CBG MEB

Public Assessment Report

Scientific discussion

Diclofenac Regiomedica 1 mg/ml, eye drops, solution, single dose container

(diclofenac sodium)

NL/H/2859/001/DC

Date: 13 March 2015

This module reflects the scientific discussion for the approval of Diclofenac Regiomedica 1 mg/ml, eye drops, solution, single dose container. The procedure was finalised on 24 November 2014. 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 Diclofenac Regiomedica 1 mg/ml, eye drops, solution, single dose container from Regiomedica GmbH.

The product is indicated for:
- Prevention of postoperative inflammation in cataract surgery.
- Maintenance of mydriasis during cataract surgery.
- Treatment of ocular pain in photorefractive surgery for up to the 24 first post-operative hours.

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

Diclofenac sodium is a non-steroidal anti-inflammatory drug with anti-flogistic, anti-pyretic and analgesic properties. Diclofenac inhibits prostaglandin biosynthesis. It has shown to have anti-inflammatory effect after cataract surgery.

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Naclof 1 mg/ml, eye drops, solution (NL License RVG 12800) which has been registered in the Netherlands by Laboratoires Théa since 26 March 1991.
A single dose presentation, Naclof Unidose, 1 mg/ml, eye drops, solution, single dose container (NL RVG 16483) was registered in the Netherlands on 27 May 1994.

The concerned member state (CMS) involved in this procedure was Germany.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application, as bioequivalence cannot be demonstrated through bioavailability studies.

II. QUALITY ASPECTS

II.1 Introduction

Diclofenac Regiomedica is a clear and colourless solution, free of particles, with pH 6.5 – 8.0 and osmolality of 240 – 360 mOsmol/kg. Each ml contains 1 mg diclofenac sodium.

The solution is packed in 0.3 ml transparent LDPE single-dose containers in PET aluminium/PE sachets containing 5 single dose containers each.

The excipients are: macrogolglycerol ricinoleate, boric acid (E284), trometamol and purified water.

II.2 Drug Substance

The active substance is diclofenac sodium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or slightly yellowish, slightly hygroscopic, crystalline powder, which is sparingly soluble in water. No isomerism, chirality and polymorphism are present.

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 European Pharmacopoeia.

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

Quality control of drug substance
The drug substance specification of the drug product manufacturer is in line with the Ph.Eur. and the CEP, with additional requirements for microbiological quality. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches.

Stability of drug substance
The active substance is stable for 5 years 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 development of the product has been described, the choice of excipients is justified and their functions explained. The main development study was the *in vitro* comparison of three batches of test product with six batches of reference product obtained from Germany and Spain. The composition of the German and Spanish reference products is considered representative for the Dutch reference product. No clinical study was performed. However, according to the Guideline on Investigation of Bioequivalence, a waiver of clinical studies for locally acting locally applied drug products is acceptable in the case of solutions, e.g. eye drops. Here the requirements are fulfilled: same type of (aqueous) solution, same concentration of the same active substance, method and means of administration is the same and minor differences in the excipient composition are acceptable when the relevant pharmaceutical properties of test and reference product are essentially similar. Therapeutic equivalence was demonstrated based on the *in vitro* comparison data. A comparison of the impurity profile and relevant physicochemical parameters (e.g. droplet weight, relative density, pH, osmolality, viscosity, surface tension) has been performed between test and reference products. The batches of test product used to substantiate the therapeutic equivalence compared to the originator batches were manufactured according to the finalized manufacturing process and formula. The choice of sterile filtration as a sterilisation method has been adequately justified. Terminal sterilisation in the final container by heating is not due to formulation instability. It is also not possible to sterilize the product by moist heat as the container is semi-permeable. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The main steps of the manufacturing process are the preparation of the solution, sterilisation by filtration, moulding of the LDPE bottles, filling of the solution and sealing of the bottles. The last steps are performed aseptically. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scale batches.

Control of excipients
The excipients comply with the requirements of the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, pH, relative density, osmolality, uniformity of mass of delivered doses, uniformity of dosage units, extractable volume, control of integrity of the single-dose containers and the sachets, assay, degradation products and sterility.
The release and shelf-life criteria are identical. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on three full-scale batches stored at 25°C/40% RH (36 months) and 40°C/25% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline (reduced humidity conditions). The batches were packed in 0.3 ml transparent LDPE single-dose containers in PET aluminium/PE sachets containing 5 single dose containers each. At both long-term (25°C/40% RH) and accelerated (40°C/25% RH) storage conditions an increase is observed in relative density and osmolality as well as a decrease in % of

initial weight and extractable volume. Some increases in impurities are seen. A slight decrease in assay is observed. Based on the results a shelf life of 2 years can be granted.

Furthermore, an in-use stability study has been performed to be able to justify the claimed shelf-life of 28 days after opening of the sachet. Initially, the study was performed with one batch, at release and near the end of shelf life. The containers were kept outside the sachet. Combining these data with the long-term stability results would lead to a significant weight loss. The study was repeated with 2 batches near the end of shelf life and this time the containers were kept inside the opened sachet, thus preventing weight loss. No weight loss was indeed observed, however keeping the containers in the sachet does not represent worst case. In a third in-use study two newer batches have been studied. Here weight loss (or water loss) was monitored on the same samples throughout the study by determining the weight of the same intact unit-dose containers, and it was found to be negligible.
As photostability studies demonstrated that the product is sensitive to light, the storage condition 'Do not store above 25°C' is therefore followed by 'Store in the original package in order to protect from light and evaporation'.

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 Diclofenac Regiomedica 1 mg/ml, eye drops, solution, single dose container 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 Diclofenac Regiomedica 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 Naclof 1 mg/ml, eye drops, solution, 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

Biowaiver
Diclofenac is a well-known active substance 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. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

According to the Guideline on Investigation of Bioequivalence, a waiver of clinical studies for locally acting locally applied drug products is acceptable in the case of solutions, e.g. eye drops. For Diclofenac Regiomedica 1 mg/ml eye drops, solution the requirements are fulfilled: same type of (aqueous) solution, same concentration of the same active substance, method and means of administration are the same, and the qualitative composition of the excipients is the same. Moreover, pharmaceutical and physicochemical equivalence is considered demonstrated as the *in vitro* study showed that test and reference product have a comparable droplet weight, relative density, pH, osmolality, viscosity, surface tension and a comparable impurity profile. Thus the requirements are fulfilled for locally applied, locally-acting products under the EU CPMP guideline on bioequivalence (CPMP/EWP/239/95).
Diclofenac Regiomedica 1 mg/ml eye drops, solution may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

IV.3 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 Diclofenac Regiomedia.

- Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	Allergic reactions including anaphylactic reactions
	Adverse corneal events/ corneal complications
	(exacerbation of) asthma
	Mask of (onset and/or progression of) ocular infections
	Bleeding (there is a theoretical possibility that patients receiving other medications which may prolong bleeding time, or with known haemostatic defects experience exacerbation due to systemic absorption)
	Toxicity due to cytotoxic excipients such as surfactants and solubilisers
	Concurrent use of topical NSAIDs and topical corticosteroids in the face of patients with significant pre-existing corneal inflammation
Important potential risks	none
Important 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.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Naclof 1 mg/ml, eye drops, solution. No new clinical studies were conducted. The MAH

demonstrated pharmaceutical equivalence to the reference product based on *in vitro* data. Risk management is adequately addressed. This hybrid medicinal product 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 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

Diclofenac Regiomedica 1 mg/ml, eye drops, solution, single dose container has a proven chemical-pharmaceutical quality and is a hybrid form of Naclof 1 mg/ml, eye drops, solution. Naclof is a well-known medicinal product with an established favourable efficacy and safety profile.

Since Diclofenac Regiomedica is a product for ocular use (eye drops) intended to act without systemic absorption, with the same excipients as used in the reference product and the same pharmaceutical and physicochemical characteristics, it is exempted for bioequivalence study.

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 Diclofenac Regiomedica with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 24 November 2014.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached