COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Cequa 0.9 mg/ml eye drops, solution in single-dose container (ciclosporin)

NL/H/5627/001/DC

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This module reflects the scientific discussion for the approval of Cequa 0.9 mg/ml eye drops, solution in single-dose container. The procedure was finalised on 27 March 2024. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
BID	Twice daily
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
CsA	Ciclosporin A
CQA	Critical Quality Attribute
DED	Dry Eye Disease
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
ICH	International Conference of Harmonisation
KCS	Keratoconjunctivitis sicca
LOQ	Limit Of Quantification
MAH	Marketing Authorisation Holder
MDR1	Multi-Drug Resistance Protein 1
NOAEL	No-Observed-Adverse-Effect Level
NZW	New Zealand White
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
QID	Four times daily
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TK	Toxicokinetic
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Cequa 0.9 mg/ml eye drops, solution in single-dose container, from Sun Pharmaceutical Industries Europe B.V.

The product is indicated for the treatment of moderate-to-severe Dry Eye Disease (DED; keratoconjunctivitis sicca) in adult patients who have not responded adequately to artificial tears.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

This decentralised application concerns the marketing authorisation of a nanomicellar formulation for topical ocular administration (Cequa, also referred to as OTX-101 by the MAH). The marketing authorisation has been granted pursuant to Article 8(3) (full or full-mixed application (complete dossier)) of Directive 2001/83/EC. It concerns a full application including quality, pre-clinical and clinical data, where the studies conducted by the MAH are supplemented with bibliographical data.

The concerned member states (CMS) involved in this procedure were Austria, Denmark, Finland, France, Germany, Italy, Norway, Spain and Sweden.

II. QUALITY ASPECTS

II.1 Introduction

Cequa is a clear, colourless eye drops solution with a pH of 6.5 to 7.2 and osmolality of 160-190 mOsm/kg.

One ml of solution contains as active substance 0,9 mg of ciclosporin and each single-dose container contains 0,25 ml of drug product.
Therefore, each single-dose container contains 0,225 mg of ciclosporin. Accordingly, each eye drop (approximately 0,025 ml) contains 0,0225 mg of ciclosporin.

The excipients are: macrogolglycerol hydroxystearate, octoxynol-40, sodium dihydrogen phosphate dihydrate (E339), disodium phosphate (E339), sodium chloride, povidone (E1201), hydrochloric acid (for pH adjustment; E507), sodium hydroxide (for pH adjustment; E524) and water for injection.

The eye drops, solution, are packed in single-dose, low-density polyethylene (LDPE) containers. Each single-dose container contains 0,25 ml of the solution. The containers are packed in cartons.

II.2 Drug Substance

The active substance is ciclosporin, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Ciclosporin is a white or almost white powder, practically insoluble in water. There is no concern regarding differential dissolution rates of ciclosporin polymorphs.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality meets the requirements of the monograph in the Ph.Eur. and includes additional tests of the CEP. Batch analytical data demonstrating compliance with this specification have been provided for three production-scale batches.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients and their function is discussed.

The formation of micelles in the formulation is thoroughly discussed and the micelles are sufficiently characterised. The formulation and the manufacturing process parameters of the filtration, filling and packaging steps of the manufacturing process are adequately justified.

This change is adequately discussed in the application dossier, including discussion on its rationale and development and a risk assessment about the impact of the applied changes on the critical quality attributes (CQAs) of the drug product. Stability results are provided and support the change.

A thorough characterisation of the drug product obtained by the new process and comparison with earlier (clinical) batches has been provided, no significant difference in CQAs, in-process controls, release parameters and extended physicochemical characteristics could be observed. The material of the new process is considered sufficiently comparable to the old (clinical) batches.

An acceptable justification is provided for the selected sterilisation method. Functional aspects of the plastic container, such as usability, size and shape of the container and dose delivery performance have been adequately addressed. Extractables studies confirm the safety and suitability of the selected container.

Manufacturing process

The manufacturing process consists of the following phases: dissolution of the drug substance, addition of the other components to obtain the bulk solution, sterilisation method, filling and packaging. The manufacturing process description includes sufficient details.
Appropriate in-process controls have been described for the main process and for the manufacturer of the containers.
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. and, where applicable, in-house requirements. Appropriate controls are applied to non-compendial excipient octoxynol-40. These specifications are acceptable.

Microbiological attributes

The information provided about the packaging materials is sufficient, including details about suppliers and compliance to regulations of all materials involved. Compliance of the LDPE resin to relevant Ph. Eur. monographs has been confirmed. Technical drawings and photographs of the containers are provided.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, clarity and degree of coloration, identification, assay, related substances, pH, osmolality, viscosity, sterility, micelle size determination, particulate matter, uniformity of dosage units (fill weight uniformity) and weight loss (only applicable for stability studies). Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report and an acceptable risk assessment on elemental impurities has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from seven batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three full-scale drug product process validation batches stored at 25°C/40% RH (48 months) and 30°C/65% RH (12 months). The stability was tested in accordance with the ICH stability. The photostability study shows that the product is not sensitive to light. On basis of the data submitted, a shelf life was granted of 18 months. The labelled storage conditions are 'Store below 25°C. Do not freeze. Store the single-dose containers in the polyfoil aluminium pouch.'

In-use stability data have been provided demonstrating that the product remains stable for five days after first opening of the pouch.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Cequa has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Primary pharmacodynamics

No new primary pharmacodynamics studies were conducted. The MAH provided an overview on the primary pharmacodynamics of ciclosporin based on literature. Ciclosporin A (CsA) is a calcineurin inhibitor, which is an immunosuppressant, as calcineurin inhibition prevents the activation of various transcription factors necessary for the induction of cytokine genes (IL-2, IFN-γ, IL-4 and GM-CSF) during T-cell activation (Barber et al., 2005; Halloran et al., 1998; Klee et al., 1998). Keratoconjunctivitis sicca (KCS) is a T-cell-based inflammatory disease which is characterised by increased innate inflammatory mediators (matrix metalloproteinases, cytokines, chemokines); increased intercellular adhesion molecule-1 expression in the lacrimal gland and conjunctiva; increased epithelial apoptosis; conjunctival goblet cell loss; dendritic cell maturation; CD4 T-cell infiltration; and increased T-helper cell cytokines. In experimental murine models of KCS, topical CsA reduced conjunctival epithelial apoptosis and prevented goblet cell loss, of which inhibition of apoptosis appears to be a key mechanism for the therapeutic effect of CsA for KCS (Stern and Pflugfelder, 2017). Considering that CsA is a

well-known substance with clinical experience via ocular routes of administration, an overview based on literature is sufficient for primary pharmacodynamics of cyclosporine.

Secondary pharmacodynamics

No literature on secondary pharmacodynamics relevant for Cequa was provided, as this was not identified for CsA. No additional secondary pharmacodynamics studies were conducted. Considering that CsA is a well-known substance, this is acceptable.

Safety pharmacology

No dedicated safety pharmacology studies were conducted. The MAH refers to one reference from public literature on Neoral, an oral formulation of cyclosporine (25 mg and 100 mg capsules and 100 mg/ml solution) which has been registered in the Netherlands by Novartis Pharma B.V. since 1994 (Ellis, 1997). From this paper on the clinical risks of treatment with Neoral, it appears that there is no apparent risk of adverse changes to the CNS, respiratory or cardiovascular system after systemic administration of CsA. The major risks for systemic CsA are associated with nephrotoxicity, but for the intended low dose topical formulation, this is not expected. Considering that Neoral is a product containing much higher doses of CsA compared to Cequa, it is considered sufficient. According to ICH S7A, safety pharmacology studies may not be needed for locally applied agents (e.g., dermal or ocular) where the pharmacology of the test substance is well characterised, and where systemic exposure or distribution to other organs or tissues is demonstrated to be low, which is the case for this product. Overall, the provided information on safety pharmacology is limited. However, considering that CsA is a well-known active substance with sufficient clinical experience for topical ocular administration at comparable doses, in addition to extensive clinical experience with high systemic doses and the limited levels of CsA that are systemically available, this can be accepted.

The MAH provided an overview of the pharmacodynamic drug interactions of Cequa, mainly based on literature. Similar as prostaglandin (PGF2α) analogue bimatoprost for the treatment of glaucoma, ciclosporin may be a weak inhibitor of Multi-Drug Resistance Protein 1 (MDR1), which is located in the cornea. Therefore, the possibility of local drug-drug interactions between Cequa and ocularly administered prostaglandin analogues cannot be ruled out.

III.2 Pharmacokinetics

The toxicokinetics (TK) of CsA were assessed following repeat administration of OTX-101 by topical ocular instillation to New Zealand White (NZW) rabbits in the 28 day (study A: QID dosing; total daily dose per rabbit was 28, 140, and 280 µg CsA), 13 week (study B: QID dosing; total daily dose per rabbit 28, 140, or 280 µg CsA /day), and 26 week (study C: total daily dose per rabbit 46 (BID), 90 (QID), and 166 (QID) µg CsA/day.) ocular tolerability and toxicity studies. Blood samples were collected on day 1 and at the end of each study and analysed for CsA concentration by a validated liquid chromatography atmospheric pressure ionisation tandem mass spectrometry (LC-MS/MS) method.

The results of the toxicokinetic analyses demonstrated that systemic exposure to CsA was low (mean Cmax < 5 ng/ml) but quantifiable. The CsA whole blood levels, maximum concentration values (Cmax), and areas under the whole blood concentration – time curves (AUC) were dose related. The CsA whole blood concentrations and TK parameters tended to be higher in male rabbits compared to female rabbits although there was an overlap among individual animals.

Comparison of AUC values on day 1 and the final day of dosing suggested that there was no systemic CsA accumulation over the 28 day, 13 week or 26 week dosing periods at administered frequencies which were up to 2-fold higher (QID [four times daily at 2 hour intervals]) than the intended frequency of clinical dosing (twice daily [BID]).
The mean maximum CsA blood concentrations observed in the 4 week (study A), 13 week (study B) and 26 week (study C) ocular tolerability, toxicity and toxicokinetic studies were less than 5 ng/ml, and the mean AUC values were less than 13 h-ng/ml.
The systemic exposure to CsA in the nonclinical 26 week ocular toxicity study (study C) was compared to that in healthy human subjects (N=15). The OTX-101 0,09% formulation used in the 26 week toxicity study came from the same batch as that used in the OTX-101 clinical pharmacokinetic study (Study OTX-101-2016-003). In that study, human subjects were dosed by bilateral ocular administration of the intended commercial formulation of OTX-101 (0,09% CsA) BID for 7 days and once on day 8 which resulted in CsA administration of 44 µg CsA/eye/day or 88 µg CsA/day. Most CsA blood concentrations in the clinical study were below the quantitation limit of the LC-MS/MS assay.
Pharmacokinetic parameters could only be calculated for 4 out of 15 subjects on day 8. The mean ± SD AUC(0-4) (AUC from time zero to 4 hours post dose) on day 8 was 0,526 ± 0,059 h-ng/ml. In contrast, the mean ± SD AUC(0-4) values measured on day 182 at the no-observed-adverse-effect level (NOAEL) dose of 166 µg CsA/day (highest dose tested, 83 µg CsA/eye/day or 166 µg CsA/day) in the 26 week ocular toxicity/TK study in rabbits (study C) were 8.52 ± 2.77 and 5.20 ± 1.43 h-ng/ml in male and female rabbits, respectively. The exposure in male and female rabbits was 16.2-fold and 9.9-fold higher, respectively, than that observed in humans. The ocular tissue distribution of CsA was assessed in two pilot studies (study D and study E), and in a 7 day ocular tissue distribution study (study F). In the 7 day GLP study (study F), the ocular tissue distribution of CsA was assessed following single topical ocular administration of OTX-101 0,05% and the active comparator 0,05%, and repeat QID (2 hour intervals) topical ocular administration of OTX-101 (0,01%, 0,05%, and 0,1%) and the active comparator 0,05% for 7 days to NZW rabbits. Following completion of the dosing phase, blood, tears and ocular tissues (aqueous humour, choroid-retina, conjunctiva, cornea, superior eyelid, third eyelid, iris-ciliary body, lacrimal gland, lens, sclera, and vitreous humour) were collected for analysis of CsA levels using validated LC-MS/MS methods. The results demonstrated that CsA was extensively distributed in ocular tissues but exhibited minimal systemic exposure (mean Cmax <5 ng/ml). After administration of OTX-101, ocular and periocular CsA tissue levels increased in a dose-responsive manner. After repeat dosing with OTX-101 0,05% ocular tissue concentrations of CsA were higher than after administration of active comparator 0,05% except for the lacrimal glands, superior eyelid, and tears. In contrast, concentrations of CsA after repeat topical ocular administration of OTX-101 0,1% were higher than after administration of active comparator 0,05% in all ocular tissues including the lacrimal gland, except for the superior eyelid. There was an increase in AUC(0-t) with repeat dosing of the OTX-101 0,05% and active comparator 0,05% indicating accumulation in all ocular tissues with repeat daily dosing compared to a single dose. Systemic exposure to CsA also increased upon repeat QID dosing of OTX-101 0,05% compared to a single dose. However, the CsA mean Cmax value (2.01 ng/ml) in blood following repeat dosing of OTX-101 0,05% in the 7 day tissue distribution study was comparable to the mean Cmax values observed at the same dose level in the pivotal 28 day, 13 week, and 26 week toxicity studies. Thus, there was no systemic CsA

accumulation in the repeat-dose studies of up to 26 weeks, consistent with an 18 hour washout between the fourth dose of the day and the first dose of the next day.
No other OTX-101 pharmacokinetic (PK) studies were performed. The metabolism and excretion of orally administered CsA has been extensively described in the literature (Maurer et al., 1984; Vickers et al., 1992; Christians et al., 1991a; Christians et al., 1991b; Christians and Sewing, 1995; Wagner et al., 1987; Sandimmune US Prescribing Information, 2015; Neoral and Sandimmune IV Product Monograph, 2015; Neoral US Prescribing Information, 2015). Ciclosporine is poorly to moderately absorbed following oral administration, widely distributed throughout the body, including into red blood cells, and crosses placental barrier to a limited extent. Ciclosporine is primarily bound (approximately 90%) to lipoproteins in plasma. It is extensively metabolised by cytochrome P450 enzyme CYP3A in the liver and to a lesser extent in the gastrointestinal tract and kidney. Ciclosporine undergoes little to no metabolism in the eye (Acheampong et al., 1999). Ciclosporine is eliminated primarily via the biliary route into the faeces. It has also been reported to be excreted in animal and human breast milk (Lewis et al., 1983).
Ciclosporine is both a substrate and inhibitor of CYP3A and of the multidrug efflux transporter P-glycoprotein(MDR1/P-gp). It is also an inhibitor of the organic anion transporter polypeptides OATP1B1 and OATP1B3, the breast cancer resistance protein, BCRP, and a weak inhibitor of the multidrug resistance proteins, MRP1 and MRP2 (Konig et al., 1999; Wandel et al., 1999; Karlgren et al., 2012; Sandimmune US Prescribing Information, 2015; Neoral and Sandimmune IV Product Monograph, 2015; Neoral US Prescribing Information, 2015). Although many drugs are known to interact with orally administered CsA, no systemic drug-drug interactions are likely to occur following topical ocular BID administration of OTX-101 0,09% (24.4 µL/application) because of the very low CsA dose (about 88 µg CsA/day) and low blood levels seen in the ocular toxicology studies and in the clinical program conducted by the Sponsor.
Ocular administration of selected prostaglandin analogues have been reported to be both substrates and inhibitors of some efflux transporters (i.e. MRP1, MRP2) located on the cornea (Hariharan et al. 2009). Thus, local drug-drug interactions between OTX-101 ophthalmic solution and other co-administered ocular drugs in patients using OTX-101 ophthalmic solution concomitant with these ocular hypotensive agents cannot be ruled out.

III.3 Toxicology

Single dose toxicity
No single dose ocular toxicity studies with Cequa were performed. According to the Hazardous Substances Data Bank, the acute systemic toxicity of CsA appears low. The original references or studies were not submitted by the MAH. Nevertheless, taking into account the limited relevance of acute toxicity studies, this can be accepted.

Repeat-dose toxicity
The repeated-dose ocular toxicity of CsA, including the excipient Hydrogenated Castor Oil 40 (Polyoxyl 40 hydrogenated castor oil; HCO-40), has been evaluated in GLP as well as non-GLP New Zealand White (NZW) rabbit studies.

Three GLP studies were conducted in NZW rabbits. In studies A and B, rabbits were dosed with a topical nanomicellar formulation of CsA in HCO-40 to both eyes at a range of concentrations

of 0,01, 0,05% and 0,1% QID for 28 days or 13 weeks, respectively. In both studies, there were no CsA-related effects on clinical signs, body weight, food consumption, Draize evaluations, ophthalmology (including Hackett-McDonald), IOP, ERG, clinical pathology (haematology, coagulation, clinical chemistry), gross or microscopic examinations. Therefore, the highest dose was considered the NOAEL (140 µg/eye/day).
In a 26-week GLP study (study G), rabbits were dosed in both eyes with 0,05% (BID or QID) or 0,09% (QID) CsA in HCO-40, There were no CsA-related effects on clinical signs, body weight, food consumption, Draize evaluations, ophthalmology, IOP, ERG, clinical pathology or macroscopic examination. Microscopic CsA-related changes were noted in the Harderian gland and the lacrimal gland. In the Harderian gland, these included minimal to mild unilateral mixed cell infiltrate in all CsA treatment groups, in addition to minimal to mild unilateral or bilateral alveolar epithelium atrophy/degeneration with or without concurrent minimal chronic inflammation. In the lacrimal gland, minimal to mild unilateral alveolar epithelium atrophy/degeneration with concurrent minimal mixed cell infiltrate was noted in all CsA treatment groups. However, the microscopic changes were considered non adverse, they reversed following the recovery period and a clear dose-response relationship was lacking for both the effects in the Harderian gland as well as lacrimal gland. In addition, the Harderian gland is largely absent in the adult human. Therefore, the NOAEL was considered the highest dose tested (83 µg/eye/day).
Overall, CsA was well tolerated at concentrations up to 0,1% for 13 weeks, corresponding to 140 µg/eye/day or 280 µg/day. A more conservative NOAEL for the 26-week study of 166 µg/day corresponds to exposure multiples based on AUC of approximately 10- (females) to 16- (males) fold the daily human exposure after 8 days of BID dosing with OTX-101 nanomicellar ophthalmic solution (0,09% CsA).
Exposure multiples based on AUC ranged from approximately 10-24, depending on the dose administered in the repeat-dose toxicology studies in rabbits. Since study C is the closest to the intended clinical dosing with regard to the daily dose, the exposure margins of 10-16 for both sexes appear to be most relevant when comparing to the study in humans.
These exposure margins can be considered as conservative, based on the fact that only 4 out of 15 human volunteers had >3 concentrations above limit of quantification (LOQ) and could therefore be included in AUC calculations. The remaining 11 volunteers were not included in AUC calculations due to lack of exposure >LOQ. Also, the rabbit doses used for calculations were considered as NOAEL but were also the highest doses tested, thus possibly allowing for even higher exposure margins in studies using even higher doses of CsA in rabbits.
Three studies were performed using rabbits with either QID or BID dosing and these are compared to the human study where BID dosing was performed with the 0,09% CsA formulation, which is highly similar to the formulation used in the 26 weeks rabbit study. The dose administered in this study was 2-fold higher than in the human volunteer study, based on QID vs BID dosing. Exposures associated with QID dosing in rabbits were noticeably higher than expected by difference in dose levels solely, with human AUC of approximately 0,53 ng.h/ml and rabbit AUC of 5-8 ng.h/ml. Increasing the daily dose in rabbits did not result in significant increases in exposure in blood, as 280 µg/day resulted in AUC of approximately 8-13 ng/h/ml, indicating non-linear increasing in systemic exposure. A similar phenomenon was observed when comparing increases in Cmax values reported for the human volunteer study when compared to the 26 weeks rabbit study.

In non-GLP studies (studies D, E, H and I), NZW rabbits received repeated topical application of nanomicellar CsA formulation at concentrations ranging from 0,01% to 0,1%, which included 1% HCO-40, for 5, 7, 3 or 6 days, respectively. There were no test-article related effects of CsA on cage side observations, intraocular pressure (IOP), electroretinography (ERG, retinal function) and ocular histopathology. In study I, CsA was well tolerated. In study D, there was minimal ocular irritation at 0,1% CsA as evaluated by Hackett-McDonald scoring.

Upon request, the MAH discussed the absence of risk of precipitate or aggregate formation in the eye leading a possible epithelial damage. Regarding the impact of possible changes in temperature and pH on the drug product, the MAH refers to the results of freeze-drying studies, showing no significant change in critical quality attributes of the drug product. Further, the pH of the formulation is buffered near to the physiological one, therefore no effect of pH change is expected. Moreover, the results of *in vivo* studies confirm that the temperature change at moment of administration does not negatively impact the drug product distribution to different eye tissues. After single and repeat topical ocular administration of OTX-101 0,05% and the active comparator (0,05%) at 17.5 µg CsA/eye/dose, CsA was extensively distributed in ocular tissues and exhibited minimal systemic exposure (mean Cmax <5 ng/ml). The highest CsA concentrations occurred in the extraocular tissues, including the cornea, eyelid, conjunctiva, and sclera, whereas lower concentrations were observed in the intraocular tissues, including the iris-ciliary body, choroid-retina, lens, and aqueous humour. The drug product would not have been available for eye tissue distribution if ciclosporin precipitated. Therefore, it can be concluded that the product is resistant to abrupt temperature transitions.
Furthermore, dilution in the eye was discussed to be limited, and therefore the dilution in tears after administration does not impact the micelles, since even in worst case the concentration of surfactants will still be higher than the critical micelle concentration (CMC) of the system.
Overall, the risk of precipitate or aggregate formation in the eye leading to possible epithelial damage is considered low.

Genotoxicity

Regarding genotoxicity, it was indicated by the MAH that CsA is not found to be genotoxic. However, this is based on Prescribing Information and Product Monographs of other CsA containing products (Sandimmune and Neoral), and no detailed data was provided. However, the Product Monograph contains a reference to literature (Matter B.E., et al. Genotoxicity evaluation of cyclosporin A, a new immunosuppressive agent. Mutation Res 1982; 105: 257-64) in which genotoxicity was evaluated *in vitro* (Ames test and Chromosome aberration tests in Chinese hamster bone-marrow cells and the mouse dominant lethal assay)) and *in vivo* (micronucleus assay in CD-1 mice and Chinese hamsters). From this paper, it can be concluded that CsA is not genotoxic.

Carcinogenicity

Also for carcinogenicity, the MAH only referred to prescribing information from Sandimmune US, stating that carcinogenicity studies were carried out in mice and rats. This was not sufficient as no detailed data is available in such sources. However, the carcinogenicity data originated from the paper of Ryffel et al. (1983), which was provided for the reproductive and

developmental toxicity section. In this paper, tumour tables for both the mice and rat study are presented. This can be considered sufficient.
In the 78-week mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value. In the 24-month rat study, conducted at 0,5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low-dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related.
The CsA-related increase in lymphocytic lymphomas in female mice was not mentioned in the paper, but is most likely due to the immunosuppressant activity of CsA. For this indication, the relevance of this finding is limited considering the low, local dose of CsA. The low doses in mice and rats are approximately 54-fold (normalised to human equivalent dose) the human dose of 0,0015 mg/kg/day, assuming that the whole dose is absorbed.
Overall, considering the extensive clinical experience with CsA, the low systemic exposure to CsA for this product, and the absence of genotoxic potential, carcinogenicity has been sufficiently addressed.

Reproductive and developmental toxicity

The reproductive toxicity of CsA has been minimally addressed by referring to Sandimmune Prescribing information and only one referenced literature paper, but considering the extensive clinical experience with CsA and the limited systemic exposure, it is sufficient.
According to Ryffel et al. (1983), in rats, no embryotoxicity was revealed up to a dose of 17 mg/kg/day. At higher doses (30 mg/kg/day), concomitantly to toxicity observed in the dams, embryolethal effects and retarded development (lower average foetal weights and skeletal retardations) were present, but no teratogenicity was observed. In addition, the 45 mg/kg/day dose level, which was toxic for the mother animals, a high pre-/perinatal and postnatal mortality and reduced body weight development were observed in the offspring. At a dose of 17 mg/kg/day there was a significant increase in post-implantation loss. Therefore, it is not agreed that no embryotoxicity was revealed up to this dose and the NOAEL is considered 10 mg/kg/day for embryotoxicity in rats.
In rabbits, mothers tolerated CsA up to a dose of 30 mg/kg. Embryo- and fetotoxicity (skeletal retardation) were observed only at doses (100 mg/kg/day and higher) which were toxic to the dams. No teratogenic effect was detected.
Peri-/postnatal development, fertility and reproductive performance were described to not be affected at doses up to 15 mg/kg/day which were non-toxic for the parental rats. For fertility/reproductive performance, this NOAEL is not agreed. As there was 22.6% peri-/postnatal mortality at this dose, the NOAEL for fertility/reproductive performance is considered to be 5 mg/kg/day in rats.
Overall, no adverse reproductive toxicity was observed in rats at oral doses up to 5 mg/kg/day (approximately 540 times greater than the total daily human dose) and in rabbits up to 30 mg/kg/day (approximately 6400 times greater than the total daily human dose), assuming that the entire human dose is absorbed.

Local tolerance

No dedicated local tolerance studies were conducted. Considering the extensive ocular toxicity evaluations as part of the repeated dose toxicity studies, this can be accepted. No adverse effects on ocular toxicity (Draize evaluation and Hackett-McDonald ocular irritation

scoring), microscopic effects, IOP or ERG measurements were seen in the GLP studies following repeated-administration of Cequa to NZW rabbits at CsA concentrations of up to 0,1% for 13 weeks, and up to 0,09% for 26 weeks. No other toxicity studies of Cequa were conducted. The drug product does not absorb UV in the 290 nm to 700 nm spectrum, therefore the absence of phototoxicity studies is accepted. No metabolite studies were conducted. Considering that there are no metabolites present in human >10% of total radioactivity, this is acceptable. There are no drug substance or drug product related impurities which require non-clinical qualification. The MAH conducted a risk assessment of Octoxynol-40 based on literature and in silico prediction methods. Furthermore, information on other octoxynols was provided. Overall, it can be agreed with the MAH that the amount of Octoxynol-40 present in the formulation has negligible risks. In addition, Octoxynol-40 is not a new excipient and exists in approved ophthalmic products such as in the RMS marketed formulation of Acular 0,5%.

III.4 Ecotoxicity/environmental risk assessment (ERA)

Table 1. Summary of main study results for ciclosporin

Substance (INN/Invented Name): Ciclosporin			
CAS-number (if available): 59865-13-3			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}		Log Kow 2.92 (pH 7.4)	Potential PBT (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surface\ water}$, default or refined (e.g. prevalence, literature)	0,00225	µg/L	> 0,01 threshold (N)
Other concerns (e.g. chemical class)			(N)

Conclusions on studies:
Ciclosporin PEC surface water value is below the action limit of 0,01 µg/l and is not a PBT substance as log K_{ow} does not exceed 4.5.

III.5 Discussion on the non-clinical aspects

Since ciclosporin is a well-known substance, the submitted non-clinical overview to support the pharmacology, pharmacokinetics and toxicology of Cequa 0.9 mg/ml is adequate and is of sufficient high quality in view of the present European regulatory requirements.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The clinical pharmacokinetics of OTX-101 Ophthalmic Solution was investigated in a single study, OTX-101-2016-003 (An Open-Label Study Assessing the Ocular and Systemic Safety and Systemic Absorption of OTX-101 Nanomicellar Ophthalmic Solution in Healthy Volunteers). A

total of 16 subjects were enrolled in the study. Subjects received one drop of OTX-101 nanomicellar ophthalmic solution 0,09% topically into each eye, twice a day (BID) for 7 days. PK measurements were performed in order to evaluate systemic exposure for safety assessment. The data demonstrates low systemic ciclosporin exposures with values in range of 0,101 to 0,195 ng/ml. For comparison, the ciclosporin Cmax blood levels after oral administration of ~90 mg two times daily (Neoral) are around 700 ng/ml. Further, limited data was provided to characterise the systemic PK of Cequa. This is considered acceptable since the PK of ciclosporin is already well established in literature and plasma concentrations are low.

IV.2 Pharmacodynamics

The MAH provided a generally adequate overview on the pharmacodynamic aspects of OTX-101. Active ingredient is ciclosporin (CsA), a well-known and widely-used immunosuppressant and anti-inflammatory agent, whose pharmacologic, pharmacokinetic and toxicologic properties have been previously characterised.
Ciclosporin is a calcineurin inhibitor that reversibly inhibits immunocompetent lymphocytes, particularly T-lymphocytes, inhibiting pro-inflammatory lymphokine production and release (Granelli-Piperno et al., 1986; Stepkowski et al., 2000; Sandimmune US Prescribing Information, 2015).
The exact mechanism by which CsA exerts its therapeutic effect in DED is unknown. However, with inflammation being a key factor in the pathophysiology of DED, it may relate to the suppression of the inflammatory process affecting the lacrimal gland acini and ducts, and the ocular surface. Hence, CsA may increase the ability of the lacrimal glands to produce tears, and improve the homeostasis of the tear film and ocular surface in DED. The mechanism of action of ciclosporin has been described adequately in the clinical overview, as well as in section 5.1 of the SmPC.
Notably, Dry Eye Disease (DED) is also referred to as keratoconjunctivitis sicca. As per request of the RMS, the MAH amended the wording of the therapeutic indication by including both denominations of the target disease, as both are used in clinical practice and scientific literature.
No new primary or secondary pharmacology studies have been conducted by the MAH. In the light of the well-characterised pharmacology of CsA (immunosuppressor), the immune-related inflammatory pathogenesis of DED, and the nonclinical evidence of efficacy and safety of CsA in DED (Tang-Liu and Acheampong, 2005), this is acceptable.
The MAH updated the clinical overview by providing an adequate discussion of published clinical studies on topical CsA in DED. Overall, literature data are supportive of efficacy of different formulations of topical CsA in the treatment of the signs of DED.
The clinical pharmacokinetic study on healthy volunteers (OTX-101-2016-003) showed that administration of OTX-101 at the intended therapeutic dose resulted in a very low systemic exposure to cyclosporine. Hence, the risk of ciclosporin-related systemic effects associated with the use of OTX-101 can be considered negligeable.
No drug interaction studies have been performed by the MAH. Given the well-known pharmacodynamic interactions profile of cyclosporine, and the very low systemic exposure to cyclosporine associated with OTX-101, these are considered not necessary.
After topical administration, ciclosporin accumulates on the ocular surface, achieving sufficient concentrations for immunomodulation. As the epithelium of the cornea and the

conjunctiva act as natural barriers, a very small concentration of the drug penetrates through the ocular surface to intraocular tissues. As such, drug-drug interactions with other ophthalmic products can be expected primarily at the level of the ocular surface. Systemic treatments are not commonly employed in DED, and their interaction with other products at the level of the ocular surface is expected to be negligeable. Interactions with other local products have been addressed adequately in the SmPC.
Furthermore, the MAH was required to provide a discussion of the possible differences in genetic factors implicated in the pharmacodynamic response to OTX-101, especially in the light of the notion that women have a higher prevalence of the disease (Stapleton et al., DEWS II Epidemiology, 2017), and that the entire clinical development program of the product has been conducted in the US. Possible genetic factors implicated in the pharmacodynamic response to topical ocular ciclosporin have not been explicitly discussed by the MAH. However, the study populations of both pivotal studies adequately reflected the higher prevalence of DED in women. Moreover, there is no indication that the nature of the disease and response to treatment would differ between the US and European populations. For these reasons, genetic factors are presumed to be of minor relevance for the development and therapeutic effect of OTX-101, therefore this issue is not pursued further.

IV.3 Clinical efficacy

Two multicentre, randomised, double-masked, vehicle-controlled trials with similar study design are considered pivotal for efficacy:

- Study OTX-101-2014-001 was a phase 2b/3 study that compared two concentrations of OTX-101, 0,05% and 0,09%, against vehicle, in 455 subjects at 29 sites in the US (dose selection study).
- Study OTX-101-2016-001 was a phase 3 study that compared OTX-101 0,09% against vehicle in 745 subjects at 45 sites in the US.

The two pivotal studies had identical duration (12 weeks = 84 days), dosing regimen (1 drop, both eyes (OU), twice daily (BID)), and included DED patients of both sexes, >18 years old, with a clinically significant deterioration of the lacrimal function unit (comprising the lacrimal glands, ocular surfaces, eyelids, and connecting sensory and motor nerves), defined by the presence of:

- DED signs (lissamine green conjunctival staining of ≥ 3 to ≤ 9 out of 12 [scoring excluded superior zones 2 and 4]),
- moderate to severe symptoms (global Symptom Assessment iN Dry Eye (SANDE) symptom score of ≥40/100 for dryness and irritation (Schaumberg et al. 2013; Gupta et al. 2018),
- bilateral ocular involvement,
- > 6 months duration of the disease.

Both patients with moderate (SANDE scores 40–50) and severe (SANDE scores >50) DED symptoms were enrolled.
Conjunctival staining scoring excluded superior zones (2 and 4). As a justification for this approach, the MAH responded that these two zones are to some extent protected from environmental factors by the upper eyelid, as such presumably less affected in DED. Analysis

of the data with and without these two conjunctival zones yielded consistent results, hence the exclusion of these zones in the original submission did not influence the study results.
Subjects were included in case of a conjunctival staining score of ≥ 3 to ≤ 9 out of 12, hence the most severe forms of conjunctival damage (i.e., with 10-12 NEI scale) were excluded. This is specified in the SmPC section 5.1 as "Patients were also required to have bilateral DED supported by the presence of a lissamine green conjunctival staining score of ≥ 3 to ≤ 9 out of 12 (NEI scale)." All double-masked study period kits were identical in appearance. Throughout the conduct of the studies, subjects, investigators, and all personnel responsible for monitoring and medical evaluation of the data remained masked to treatment assignments.

Dose selection

The dose selection study (OTX-101-2014-001) showed that both OTX-101 0,05% and OTX-101 0,09% as compared to vehicle resulted in decreased conjunctival staining, with comparable effect between the two concentrations. Analysis of mean change from baseline in total corneal fluorescein staining score at day 84 (secondary efficacy endpoint) yielded consistent results. No difference between either OTX-101 dose from vehicle in global symptom score was found. Post-hoc analysis of subjects with clinically relevant increase of tear production (i.e., Schirmer's test ≥ 10 mm) showed differences between OTX-101 0,09% compared to vehicle, but not between OTX-101 0,05% group compared to vehicle. Hence, the OTX-101 0,09% appeared to be more effective than OTX-101 0,05% in increasing tear production: this justified the selection of the 0,09% concentration for further development.

Efficacy endpoint

Efficacy endpoints of the two pivotal studies were measures of both signs and symptoms of DED. In the OTX-101-2014-001 study, there were two co-primary efficacy endpoints, measuring the mean change from baseline at day 84 of total conjunctival staining score in the designated study eye, and global SANDE symptom score.
Based on the increase in tear production associated with OTX-101 0,09% observed in study OTX-101-2014-00 (see dose selection), the primary efficacy endpoint chosen for OTX-101-2016-001 was increase of ≥ 10 mm from baseline in Schirmer's test score at day 84 based on data for both eyes.
Secondary efficacy endpoints included objective measures of conjunctival integrity, as assessed by lissamine green conjunctival staining scores (total and temporal), and of corneal integrity, as assessed by corneal staining score (total and central), as well as subjective measures of DED symptoms, as assessed by SANDE symptom score.
Pivotal studies showed that treatment with OTX-101 0,09% resulted in a significant and clinically relevant increase (≥ 10 mm) in tear production, and in improvements of ocular surface integrity (conjunctival and corneal) in the overall moderate to severe patient population compared to vehicle. However, disease severity is a known effect modifier for signs of DED. As the observed treatment effects may be more pronounced in (driven by) the subgroup of patients with a more severe condition, subgroup analyses based on clinical severity (i.e., moderate and severe patient groups individually) were requested to demonstrate efficacy per subgroup on the different efficacy endpoints.
Accordingly, the MAH conducted secondary analyses of the percent number of responders for Schirmer's test, mean change from baseline for Schirmer's test, conjunctival staining, and total corneal staining at day 84 in the above mentioned subgroups. Subgroup analyses of the Schirmer's test (percent number of responders and mean change from baseline) did not

suggest that the increase in tear production would be more pronounced in the most severely affected patients. Improvements in ocular surface integrity however, and particularly of total corneal staining, appeared to be more pronounced in the subjects with a more severe degree of staining at baseline. In the pooled data however, treatment effects reached significance in every subgroup. All measures were not influenced by the severity of symptoms at baseline as measured by the total SANDE score. Altogether, the totality of the data was considered supportive of efficacy of OTX-101 across the entire moderate to severe study population irrespective of baseline severity.
In addition, the MAH was requested to clarify the use of artificial tears (AT) prior and during the pivotal trials. The MAH confirmed that the majority of study participants used ocular lubricants prior to screening. After screening, all subjects underwent a run-in period of approximately two weeks with the vehicle, and were then newly evaluated for eligibility criteria with regards to conjunctival staining (≥ 3 to ≤ 9) and DED symptoms (SANDE symptom score of ≥ 40 / 100 for dryness and irritation). Eventually, 130/585 (22.2%) and 178/923 (19.3%) of the screened participants in study OTX-101-2014-001 and OTX-101-2016-001, respectively, were excluded. This selection process enabled to include DED subjects with signs and symptoms persisting despite the use of ocular lubricants for at least two weeks. Once enrolled, the use of AT was not permitted, and only a small proportion of the participants used rescue medications during the studies. The MAH performed subgroup analysis based on history of AT use, which however has limited interpretability as all the included participants were treated for two weeks with AT. In consideration that:
- artificial tears are first line treatment in DED and, if there is no benefit with artificial tears, an alternative treatment, such as ciclosporin, should be considered (Semp et al., 2023),
- the majority of the study participants had a history of artificial tears use with insufficient response,
- all the included subjects had no benefit with artificial tears after two weeks of compliant use,
- the amendment of the indication specifying that treatment is recommended in subjects who have not responded adequately to artificial tears was agreed during procedure.

Results across trials were presented in terms of statistical significance. To enable better comparisons between the pivotal studies, the MAH provided a side-by-side presentation of the main results in terms of least square (LS) mean and standard error (SE). Treatment differences of changes to baseline in corneal and conjunctival staining were greater in study OTX-101-2014-001 compared to study OTX-101-2016-001. However, proportion of responders in Schirmer's test (≥ 10 mm) and complete clearing of central corneal fluorescein staining were comparable between the two studies.
A SANDE global symptom score of ≥40 (on a scale of 100) was required in both studies at baseline, where scores of 40–50 correspond to moderate symptoms of DED, and scores >50 indicate severe symptoms (Schaumberg et al., 2013). Baseline and post-treatment symptoms scores (mean, min, max) for each treatment group were provided, permitting to see that both treatment groups showed an approximate 30% reduction in symptoms over the course of the studies, without differences between treatment arms.
In fact, improvement of ocular surface integrity (cornea and conjunctiva) and tear production was not accompanied by symptoms relief with OTX-101 as compared to vehicle. As per request of the RMS, the MAH provided a critical discussion of the possible reasons underlying the observed discrepancy in the therapeutic effect of OTX-101 on the signs, but not the symptoms of DED. Lack of efficacy of OTX-101 on DED symptoms compared to vehicle is not

surprising. This was also observed for Ikervis, and is consistent with the known disease phenomenology which is characterised by poor correlation between clinical signs and symptoms. As discussed during the centralised procedure for Ikervis (EMA/CHMP/473489/2014), this could be plausible pathophysiologically, due to potential loss in ocular surface sensitivity. Particularly, in patients with a high degree of ocular surface damage, which could take long time (possibly even years) to recover. Moreover, the use of any vehicle would be expected to alleviate the symptoms of dry eyes, as they have wetting/lubricating properties. For these reasons, it may be challenging to demonstrate an effect of a medicinal product on the symptoms of DED within the time constraint of a clinical trial. Therefore, an effect on the signs alone could be considered of clinical relevance for these patients, provided the effect is sufficiently large.
Consistent with that, group analysis of SANDE symptoms scores in the subpopulation of subjects with clinically significant increase of tear production (Schirmer's test ≥ 10 mm) showed no significant symptom improvement in this subgroup, confirming the substantial lack of correlation between signs and symptoms in DED, at least in the short term.
In fact, effectiveness of OTX-101 was evaluated for 12 weeks in the clinical studies, and no data about long-term efficacy were provided, hence no conclusions can be made on maintenance of efficacy. Study results derived from the Ikervis and Restasis program support efficacy of topical ocular ciclosporin in DED up to 6 months. The MAH proposed to include a precaution in section 4.2 of the SmPC to assess the response to treatment every 3 months, in line with the provided clinical data. This is agreed by the RMS, as only responsive patients would continue the treatment, whereas, in case of worsening, other options would be considered, in line with recent treatment guidelines from the European panel of experts in DED (Messmer et al., 2023).
However, DED is a chronic condition requiring long term treatment. Additional discussion was provided by the MAH at D100, including the addition of the statement that subjects should be reviewed at least at 3-monthly intervals. Moreover, the mechanism of action (MoA) of cyclosporine for the treatment of DED is well known and based on the MoA loss of efficacy is not anticipated. There was also no loss of effect seen during the 6 months studies of Ikervis and Verkazia. It is not expected that for the same active substance in the same target population for the same treatment a loss of effect would be observed in one product and not for the other two products. It is thus question if when short term efficacy is shown, long term efficacy should be demonstrated by default. The same holds for the safety.

IV.4 Clinical safety

Safety data of OTX 101 are derived from the two Phase 2b/3 and Phase 3 pivotal studies (OTX-101- 2014-001 and OTX 101-2016-001, duration 3 months), and one open-label extension study of one year (OTX-101-2016-00), for a total of 524 DED patients treated with OTX 101. The safety data package is considered sufficient. Treatment-emergent AEs were reported in 203 subjects (38.7%) in the OTX- 101 0,09% group, and 142 subjects (27.1%) in the Vehicle group (total 345 subjects, 33%).

Instillation site pain
OTX-101 was in general well tolerated. Most common AEs were instillation site pain and conjunctival hyperaemia. Instillation site pain was described as mild stinging and/or burning for several minutes following each instillation. The occurrence of pain right after instillation,

the relatively high frequency of this symptom, and its higher prevalence in the OTX-101 group, could have resulted in the unmasking of patients in the pivotal studies. Moreover, as a response to eye irritation and pain, reflex tears are produced, which (for several minutes, twice a day) may have contributed to the improvement of the signs of DED (tear production assessed with Schirmer test without anesthesia, and ocular surface deterioration) associated with the treatment with OTX-101. Subgroup analysis showed that efficacy results were not driven by the occurrence of instillation site pain as a side effect, which could have resulted in potential unmasking and reflex tearing. On the contrary, efficacy on signs was more pronounced in the patients that did not experience instillation site pain. This may indicate that the product could be more effective when not washed away by tears.

Conjunctival hyperaemia

Conjunctival hyperaemia was the second most common reported AE. In the pivotal studies, the MAH considered this event not always related to the study treatment because conjunctival redness is also a characteristic of the underlying disease. It is questioned whether this sign can be disentangled to the study treatment as proposed by the MAH, as it is a well-characterised AE associated with topical ocular administration of ciclosporin (Barber et al, 2005), and may also be the expression of lack of efficacy. Moreover, conjunctival hyperaemia was considered as treatment-related in the safety extension study, where it was reported at a higher frequency (10,1%) than in the subjects treated with OTX-101 in the pivotal studies (5.7%). The MAH suggested that discrepancies between causality assessment of conjunctival hyperemia (i.e., related or unrelated to the study treatment) between the pivotal and extension studies were possibly related to updated scientific knowledge based on the clinical experience acquired with other marketed products. Indeed this is plausible, and may account for reporting more known AEs in the subsequent extension study. The prolonged use of the investigational product was not significantly related to a higher incidence of conjunctival hyperemia, the occurrence of which is adequately reflected in the SmPC.

Headache and throat irritation were included as treatment-related AEs since the investigator classified these reports as such. However, the MAH does not agree with this designation and proposed to omit these AEs from the SmPC. Due to the anatomical connection with the nasolacrimal duct and the fact that up to 80% of topically administered ophthalmic products diffuse into the systemic circulation through the (highly vascularised) nasopharyngeal mucosa, the possibility of throat irritation associated with topical ocular ciclosporin cannot be excluded. The occurrence of headache is also not implausible, especially if associated with instillation site / eye pain. The MAH was therefore requested to include headache and throat irritation as treatment-related AEs in section 4.8 of the SmPC, which was agreed

OTX-101 has been marketed in USA (Oct 2019) and Canada (Jan 2022). Early post marketing reports of AEs linked to OTX-101 were predominantly eye irritation, eye pain, ocular hyperaemia, and lacrimation. Eye infections have been also reported (although less commonly), but not included as adverse drug reaction in the proposed SmPC. It is recognised that patients receiving immunosuppressants, including ciclosporin, are at greater risk of infections, both generalised and localised. Topical ocular ciclosporin may increase the risk of ocular infections, existing infections may worsen, and a small number of eye infections has been reported in association with OTX-101, whereas the risk of generalised infections is plausibly smaller due to the low systemic exposure of the product

Hence, the MAH was requested to include the risk of localised (ocular and peri-ocular) infections in Section 4.8 of the SmPC, which was agreed.

Long term safety was in line the initial phase of the study. No unexpected findings were reported in the open label extension phase.

IV.5 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 Cequa. At the time of approval, the most recent version of the RMP was version 0,2 dated 22 August 2023.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	Cancer of the eye or skin around the eye (periocular skin cancer, conjunctival or corneal tumour)
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.6 Discussion on the clinical aspects

For this authorisation, the MAH submitted one pivotal study on pharmacokinetics and two pivotal studies for efficacy. The MAH also submitted additional data available from the literature on the pharmacology of ciclosporin. Risk management is adequately addressed. The clinical aspects of this product are approvable.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(1) and 59(3) of Council Directive 2001/83/EC, and Article 63(2) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English. The test consisted of: a pilot test with two participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the PL 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

Cequa 0.9 mg/ml eye drops, solution in single-dose container has a proven chemical-pharmaceutical quality. The documentation in relation to this product is of sufficiently high quality in view of the European regulatory requirements. The overall benefit-risk is considered approvable.

In the Board meeting of 4 May 2023, the following was discussed:

First round, Quality aspects
Major objections have been raised regarding the pharmaceutical development of the product, the sterilisation filters, the sterility of the packaging, the possible formation of nitrosamine impurities and the shelf life.

First round, Clinical aspects
Clinical studies comparing Cequa with vehicle indicate that patients treated with Cequa show a clinically relevant increase (≥ 10 mm) in tear production (compared to vehicle). An improvement in *ocular surface integrity* is also seen. The safety profile appears to be tolerable.

- No effect on symptoms is seen in the studies.
- The indication should be adjusted.
- The effect over a period longer than twelve weeks is unclear. In an *other concern*, the company is requested to substantiate the maintenance of the effect over a longer period
- The MAH is requested to perform a subgroup analysis so that it can be assessed whether the effect is comparable in patients with moderate and patients with more severe signs and symptoms.

In the Board meeting of 4 December 2023, the following was discussed:

Second round, Quality aspects
Of the five major objections formulated in the previous round, three remain. These concern pharmaceutical development, the risk assessment regarding the possible formation of nitrosamine impurities, and shelf life.

Second round, Clinical aspects

- The MAH performed a subgroup analysis. This analysis showed that the effect is comparable in patients with moderate and patients with more severe signs and symptoms. This outcome resolved the major objection regarding this issue.
- The MAH adjusted the indication. The indication is now better into line with the study population.

After the fourth assessment round, all outstanding questions are resolved. The chemical-pharmaceutical documentation in relation to the product is of sufficient high quality in view of the present European regulatory requirements. The Medicines Evaluation Board in the Netherlands recommends granting a Marketing Authorisation for the product in question in view of the quality data presented.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that the benefit-risk balance for Cequa 0.9 mg/ml eye drops, solution in single-dose container is positive and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 27 March 2024.

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STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5627/001 /IB/001	Change in pack size of the finished product. Change in the number of units (e.g. tablets, ampoules, etc.) in a pack. Change outside the range of the currently approved pack sizes.	Yes	07-11-2024	Approved	-
NL/H/5627/001 /IA/002	Change in pack size of the finished product. Change in the number of units (e.g. tablets, ampoules, etc.) in a pack. Change within the range of the currently approved pack sizes.	Yes	11-3-2025	Approved	-
NL/H/5627/IA/ 003/G	Change in the shelf-life or storage conditions of the finished product. Change to an approved stability protocol. Change in test procedure for the finished product. Minor changes to an approved test procedure. Change in test procedure for an excipient. Minor changes to an approved test procedure.	No	08-05-2025	Approved	-

	Change to importer, batch release arrangements and quality control testing of the finished product. Replacement or addition of a site where batch control/testing takes place. Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance. Minor changes to an approved test procedure.				
NL/H/5627/001/IB/004	Change in the shelf-life or storage conditions of the finished product. Extension of the shelf life of the finished product. As packaged for sale (supported by real time data).	Yes	14-05-2025	Approved	-
NL/H/5627/001/IB/005	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products. Other variation.	No	13-8-2025	Approved	-