Public Assessment Report
Scientific discussion

Dexketoprofen B. Braun 0.5 mg/ml solution for infusion

Dexketoprofen trometamol

ES/H/0430/01/DC

Applicant: B. Braun Medical, S.A.

This module reflects the scientific discussion for the approval of **Dexketorpofen B. Braun 0.5 mg/ml solution for infusion.** The procedure was finalised on September 2017. For information on changes after this date please refer to the module óUpdateô.

INTRODUCTION

This decentralised application concerns a hybrid version of dexketoprofen trometamol, under Dexketoprofen B. Braun 0.5 mg/ml solution for infusion trade name. In this Assessment Report, the name Dexketoprofen is used.

The applicant opts to submit an application for marketing authorization for Dexketoprofen 0.5 mg/ml solution for infusion, a newly ready to use solution with dexketoprofen as the active substance.

The medicinal product to be registered contains 0.5 mg/ml dexketoprofen as the active substance. Consistently, this application is filled with reference to Article 10.3 of Directive 2001/83/EC, as amended, with respect to parenteral dexketoprofen preparations already marketed as Enantyum® by Laboratorios Menarini, first approved in an EU Member State 2002.

The reference medicinal product and the medicinal product being subject to this application do not have the same quantitative composition in terms of active substance per unit (ml), i.e. they differ in pharmaceutical form (solution for infusion versus solution for injection or concentrate for solution for infusion). The reference product can be administered intramuscularly and intravenously and the applied product is to be administered intravenously only. Accordingly, Article 10.3 of Directive 2001/83/EC, as amended, is applicable.

With Spain as the Reference Member State in this Decentralized Procedure, B. Braun Medical, S.A., is applying for the Marketing Authorisations of Dexketoprofen B. Braun 0.5 mg/ml solution for infusion in PT.

The therapeutic indications of the dexketoprofen is to treat symptomatic of acute pain of moderate to severe intensity, when oral administration is not appropriate such as post-operative pain, renal colic and low back pain.

A comprehensive description of the product information is given in the SmPC.

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation for **Dexketoprofen B. Braun 0.5 mg/ml solution for infusion**.

I. SCIENTIFIC OVERVIEW AND DISCUSSION

II-1 Quality aspects

Drug substance

The drug substance is dexketoprofen trometamol. There is no Ph. Eur. monograph for this drug substance. The applicant has used the ASMF procedure.

Description of the manufacturing process is adequate. Elucidation and characterization of the drug substance are sufficient, including an acceptable proposal on impurities to control.

Specification for drug substance is considered adequate. Analytical methods are correctly described and their validation is performed according to ICH.

The proposed container for storage is similar than the one used in the stability studies.

Stability studies have been performed according to ICH/CPMP guidelines and guarantee the proposed retest period and storage conditions.

Drug Product

The drug product is a sterile solution of Dexketoprofen Trometamol in water for injection. Excipients are of Ph. Eur. quality and are commonly used in this dosage form.

All the manufacturers involved in the different steps of the drug product manufacture have been submitted. A flow chart of the manufacturing process, indicating critical steps and controls, is included. Industrial batch sizes were provided. Process validation data presented are considered sufficient.

Excipients specifications are according their respective Ph. Eur. monographs and are adequate for their function in the formulation.

The specification proposed is acceptable. Analytical methods are adequately described and their validation is performed according to ICH. Number and size of the analysed batches are considered sufficient.

Proposed packaging material is adequate for the proposed dosage form and coincides with the one used in the stability studies.

Stability studies have been performed according to ICH. The proposed shelf-life and storage conditions can be accepted.

II-2 Non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology of the active substance has been provided, which is based on up-to-date and adequate scientific literature.

The submitted application concerns solution for infusion with the active substances in the same form as the reference product.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate and the Member States agreed that no further non-clinical studies are required.

Environmental Risk Assessment (ERA)

No ERA was submitted. The medicinal product has the same quantitative and qualitative composition in active substances and a similar pharmaceutical form to the reference product. The introduction on the market of this medicinal product will not mean an increased exposure to the environment, since the generic medicinal product is intended to substitute the reference medicinal product as well as other generic products in the market.

In accordance with the Guideline on the Environmental Risk Assessment for medicinal products for human use (CPMP/SWP/4447/00), the absence of this Environmental Risk Assessment is therefore justified.

II.3 Clinical aspects

Introduction

According to the Guideline on the investigation of bioequivalence ñBioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. However, if any excipients interact with the drug substance (e.g. complex formation), or otherwise affect the disposition of the drug substance, a bioequivalence study is required unless both products contain the same excipients in very similar quantity and it can be adequately justified that any difference in quantity does not affect the pharmacokinetics of the active substanceò.

Therefore, the Applicant claims that, a bioequivalence study is not required due to the medicinal product object of the application is supplied as solution for infusion to be administered intravenously and contains the same amount in drug substance (50 mg) as the reference product Enantyum 50 mg/2 ml solution for

injection or concentrate for solution for infusion, and has the same indications, route of administration and posology when both products are ready to use.

The absence of bioequivalence studies is acceptable. The applied product is to be administered as an intravenous solution containing the same active substance in the same concentration as the currently authorised product, which can be diluted from 2 mL to 30 or 100 ml. At this maximum dilution the reference product has the same concentration as the applied product 0.5 mg/ml. In addition, the differences in excipients between the applied product and the innovator product are considered acceptable (see the table below). For this type of product, no bioequivalence studies are required according to the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1) since the bioequivalence is self-evident.

Biowaiver

Dexketoprofen B. Braun 0.5 mg/ml solution for infusion is a sterile solution of dexketoprofen trometamol in water for injections at time of administration that has the same qualitative and quantitative composition in drug substance (dexketorpofen trometamol), and the differences in excipients are considered acceptable.

According to the ñGuideline on the Investigation of Bioequivalenceò a bioequivalence study is not required for an aqueous parenteral solution that is administered at the same concentration / dose, in which the differences in excipients are considered acceptable.

Bioequivalence

Not Applicable (see above)

Risk Management Plan

A risk management plan in accordance with the requirements of Directive 2001/83/EC as amended has been submitted.

No additional risk minimization activities were required beyond those included in the product information.

Discussion on the clinical aspects

Efficacy and safety of the active substance dexketoprofen trometamol is well documented for the reference medicinal product.

III OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Based on the submitted evidence Dexketoprofen B. Braun 0.5 mg/ml solution for can be considered equivalent to Enantyum® 50 mg/2 ml concentrate for solution for infusion or injection (Laboratorios Menarini, S.A.)

The SmPC, PIL and labelling are considered satisfactory and consistent with the information for the reference medicinal product. The user testing of the Package Information Leaflet has been tested in accordance with Article 59(3) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

The benefit/risk balance was considered to be positive.

Agreement between Member States was reached during the procedure. The decentralised procedure was finalised with a positive outcome in September 2017.