steroids. Animals show an incidence of abortion, placental insufficiency, cleft palate, and other effects after high doses of steroids. Rats showed minor anomalies of the skull, jaw and tongue. These effects however were mainly seen after systemic administration of high levels of prednisolone.

Local ocular tolerance of a 0.5% prednisolone gel was evaluated in a 28-day study in rabbit eyes after four or six daily applications into the conjunctional sac. Following 4 daily applications, treatment was well tolerated locally. Following 6 daily applications, treatment induced a conjunctival discharge. Ocular histopathology demonstrated that both treatment regimens did not induce any histopathological alterations. In summary, the study demonstrated the acceptable local tolerance of a 0.5% prednisolone concentration.

Environmental Risk Assessment (ERA)

A justification for not submitting a full environmental risk assessment for non-GMO human medical products (see EMEA/CHMP/SWP/4447/00 corr1, EMA, 2006) has been submitted in this application. The product in question is an anti-inflammatory eye salve named Ultracortenol (described as a Well-established use product as the medication was first introduced in 1958); the active substance is the synthetic corticosteroid prednisolone pivalate. Prednisolone is already authorized in the EU in various formulations and no new indications will be claimed.

It is agreed that the PEC_{SW} value for prednisolone in Ultracortenol falls below the trigger value for ERA Phase IIA and that the Ultracortenol contribution of prednisolone is unlikely to increase overall synthetic corticosteroid exposure to the environment. The justification for not submitting a full ERA is acceptable.

IV. CLINICAL ASPECTS

Pharmacokinetics

This is an application for an already registered medicinal product for topical ocular use only. Therefore, no new bioavailability studies have been performed and are not deemed necessary. Prednisolone is absorbed into aqueous humor, cornea, iris, choroid, ciliary body, and retina. Prednisolone is metabolized mainly in the liver but also other body tissues. Several metabolites are described for prednisolone. The half-life of prednisolone acetate in the cornea has been cited as being 17-89 minutes, that in aqueous humor 80-156 minutes. Prednisolone is excreted in the urine as free and conjugated metabolites with an appreciable proportion of unchanged prednisolone. It can cross the placenta and is distributed into breast milk in small amounts.
The clinical overview presents a thorough overview over the pharmacokinetics of the topical ophthalmic application of prednisolone which is considered satisfactory.

Pharmacodynamics

The corticosteroid prednisolone is an effective anti-inflammatory drug, widely used for systemic or topical application. Anti-inflammatory effects result from decreased formation, release and activity of the mediators of inflammation (eg. kinins, histamine, liposomal enzymes, prostaglandins, leukotrienes) which reduce the initial manifestations of the inflammatory process. Moreover, nearly all immune cell types such as macrophages, monocytes, lymphocytes, mast cells and eosinophils are influenced by inhibiting chemtaxis, adhesion and phagocytosis activity.
The clinical overview presents a thorough overview of the pharmacodynamics of the topical ophthalmic application of prednisolone which is considered satisfactory.

Clinical efficacy

Prednisolone is regarded as one of the most potent steroids for nonspecific suppression and regulation of inflammation such as allergic conjunctivitis, non-bacterial, non-viral or non-fungal inflammations or inflammations of the eye after surgery. Ultracortenol has received marketing autorisationin SE in 1958 and its efficacy for the claimed indications have since been confirmed through clinical practice and a vast array of clinical trials and publications.
A phase III and a phase IV clinical trial undertaken by the previous holder of marketing authorization CIBA Vision, have shown to reduction of inflammation post-cataract surgery and ophthalmic prednisolone preparations have been in clinical use for this indication.
The applicant presents the results of the main clinical studies, supportive studies proving efficacy of topical ocular prednisolone preprations in the treatment of conjunctivitis of allergic origin, conjunctivitis vernalis, non-infectious keratitis, uveitis (iritis, iridocyclitis).
Treatment has become well established in clinical use and was implemented in clinical recommendations, guidelines, manuals etc listed by the applicant in the clinical overview. Efficacy of 0.5% prednisolone ophtalmic preparations has been shown to be equivalent with 1.0 % prednisolone preparations. Topical ophthalmic NSAID preparations appear to be similarly effective compared to topical steroids in suppressing inflammation in some conditions but lack the antiallergic properties and are less well tolerated locally. When comparing different topical corticosteroid preparations for the eye regarding their anti-inflammatory potency in the eye, prednisolone acetate 1.0% ophthalmic suspension has been shown to be highest, followed by dexamethasone alcohol 0.1 % suspension and fluorometholone alcohol 0.1% suspension. Least effective are prednisolone phosphate 1.0 % ophthalmic solution and dexamethasone phosphate 0.1 ophthalmic solution, respectively.
Summarising, the overall clinical evidence demonstrates that prednisolone is an effective steroid for suppression of inflammations of various origin and has also potent antiallergic properties. Available evidence indicates that formulations for ophthalmic use which contain prednisolone as the principle active ingredient are suitable for the treatment of allergic conjunctivitis and unspecific ocular inflammatory disorders of the eye of non-infectious origin.

Clinical safety

Ultracortenol 0.5% eye ointment has received marketing authorisation in Sweden in 1958 and has since been proven to be safe and well-tolerated when used according to the product information. The applicant presents a thorough overview over safety aspects of topical ophthalmic steroid use and even systemic safety aspects. 0.5% and the 1% prednisolone preparations have been shown to be safe and well tolerated in doses of 1 drop 3 times daily over the course of two weeks.

The rate of adverse effects is low when used as short-term treatment and systemic side effects are mainly seen in long term treatment. Transient burning/stinging as well as blurred vision are expected and reported adverse effects. Burning sensation, blurred vision and headache have been included as possible side effects in the product information.

Increase in IOP is a well -known adverse effect of ocular topical corticosteroids and this is reflected in the SmPC with medically uncontrolled glaucoma being a contraindication. About 5% of the population seem to be high-responders, especially patients with primary open-angle glaucoma. About 66-70% of patients react with an increase of up to 5 mm Hg, reaching up to 19 mm Hg. There appears to be a clear dose-correlation of this adverse effect. Increase in IOP is also listed as warning and undesirable effect in the SmPC. The IOP must be monitored in long term treatment with view to the potential risk of damage to the optic nerve.

Treatment with corticosteroids might lead to later eye infections or mask acute eye infections leading to keratitis and corneal perforation. Infections need to be therefore treated with antibiotics, antivirals or antifungals respectively. Viral, bacterial and fungal infections should not be treated simultaneously with topical corticosteroids. Ultracortenol eye ointment is contraindicated in patients with bacterial, viral or fungal infections of the eye.

A very important adverse effect mainly attributed to long term topical corticosteroid treatment is cataract. Immune suppression and possible impairment of wound healing are further possible side effects of corticosteroids. The adverse effects mydriasis, ptosis, epithelial punctate and possible corneal or scleral malacia have also occurred.

Long-term treatment should be avoided in children according to section 4.2 and 4.4 of the SmPC and if treatment is longer than 10 days, special warnings and precautions for the use of the product have to be considered according to the SmPC.

Atropine or other anticholinergic agents, when simultaneously administered with Ultracortenol, may increase intraocular pressure in predisposed patients.

Short term treatment of the topical application form is unlikely to result in effects to the unborn. Nevertheless, benefit to the mother/risk to the foetus need to be carefully considered as stated in the SmPC. Ultracortenol can be safely used during breastfeeding.

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 Ultracortenol, 5 mg/g, eye ointment.

Safety specification

Important Identified Risk	None
Important Potential Risks	None
Important Missing Information	None

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 0.3, signed 24/06/2019, is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers the application for Ultracortenol approvable. A national marketing authorisation was granted in the RMS **1958-09-30**.
The product information is acceptable, and the benefit risk balance is considered positive.
There is no need for conditions under Article 21a/22 of Directive 2001/83.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The mutual recognition procedure for Ultracortenol, 5 mg/g, eye ointment was positively finalised on 2020-10-22.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se