COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Parecoxib Chenpon 40 mg powder for solution for injection

(parecoxib sodium)

NL/H/4346/001/DC

Date: 14 October 2019

This module reflects the scientific discussion for the approval of Parecoxib Chenpon 40 mg powder for solution for injection. The procedure was finalised on 14 August 2019. 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
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
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
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 Parecoxib Chenpon 40 mg powder for solution for injection from Chenpon DE GmbH.

The product is indicated for the short-term treatment of postoperative pain in adults.
The decision to prescribe a selective cyclooxygenase-2 (COX-2) inhibitor should be based on an assessment of the individual patient's overall risks (see sections 4.3 and 4.4 of the SmPC).

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Dynastat 40 mg powder for solution for injection (EU/1/02/209) which has been registered by Pfizer Limited since 22 March 2002 via a Centralised Procedure.

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

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Parecoxib Chenpon is a white or almost white cake or powder, packed in type I clear colourless glass vials (5 ml) with a coated butyl rubber stopper, sealed with a blue flip-off cap on the aluminium overseal. Each vial contains 40 mg parecoxib (as 42.36 mg parecoxib sodium). After reconstitution, the concentration of parecoxib is 20 mg/ml. Each 2 ml of reconstituted powder contains 40 mg of parecoxib.

The excipients are: disodium phosphate, phosphoric acid and/or sodium hydroxide (for pH adjustment).

II.2 Drug Substance

The active substance is parecoxib sodium, an established active substance not described in a pharmacopoeia. The active substance is a white to off-white crystalline powder and is soluble in water. The substance does not contain a stereogenic centre. Polymorphic forms of the drug substance exist, but control thereof is not considered necessary as the drug substance is to be dissolved in water for injections.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing the active substance s a 2-step process. No class I solvents are used. The active substance has been adequately characterized. The specifications of the starting material, reagents and solvents were provided. Potential genotoxic impurities were sufficiently discussed and adequately controlled as per the ICH M7 Guideline (where required).

Quality control of drug substance

The active substance specification is established in-house by the MAH and is almost identical to the specification of the ASMF-holder. 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 3 batches.

Stability of drug substance

Stability data on the active substance have been provided for 3 full-scale batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). Under both conditions no upward or downward trends for any of the tested parameters were observed. A retest period of 24 months has been granted without special storage conditions.

II.3 Medicinal Product

Pharmaceutical development

For formulation development the generic drug product was designed to be exactly the same as the reference product to ensure the quality of the drug product. The MAH analysed the reference medicinal product Dynastat 40mg powder for solution for injection. The physicochemical characterisation of one batch and its composition were analysed to propose a generic product that is pharmaceutically equivalent. Development of the drug product is adequately described and the choice of excipients has been explained and justified. No novel excipients are used. There are no overages used in the formulation of parecoxib 40 mg. To ensure the labelled quantity of drug, an overfill is employed during the manufacturing process.

Manufacturing process

The manufacturing process has been described in sufficient detail. The manufacturing process comprises several steps: solution preparation, sterilizing filtration, filling and partial stoppering, lyophalisation and capping. Relevant mixing times, speeds and temperatures have been reflected. 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 meet the requirements of the current Ph. Eur. monographs. These specifications are acceptable.

Quality control of drug product

The drug product tests/specifications are considered generally acceptable and appropriate for the quality control of the proposed dosage form. Analytical methods were described and considered validated. Stability indication nature of relevant methods is demonstrated. Batch analysis results of three batches were included, demonstrating compliance with the proposed specification. The monitoring of heavy metals/elemental impurities was discussed in detail in line with Guideline ICH Q3D 'Elemental impurities'.

Stability of drug product

Stability data have been provided for three batches stored at accelerated conditions (40°C/75% RH) for six months and at long term (25°C/60% RH) conditions for 12 months. No specific changes or patterns are noted. The shelf-life of 24 months is considered acceptable with the data provided. The product does not require any special storage conditions.
Photostability studies have been performed as per ICH guidance. It was demonstrated that the product is not sensitive to light.

In-use stability

The product was reconstituted as recommend in section 6.6 of the SmPC, with sodium chloride 9 mg/mL (0.9%), glucose 50 mg/mL (5%) and sodium chloride 4.5 mg/mL (0.45%) and glucose 50 mg/ml (5%). The obtained concentration was 0.5 mg parecoxib/ml. The results show that the reconstituted product remains stable for a period of 30 hours irrespective of solvent, where it is to be noted that bacterial endotoxins is tested up to 12 hours. A maximum shelf life of the reconstituted product of 24 hours is included in the SmPC.

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 Parecoxib Chenpon 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 Parecoxib Chenpon 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 generic formulation of Dynastat, 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

Parecoxib sodium 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

Biowaiver

Parecoxib Chenpon 40 mg powder for solution for injection is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Dynastat 40 mg is

entirely the same as the originator. Therefore, it 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 Parecoxib Chenpon.

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

Important identified risks	• Severe cutaneous adverse reactions • Cardiovascular thrombotic events • Gastrointestinal ulceration-related events • Renal failure and impairment • Hypersensitivity reactions • Use in patients with congestive heart failure • Use in patients with hepatic impairment • Severe hypotension • Use during pregnancy, lactation, or in women attempting to conceive • Masking of signs of inflammation • Discontinuation of antiplatelet therapies
Important potential risks	• Administration other than IV or IM
Missing information	• Use in children and adolescents aged ≤ 17 years • Use in long-term treatment (>7 days) • Repeated use in acute exacerbation of chronic • conditions • Safety profile after dose increase • Off-label use

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 Dynastat. No new clinical studies were conducted. The MAH demonstrated equivalence based on comparative chemical-pharmaceutical data. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has not been performed. Reference is made tot the approved PL for the reference product Dynastat 40 mg powder for solution for injection, which has been fully user-tested. The PL for Parecoxib Chenpon is similar to that of the reference product in content and format. Therefore the member states agreed that separate user testing is not required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Parecoxib Chenpon 40 mg powder for solution for injection has a proven chemical-pharmaceutical quality and is a generic form of Dynastat 40 mg powder for solution for injection. Dynastat is a well-known medicinal product with an established favourable efficacy and safety profile.

Since essential similarity has been sufficiently demonstrated based on quality attributes, no bioequivalence study is deemed necessary.

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 Parecoxib Chenpon with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 August 2019.

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