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Public Assessment Report

Scientific discussion

Eleus 0.5 mg/ml eye drops, emulsion in single-dose container. (Clobetasol propionate)

ES/H/0900/001/DC

Date: 16/03/2026

This module reflects the scientific discussion for the approval of Eleus 0.5 mg/ml eye drops, emulsion in single-dose container. The procedure was finalised at 06 May 2025. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Eleus 0,5 mg/ml colirio en emulsion en envase unidosis, from Laboratorios Salvat S.A.

The product is indicated for*:* treatment of inflammation associated with cataract surgery in adults.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

The product Uvesol 0.5 mg/ml eye drops, emulsion in single-dose container, from Laboratorios Salvat, S.A. consists an oil-in-water nanoemulsion comprised of the active substance clobetasol propionate (0.5 mg/mL).
The maximum daily dose is 0.060 mg of Clobetasol propionate.
Uvesol 0.5 mg/ml eye drops, emulsion is packaged in formed low-density polyethylene (LDPE) single-dose container.

II.2 Drug Substance

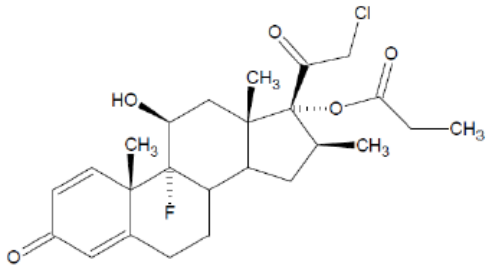
The CEP procedure is used to support the quality of the drug substance.

General Information

Nomenclature:

INN: Clobetasol propionate
Chemical name: 21-Chloro-9α-fluoro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl propionate
CAS: 25122-46-7

Chemical structure:



Empirical Formula: $C_{25}H_{32}ClFO_5$
Molecular weight: 466.97 g/mol

General Properties:

Appearance: White or almost white crystalline powder.
Solubility: Practically insoluble in water, freely soluble in methylene chloride and acetone, sparingly soluble in ethanol (96%).
Polymorphism: It does not exhibit polymorphism.
Melting range: 196 ºC.

The control tests and specifications for drug substance product are adequately drawn up.

Stability studies have been performed with the drug substance and they have been assessed by EDQM and the proposed retest period is included in the CEP or sufficient stability data have been provided in the dossier.

II.3 Medicinal Product

Description of the product

The drug product is an oil-in-water nanoemulsion comprised of the active substance clobetasol propionate (0.5 mg/mL).
The qualitative composition of the finished product is as follows:
Clobetasol propionate
Polysorbate 80
Medium chain triglycerides
Benzalkonium chloride
Disodium edetate
Povidone K29-32
Trometamol
Glycerol
Water for injection

The packaging material intended for the commercial use consists in a low-density polyethylene (LDPE) single-dose ampoule with a volume of approximately 0.20 mL.

Pharmaceutical Development

The development of the product has been described, the choice of excipients is justified and their functions explained.
The physicochemical characteristics of the active substance that may affect the pharmaceutical form are identified and their control strategy is justified.

Manufacture of the product

The manufacturing process is fully described and in-process controls are appropriate considering the nature of the product and the manufacturing process. The industrial batch size is well-defined.
Sufficient validation data are provided.

Excipients

Excipients used are well known and of appropriate quality.
None of the excipients is of animal origin.

Product specification, analytical procedures, batch analysis

The finished product specifications are adequate to control the finished product. Provided description and validation data for the analytical methods are adequate. Batch analysis data have been submitted and the results show that the finished product meets the proposed release specification.

Container closure system

The finished product is packaged in a low-density polyethylene (LDPE) single-dose ampoule with a volume of approximately 0.20 mL. The choice of the container closure system is justified considering the nature of the finished product. Compliance with the relevant requirements and/or regulations is confirmed.

Stability

Stability studies have been performed in accordance with current guidelines. The proposed protocol is considered adequate. The packaging material is the same as that intended for marketing. Proposed shelf-life and storage conditions are properly established.

Shelf-life: 36 months.

Storage conditions: This medicinal product does not require any special temperature storage conditions. Store the single-dose containers in the pouch in order to protect from light.

In use shelf-life: After first opening of the single dose container: use immediately and discard the single-dose container after use.

Once the pouch is opened, the single dose containers should be used within 30 days.

The quality of Eleus 0.5 mg/ml eye drops emulsion in single-dose container is found adequate. There are no objections to the approval of Eleus.5 mg/ml eye drops emulsion in single-dose container from a quality point of view. The product information is acceptable. The application is therefore recommended for approval.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Clobetasol propionate is a corticosteroid with well-established anti-inflammatory activity. Two *in vivo* ophthalmic studies confirmed pharmacodynamic activity, showing a reduction in prostaglandin E_2 levels of up to 78%. No dedicated secondary pharmacology studies were performed; literature indicates potential for immune suppression, HPA axis effects, and increased IOP, consistent with corticosteroid class effects. No new safety pharmacology studies were conducted, as systemic exposure after ocular administration is expected to be minimal. Clobetasol is a potential CYP3A4 substrate; therefore, interactions with CYP3A4 modulators cannot be excluded.

III.2 Pharmacokinetics

In rabbits, repeated-dose studies (up to 264 µg/day for 29 days) showed low systemic exposure at the anticipated human dose (Cmax ~1.2 ng/mL, undetectable at 4 h) and dose-dependent accumulation at higher doses. Ocular distribution was limited to anterior segment tissues, with no penetration into posterior structures and no melanin binding. Systemic distribution in rats after SC dosing was highest in liver, GI tract, kidneys, and endocrine organs. Clobetasol is metabolised via standard glucocorticoid pathways (3α-/5β-reductases, CYP3A4) to inactive glucuronide-conjugated metabolites. Excretion occurs mainly via feces, with minor urinary elimination; ophthalmic administration is expected to follow a similar pattern. No PK interaction studies were conducted, but literature indicates glucocorticoids may induce hepatic enzymes (notably CYP3A4).

III.3 Toxicology

Literature data report oral LD_{50} values of ~3000 mg/kg in mice and rats, and LD_{50} values of 82–156 mg/kg (mice) and 351–414 mg/kg (rats) following SC or IP administration.

Published data include a three-month subcutaneous study in rats showing reduced activity and dose-related mortality at ≥25 µg/kg, with necropsy findings of lung abscesses, adrenal and thymus atrophy. In a six-month study, no deaths occurred up to 40 µg/kg, but body weight reduction, spleen and thymus size decrease, pulmonary changes, hematological alterations, and adrenocortical vacuolisation were observed at higher doses.

Ocular toxicity was assessed in pivotal GLP repeated-dose toxicity studies in rabbits following ophthalmic administration of Clobetasol SD at 16.5 or 33.0 µg/eye QID for 28 days. These studies

revealed transient, mild ocular effects, with no impact on intraocular pressure (IOP) or ocular irritation. The lowest observed adverse effect level (LOAEL) for ocular toxicity was 0.132 mg/eye. Systemic findings included increased liver and kidney weights, hepatocellular vacuolation, elevated liver enzymes, and lymphopenia, most of which resolved within two weeks after treatment cessation. A no observed adverse effect level (NOAEL) for systemic toxicity could not be established due to corticosteroid-related effects.

No genotoxic potential was identified in published *in vitro* and *in vivo* studies, including bacterial reverse mutation, chromosomal aberration, and mouse micronucleus tests.

No long-term studies were performed with clobetasol propionate ophthalmic emulsion. Carcinogenicity testing is not considered necessary given the short intended treatment duration (≤14 days).

No dedicated reproductive toxicity studies were conducted with clobetasol propionate 0.5 mg/ml ophthalmic solution. Literature data from studies in animals with clobetasol propionate have shown reproductive toxicity following systemic administration. In embryo-fetal development studies in mice, clobetasol propionate was fetotoxic at the highest subcutaneous dose tested (1 mg/kg) and teratogenic at all subcutaneous dose levels tested up to 0.03 mg/kg. Abnormalities observed included cleft palate and skeletal malformations. These doses are approximately 49 times and 1.5 times, respectively, the daily clinical dose, based on body surface area and assuming 100% systemic absorption. In similar studies in rabbits, clobetasol propionate was teratogenic at subcutaneous doses of 3 and 10 µg/kg. Defects observed included cleft palate, cranioschisis, and other skeletal malformations. These doses are approximately 0.6 times and 2 times, respectively, the daily clinical dose, also estimated based on body surface area and assuming 100% systemic absorption.

No ocular irritation was observed in 28-day ophthalmic studies or IOP assessments. However, *in vitro* skin sensitization tests have showed that neither Clobetasol SD nor its vehicle induced CD54/CD86 expression, indicating both formulations are non-sensitizing.

III.4 Ecotoxicity/environmental risk assessment (ERA)

An OECD Guideline 107 study determined the partition coefficient (octanol/water) of clobetasol propionate, with a log Kow of 3.5, consistent with literature data. As log Kow > 3, a bioconcentration factor (BCF) was assessed according to OECD TG 305 to evaluate the potential for secondary poisoning. The results indicate that clobetasol propionate does not accumulate in fish (BCF < 100 L/kg).

For Phase II assessment, the Applicant submitted an OECD TG 211 study on Daphnia magna reproduction, reporting an EC_{10} of 3.269 mg/L and a NOEC of 0.83 mg/L. Based on these results, the PEC/PNEC ratio is below 1, suggesting that clobetasol propionate is unlikely to pose a risk to surface water at this trophic level.

However, as environmental effects and risks are not fully characterised, a potential risk to the environment cannot be excluded. In line with EMA guidance (Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use, EMEA/CHMP/SWP/4447/00 Rev. 1 – Corr.*), precautionary measures include an indication of potential environmental risks in the product information.

The Applicant has committed to conduct additional post-authorisation studies in accordance with EMA recommendations, including adsorption/desorption (OECD TG 106), ready biodegradability (OECD TG 301), aerobic water-sediment simulation (OECD TG 308, assuming the substance is not readily biodegradable), toxicity to algae (OECD TG 201), at least one sediment toxicity study (Lumbriculus sp.; OECD TG 225 and/or Chironomus; OECD TG 218/219 or TG 233), activated sludge respiration inhibition (OECD TG 209) and a Fish full life-cycle test (OECD TG 240).

IV. CLINICAL ASPECTS

IV.1 Introduction

A cataract is an opacity of the lens of the eye that may cause blurred or distorted vision, glare problems, or, in very advanced cases, blindness. Cataracts occur frequently with increasing age and can also occur in children. Cataract is a significant cause of blindness worldwide [1]

The current standard of management of a visually significant cataract is surgical removal of the cataractous lens and its replacement with an intraocular lens.[2] Phacoemulsification with intraocular lens implant in the capsular bag is the standard of care[3].

Following cataract surgery, inflammation occurs in the eye. The severity of postoperative inflammation varies and in most cases is self limiting. Uncontrolled inflammation may lead to serious side effects, such as posterior synechia, uveitis, and secondary glaucoma . Corticosteroid or nonsteroidal antiinflammatory drug (NSAID; eg, ketorolac, nepafenac, bromfenac) drops are often prescribed postoperatively to reduce pain, inflammation, and the likelihood of macular edema, an inflammatory complication that may limit recovery of vision.

Clobetasol propionate is a synthetic corticosteroid of the glucocorticoid class. The compound is an analog of prednisolone and has a high degree of glucocorticoid activity and a slight degree of mineralocorticoid activity.

The initial claimed indication was: *Treatment of inflammation and pain associated with ocular surgery in adults.*

IV.2 Pharmacokinetics

No pharmacokinetic (PK) studies have been carried out with Clobetasol propionate 0.5 mg/ml eye drops, emulsion in humans by the applicant. The human systemic exposure to clobetasol propionate from ophthalmic administration of the emulsion was extrapolated using the relative plasma volumes of rabbits and humans, or the human equivalent dose (HED) from the rabbit studies. (See Non-clinical AR)

There are no medicinal products containing clobetasol administered as eye drops approved in EU. As reference, a similar product containing the same active substance and formulated also as an ophtalmic suspension (Clobetasol propionate ophthalmic suspension 0.05%; Formosa Pharmaceuticals Inc), is approved in US for the same indication. According to the labelling peak plasma clobetasol propionate concentrations (Cmax) were measured in 40% of PK profiles and ranged from 0.040 to 0.182 ng/mL. Time to peak concentration (Tmax) was observed between 0.5- 1 hour post-dose. Clobetasol propionate concentrations declined to lower than LLOQ after 4 to 5 hours post-dose.

IV.3 Pharmacodynamics

Primary PD studies have been conducted by the applicant to investigate the efficacy of Clobetasol SD in animal models of inflammation associated with ocular surgery and of anterior uveitis. The results were as expected for a corticosteroid and were in line with published nonclinical and clinical studies (See Non-clinical AR).

No clinical pharmacodynamic studies have been conducted by the applicant, due to the wellknown mechanism of action of corticosteroids, including clobetasol propionate. The effect of corticosteroids by ophthalmic route of administration for the intended indication is already described for other corticosteroids.

IV.4 Clinical efficacy

To support the application, the applicant submitted two identical phase III multicentre, randomized, double-masked, studies that were run in parallel (CLOSE-1 and CLOSE-2). Studies CLOSE-1 and CLOSE-2 compared the efficacy and safety of Clobetasol propionate 0.5 mg/ml eye drops emulsion in single-dose container to placebo (vehicle) when administering one drop QID (quarter in die) during 14 days after routine unilateral cataract surgery.

Both studies were conducted in the United State (US) and recruited patients aged 18 years and older who had undergone routine, unilateral cataract surgery.
The results of both studies showed the superiority of clobetasol propionate treatment compared to placebo for the primary efficacy endpoint (proportion of patients with anterior chamber cell grade of "0" (absence of cells) compared to placebo at Day 8).
The lack of statistical difference for the key secondary endpoint (pain control) in CLOSE-2 and the lack of clinical relevance of the achieved pain relief in CLOSE-1 lead to the overall conclusion that no clinically relevant pain relief of clobetasol propionate eye drops had been shown. The extrapolation of results from CLOSE-1 and CLOSE-2 studies (in cataract surgery) to all types of ocular surgery was not adequately justified and no discussion was provided to show that cataract surgery is an adequate model of the inflammation induced by all types of ocular surgical procedures. Therefore, the indication was revised to: *Treatment of inflammation associated with cataract surgery in adults.*

IV.5 Clinical safety

The clinical safety profile of Clobetasol propionate 0.5 mg/ml eye drops emulsion in single-dose container is well-supported by data from two phase III clinical trials (CLOSE-1 and CLOSE-2), which included a total of 426 patients in the safety population.

The safety data demonstrate that the product is generally well-tolerated, with the majority of treatment-emergent adverse events (TEAEs) being mild to moderate in intensity and largely related to the expected ocular effects following surgery, such as eye pain or photophobia. The incidence of serious adverse events (SAEs) was low, and no deaths were reported during the clinical trials.

The safety profile of Clobetasol propionate 0.5 mg/ml eye drops emulsion in single-dose container is consistent with the known effects of corticosteroids, particularly regarding the potential for increased intraocular pressure.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan (version 0.3, 22 July 2025), 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 Eleus 0.5 mg/ml eye drops emulsion in single-dose container (clobetasol propionate).

There are neither proposed additional pharmacovigilance activities nor proposed additional risk minimisation measures planned for Eleus 0.5 mg/ml eye drops emulsion in single-dose container (clobetasol propionate).

V. USER CONSULTATION

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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

The quality of Eleus 0.5 mg/ml eye drops emulsion in single-dose container is found adequate. There are no objections to the approval of Eleus.5 mg/ml eye drops emulsion in single-dose container from a non-clinical and clinical point of view. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.