Public Assessment Report

Scientific discussion

TOMIDEXOFTA 3 mg/ml + 1 mg/ml, eye drops, solution

(tobramycin 3 mg/dexamethasone sodium phosphate 1.30 mg)

NL/H/2462/001/DC

Date: 27 November 2015

This module reflects the scientific discussion for the approval of TOMIDEXOFTA 3 mg/ml + 1 mg/ml, eye drops, solution. The procedure was finalised on 9 December 2014. For information on changes after this date please refer to the ‘steps taken after finalisation’ at the end of this PAR.
I. **INTRODUCTION**

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for TOMIDEXOFTA 3 mg/ml + 1 mg/ml, eye drops, solution, from Sooft Italia S.p.A.

The product is indicated for control of signs of inflammation and prophylaxis of secondary infections after ocular surgery under strict ophthalmic supervision.

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

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Tobradex, eye drops, suspension containing 3 mg tobramycin and 1 mg dexamethasone per ml. This reference product has been registered in the Netherlands by Alcon Nederland B.V. since 26 April 1991.

The concerned member states (CMS) involved in this procedure were Italy, Romania and Spain.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC. The proposed product differs from the reference product with regard to pharmaceutical form (eye drops, solution vs eye drops, suspension) and active substance (dexamethasone vs dexamethasone sodium phosphate). Equivalence cannot be demonstrated through bioequivalence studies for this product.

II. **QUALITY ASPECTS**

II.1 Introduction

TOMIDEXOFTA is a clear colourless solution with pH 6.5-7.5 and osmolality of 240 - 360 mOsmol/kg. One ml of solution contains 3 mg tobramycin and 1.30 mg dexamethasone sodium phosphate equivalent to 1 mg dexamethasone.

The solution is packed in a white LDPE bottle and dropper with a white PP screw cap.

The excipients are: benzalkonium chloride, tyloxapol, sodium chloride, sodium sulphate anhydrous, boric acid, water for injections, sulphuric acid and/or sodium hydroxide to adjust pH.

II.2 Drug Substances

The active substance tobramycin is an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white powder, which is sparingly soluble in water.

Dexamethasone sodium phosphate is also described in the Ph.Eur. It is a white or almost white powder which is freely soluble in water.

The CEP procedure is used for both manufacturers of 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 European Pharmacopoeia.

Manufacturing process

CEPs have been submitted; therefore no details on the manufacturing process of the drug substances have been included.
Quality control of drug substance
Tobramycin meets the requirements of Ph. Eur., and additional requirements on the CEP for (unknown) related substances.
Batch analysis results for 3 batches are provided. All results from both the active substance manufacturer as well as the drug product manufacturer are in accordance with the set drug substance specifications.
Dexamethasone sodium phosphate meets the requirements of Ph. Eur., and additional requirements on the CEP for any other impurity and residual solvents. Batch analysis results for 3 batches are provided. All results from both the ASM as well as the drug product manufacturer are in accordance with the set drug substance specifications.

Stability of drug substance
The re-test period for tobramycin is 60 months, and for dexamethasone the retest period is 3 years if stored under the stated conditions. Assessment thereof was part of granting the CEPs and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The drug product TOMIDEXOFTA 3 mg/ml + 1 mg/ml is an eye drop solution and the reference medicinal product, Tobradex, is an aqueous suspension. Due to the impossibility to demonstrate the physical-chemical and efficacy similarity between both products, the MAH conducted a clinical trial to evaluate if the test product (tobramycin/dexamethasone 0.3%/0.1% eye drops) has the same efficacy and safety as the reference product. The clinical study was performed for comparison of TOMIDEXOFTA with the innovator product Tobradex colirio eye drops and a tobramycin vehicle. The batch used in the study was manufactured according to the final manufacturing process. It is confirmed that a complete certificate of analysis for the test bio-batch is provided with results meeting the set specifications. The MAH has sufficiently described the pH, solubility aspects, partition coefficient (log P), degradation aspects, and aspects of bioavailability of ocular use as well as efficacy of both dexamethasone and dexamethasone sodium phosphate salt, based on literature references. The sterilization method chosen is filtration of the formulation under aseptic conditions of manufacturing, as the container is not suitable for moist heat conditions of sterilization due to the fact that high temperatures deform the bottles.
The presence of benzalkonium chloride in the formulation and its preservative effectiveness is sufficiently demonstrated. The final proof of the choice of a proper formulation are the results from the clinical study, as discussed in section IV of this report.

Manufacturing process
The manufacture comprises steps of sterilization (autoclaving of various materials, radiation of bottles, droppers and caps), production of Water for Injections (WFI), weighing process of the components, preparation of the bulk solution, filtration of the solution, filling into primary packaging, labelling and secondary packaging. Various adequate in-process controls are applied.
Regarding the full-scale batches a process validation study has been performed based on three batches. All results are satisfactory and meeting the set acceptance criteria. Process validation are considered acceptable and satisfactory.

Control of excipients
All excipients except tyloxapol are in accordance with the corresponding Ph.Eur. monograph. Tyloxapol is controlled according to the USP/NF monograph. These specifications are acceptable.

Microbiological attributes
TOMIDEXOFTA is a sterile formulation. It meets the requirements of method described in European Pharmacopoeia for sterile products. The product contains benzalkonium chloride as a preservative. A preservative efficacy study was carried out to ensure the efficacy of the chosen preservative and at an optimum concentration.

Quality control of drug product
The product specification includes tests for identification, appearance, pH, relative density, extractable volume, uniformity of mass of the delivered doses, osmolality, control of integrity, degradation products of tobramycin and dexamethasone, assays and sterility.
The MAH applies the specification on degradation products of dexamethasone from the method of the BP Monograph, and the USP method and specifications for the determination of tobramycin degradation products in drug product. All other test parameters and all related release and shelf life specifications are either usual, pharmacopoeial or otherwise acceptable. All other requirements are in accordance with Ph. Eur. monograph Eye Preparations 01/2008:1163 including sub-section eye drops. Batch analysis results have been provided for 3 batches. All results meet the specifications.

Stability of drug product
The MAH provided stability data on pilot-scale batches stored during 36 months at 25°C/40% RH and full-scale batches stored during 18 months at 25°C/40% RH & 12 months at 30°C/65% RH. Under these conditions results for tobramycin and dexamethasone degradation products met the requirements. Significant changes of dexamethasone content were seen during accelerated studies (6 months at 40°C/25% RH).
The shelf-life claim of 30 months was granted based on the provided data. The storage condition is “Not above 30°C” due to out-of-spec results for dexamethasone content during the accelerated studies. Protection from light is not necessary.
In-use stability studies have been performed at 0-14-28 days. After first opening the product should be used within 28 days.

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 TOMIDEXOFTA 3 mg/ml + 1 mg/ml, eye drops, solution 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 Ecotoxicity/environmental risk assessment (ERA)
Since TOMIDEXOFTA 3 mg/ml + 1 mg/ml is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects
This product is a hybrid formulation of Tobradex, eye drops, suspension, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction
Tobramycin and dexamethasone sodium phosphate are well-known active substances with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data.

The drug product applied for, TOMIDEXOFTA 3 mg/ml + 1 mg/ml is an eye drop solution whereas the reference product, Tobradex eye drops, is an aqueous suspension. As it is not possible to demonstrate similarity between both products based on physicochemical properties, a clinical trial was conducted. The study to evaluate whether the hybrid formulation has the same efficacy and safety as the reference product is briefly described below.

IV.2 Clinical efficacy and safety

The MAH submitted the results of a randomised double-blind, pseudo-vehicle and reference controlled double blind parallel group study evaluating the efficacy of TOMIDEXOFTA 3 mg/ml + 1 mg/ml eye drops solution (Sooft Italia S.p.A., Italy) as compared to Tobradex colirio, eye drops suspension (Alcon Cusi S.A., Spain) with tobramycin/vehicle as ‘placebo’ in the treatment of pain and inflammation after cataract surgery.

Design
The study was designed as a randomised, multicentre, double-blind, pseudo-vehicle and reference controlled parallel group equivalence study. The treatment period was 14 days with a post treatment visit at day 28. Ninety subjects who had a cataract extraction and implantation of an intraocular lens were to be included.

Patients were randomised to study treatment, reference treatment or ‘placebo’ (TOBREX®, Tobramycin/vehicle). Patients received one eye drop three hours previous to the surgery with a maximum of 5 drops pre-surgery, one drop every 15 minutes in the first 45 minutes after the surgery, then from one hour after the surgery one drop, three to five times a day, when needed until the end of the study.

Endpoints
The primary efficacy endpoint is the responder rate at day 28. A responder is defined as the number of patients (percentage of responders) with a 50% improvement in the eye symptom sum score between baseline and end of treatment (after 28 days). The eye symptom sum score is the sum of scores of Ocular Hyperaemia, Staining, Corneal Infiltration, Mydriasis, Ocular Tingling and Ocular Itching. Each individual item is scored by the investigator as present (score 1) or absent (score 0).

Secondary endpoints concern the aqueous flare score, intraocular pressure (IOP), pain score (Visual Analogue Scale - VAS), ocular discomfort frequencies.

Methodology
The role and rationale of the “pseudo-placebo” was not discussed in study report or in the study protocol. Formally the control is a pseudo-placebo as it contains an active component i.e. tobramycin. It might be argued this is of no concern as tobramycin has no anti-inflammatory effect and this was the study objective. Based on this the pseudo-placebo can be accepted. The equivalence margin was set at 20%, which is considered too large.

Efficacy results
In table 1 the disposition of the patients and the age is presented. There were no drop-outs or protocol violations.

Table 1 Patient’s disposition and age

<table>
<thead>
<tr>
<th></th>
<th>TOMIDEXOFTA</th>
<th>TOBRADEX colirio</th>
<th>TOBRAMYCIN 0.3% eye drops</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>n-completed</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Received all doses and attended all</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>
All patients completed the trial and there were no protocol violations. As the trial was embedded in the routine follow-up of the normal post-operative care after cataract extraction this may be not as exceptional as it appears.

Table 2. Responders at day 14 and 28; difference vs reference and control

<table>
<thead>
<tr>
<th></th>
<th>TOMIDEXOFTA</th>
<th>Tobradex colirio</th>
<th>Tobrex 0.3%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td><strong>Responders-day 14</strong></td>
<td>100%</td>
<td>96.7%</td>
<td>43.4%</td>
</tr>
<tr>
<td>Difference vs. control</td>
<td>56.7%</td>
<td>53%</td>
<td>-</td>
</tr>
<tr>
<td>Difference vs ref</td>
<td>3.3%</td>
<td>-8.3% ; 16.7%</td>
<td>-</td>
</tr>
<tr>
<td><strong>Responders-day 28</strong></td>
<td>100%</td>
<td>96.7%</td>
<td>86.7%</td>
</tr>
<tr>
<td>Difference vs control</td>
<td>13.3%</td>
<td>10%</td>
<td>-</td>
</tr>
<tr>
<td>Difference vs ref</td>
<td>3.3%</td>
<td>-8.3% ; 16.7%</td>
<td>-</td>
</tr>
</tbody>
</table>

A total of 100% of the patients treated with the test product (TOMIDEXOFTA eye drops) were responders with an at least 50% reduction in the eye symptom sum score at 14 days of treatment and at follow-up visit at 28 days. In the group treated with the reference product Tobradex colirio, in 96.7% of the patients the sum score for ocular discomfort symptoms decreased of at least 50% compared to baseline at day 14 of treatment and at 28 days. In the group treated with the control product Tobrex, in 43.4% of the patients the sum score for ocular discomfort symptoms decreased of at least 50% compared to baseline at day 14 of treatment and 86.7% at 28 days.

The 95% confidence interval for the difference in response rates has a distance from the difference to the CI limit. Considering the similarity margin of 20% TOMIDEXOFTA eye drops aqueous solution is similar to Tobradex colirio aqueous suspension.

Between day 14 and 28 patients did not receive treatment. Hence day 14 are the values still on treatment and may be considered more important than day 28. Considering the much lower response rate in the control group, assay sensitivity is shown.

The predefined margin of 20% implies that in the worst case a responder rate of 80% vs. 100% would have been considered equivalent. This margin is not accepted. However, equivalence can be concluded based on the actual values of the lower and upper limit of the confidence intervals observed (indicated in bold).

The eye sum score was also analysed in terms of changes to baseline. The difference from baseline during the 14 days treatment were significantly higher in active treatment groups as compared with the control group. The differences between the two active treatment groups were very small reflected by the mean differences and corresponding confidence intervals.
No major differences were detected for the 6 single eye symptoms (ocular hyperaemia, staining, mydriasis, ocular infiltration, ocular tingling and ocular itching), for the ocular pain score, Aqueous Flare Score and Intraocular Pressure and pain.

Safety results
In the present clinical trial, a low percentage of side effects was identified that were mild and not severe. No patients were withdrawn due to adverse event.

A summary of adverse events is presented in table 3. Events in this study were similar for the two studied medications and primarily they were ophthalmic events including ophthalmic shingles, including ophthalmic shingles, postoperative ocular hypertension, ocular hypertonia and herpetic keratitis.

Table 3. Summary of adverse events by system organ class

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tobramycin/Dexamethasone eye drops</th>
<th>TOBRADEX® colirio, Alcon (Spain)</th>
<th>TOBREX® (Spain)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects exposed</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Number of patients reporting at least one adverse event</td>
<td>5</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Total number of withdrawals</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Withdrawal due to adverse event</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Withdrawal due to adverse event</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Withdrawal due to adverse event</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total number of adverse events</td>
<td>5</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Adverse events at least possible drug related</td>
<td>4</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Nature of adverse events</td>
<td>Number of episode(s)</td>
<td>% subjects exposed</td>
<td>Number of episode(s)</td>
</tr>
<tr>
<td>Ophthalmic Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative ocular hypertension</td>
<td>3</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Macular edema</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Corneal edema</td>
<td>1</td>
<td>3.3</td>
<td>1</td>
</tr>
<tr>
<td>Herpetic keratitis</td>
<td>1</td>
<td>3.3</td>
<td>1</td>
</tr>
<tr>
<td>Uveitis cyclic membrane</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever (flu)</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

It is concluded in the study report that the efficacy and tolerability of the aqueous solution preparation of TOMIDEXOFТА eye drops has been proven to be similar to that of the marketed reference formulation in suspension based on the primary efficacy parameter number of patients with an at least 50% reduction (responder) in the main ocular discomfort symptom sum score (ocular hyperaemia, staining, mydriasis, ocular infiltration, ocular tingling and ocular itching), Ocular pain, Aqueous Flare Score and Intraocular Pressure. No differences have been detected in tolerance.

Conclusion
Based on the current study results therapeutic equivalence of the test product and reference product can be concluded with respect to the anti-inflammatory effect.

The study design does not allow to conclude equivalence with respect to the anti-bacterial effect.

Given the routine of antibacterial prophylaxis and low infection rates, this is not considered necessary. Therefore, the clinical study is considered acceptable.

IV.3 Risk Management Plan

The MAH has not submitted a risk management plan (RMP). The MAH declared that no such plan is deemed necessary. Essential similarity is claimed with a reference medicinal product for which no safety concerns requiring additional risk minimisation activities have been identified, and therefore no risk management plan was presented. This is acceptable, as an RMP was not required at the time of dossier submission for this medicinal product.
IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product TOBRADEX colirio eye drops, suspension. The MAH demonstrated through a clinical study that TOMIDEXOFTA eye drops, solution is therapeutically equivalent to the reference product. The concerned product is approved on the basis of a hybrid application and can be used instead of the reference product.

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 test consisted of two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

The results of the user testing are acceptable according to the guideline on the readability, because the criterion “90% of literate adults are able to find the information requested within the package leaflet, of whom 90% can show that they understand it” is fulfilled.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

TOMIDEXOFTA 3 mg/ml + 1 mg/ml, eye drops, solution has a proven chemical-pharmaceutical quality and is a hybrid form of Tobradex, eye drops, suspension. Tobradex is a well-known medicinal product with an established favourable efficacy and safety profile.

Since essential similarity cannot be demonstrated between the test eye drop solution and reference eye drop suspension based on comparative in-vitro data, a therapeutic equivalence study was conducted, showing satisfactory results.

The Board followed the advice of the assessors.

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 essential similarity has been demonstrated for TOMIDEXOFTA 3 mg/ml + 1 mg/ml, eye drops, solution with the reference product, and have therefore granted a marketing authorisation. The decentralized procedure was finalised with a positive outcome on 9 December 2014.

There were no post-approval commitments made during the procedure.
<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
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