COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Stercore 1 mg and 2 mg film-coated tablets

(prucalopride succinate)

NL/H/5328/001-002/DC

Date: 25 August 2022

This module reflects the scientific discussion for the approval of Stercore, 1 mg and 2 mg film-coated tablets. The procedure was finalised on 6 April 2022. 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 Stercore, 1 mg and 2 mg film-coated tablets, from Medochemie Limited.

The product is indicated for the symptomatic treatment of chronic constipation in adults in whom laxatives fail to provide adequate relief.

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 Resolor 1 mg and 2 mg, film-coated tablets which have been registered in the EEA by Takeda Pharmaceuticals International AG Ireland Branch since 15 October 2009 via a centralised procedure (EMEA/H/C/001012).

The concerned member states (CMS) involved in this procedure were Bulgaria, Cyprus, Malta, Romania and Slovakia.

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

II. QUALITY ASPECTS

II.1 Introduction

Stercore, 1 mg and 2 mg are round, biconvex, film-coated tablets, packed in OPA/Al/PVC-Al perforated blisters.

- The 1 mg strength is a white tablet with the embossed “10” on one side, plain on the other side, with a diameter of 6 mm. Each tablet contains as active substance 1 mg prucalopride (as succinate).
- The 2 mg is a pink tablet with the embossed “20” on one side, plain on the other side, with a diameter of 8 mm. Each tablet contains as active substance 2 mg prucalopride (as succinate).

The excipients are:
Tablet core - microcrystalline cellulose, (E460), lactose monohydrate, colloidal anhydrous silica (E551) and magnesium stearate (E572).
Film-coating - hypromellose (E464), lactose monohydrate, titanium dioxide (E171), and triacetin (E1518). The 2 mg tablet also contains red iron oxide.

II.2 Drug Substance

The active substance is prucalopride succinate, an established active substance not described in any pharmacopoeia. Prucalopride is a crystalline, white to off-white powder which is very soluble in water. The drug substance does not exhibit polymorphism and does not contain any chiral centres.

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 process of Prucalopride succinate, is a synthetic process that consists of seven steps for chemical transformation followed by salt formation and final purification with different solvents. No class-1 solvents or metal catalysts or reagents are used in the synthesis. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification is established in-house by the MAH, based on the specification as described in the ASMF. The specification includes tests for appearance, average weight, disintegration, identification of drug substance and colourants, dissolution, assay, uniformity of dosage units, related substances and microbial examination. The proposed specifications are acceptable. Furthermore, the analytical methods have been adequately described and validated. Batch analytical data demonstrating compliance with the drug substance specification have been submitted for two batches produced by the drug product manufacturer and three batches produced by the ASMF holder.

Stability of drug substance

Stability data on the active substance have been provided for three production scaled batches stored at 25°C/60% RH (48 months) and 40°C/75% RH (6 months). No trends in any stability parameter have been observed. Based on these results, the proposed re-test period of 48 months with the storage condition 'Store in well closed containers' can be accepted.

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 is justified and their functions explained. The current drug product contains the same

excipients in the tablet cores as the innovator product Resolor. The amounts of excipients were optimised for both strengths. Dissolution studies at 3 pH's were performed with the optimised formulation. The results showed (>85% dissolved within 15 min); these results are in line with the innovator product. Based on these results, the BSC class-1 waiver was accepted. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation data on the product have been submitted for three batches of each strength. The validation was adequately performed.

Control of excipients

The excipients comply with the Ph. Eur. Requirements, except for the film coating. The film-coating consists of components that all comply with their Ph. Eur. Requirements and with EU Regulation 231/2012/EC for red iron oxide (2 mg tablets). The functionality related characteristics for the Ph. Eur. excipients have been discussed, and the MAH has set limits for those functionality related characteristics that are critical for the quality of the drug product. These specifications are acceptable.

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, average weight, disintegration, identification of drug substance and colourants, dissolution, assay, uniformity of dosage units, related substances and microbial examination. For one impurity test, there is a difference between the limit value for the release and shelf life, both limits are within the acceptable levels. For all other tests, the same limit is applicable for both release and shelf-life. The proposed specification is acceptable. Furthermore, the analytical methods have been adequately described and validated. Batch analytical data from three batches per strength 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 from three batches per strength in accordance with applicable European guidelines (ICH stability guidelines). The batches were stored in Alu/Alu blisters at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). There was an upward trend observed in the concentration of some impurity compounds. However, all concentrations remined well within the limits up to the proposed shelf-life. Photostability studies showed that the product is stable when exposed to light. Based on the submitted stability data, a shelf life of 30 months was granted. No specific storage conditions need to be included in the SmPC or on the label.

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

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Stercore 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 Stercore 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 Resolor 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

Prucalopride succinate 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.

For this generic application, no *in vivo* bioequivalence studies were performed. A BCS class I biowaiver has been requested.

IV.2 Pharmacokinetics

Biowaiver

According to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) *in vivo* bioequivalence studies may be exempted if an assumption of equivalence in *in vivo* performance can be justified by satisfactory in *vitro* data. For this product, a BCS-based biowaiver is applicable for immediate release, through the waiver approach for solid pharmaceutical products for oral administration with systemic action having the same pharmaceutical form. The waiver can be accepted when the following characteristics are demonstrated with *in vitro* studies:

- The drug should not have a narrow therapeutic index
- The drug substance has high solubility and complete absorption (BCS class I)
- The test and reference product have either very rapid (>85 % within 15 min) or similarly rapid (85% within 30 min) *in vitro* dissolution characteristics
- Excipients that might affect bioavailability are qualitatively and quantitatively the same. In general, the use of the same excipients in similar amounts is preferred.

The characteristics described in the biowaiver were assessed. Based on the submitted information and *in vitro* data, it has been demonstrated that prucalopride succinate (drug substance) cannot be considered as a drug with narrow therapeutic index. The classification BCS class I was confirmed due to the demonstrated high solubility and complete absorption of the drug substance. The test and reference products show very rapid (>85 % within 15 min) *in vitro* dissolution. Furthermore, the excipients used in the test and reference products are the same and they are used in usual amounts. However, there is a difference in the amount of lactose and cellulose between the test and reference product. It was demonstrated that this has not impact on the bioavailability of prucalopride and/or solubility characteristics of the products. Based on the results, the waiver is accepted. Submission of *in vivo* bioequivalence studies is not required.

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 Stercore 1 mg and 2 mg film-coated tablets. The risk management plan was updated according the last approved version of the reference product. In table 1, a summary of the approved version is given.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• Palpitations
Important potential risks	• Cardiovascular and cerebrovascular ischaemic events • Ischaemic colitis • QT prolongation, and related ventricular arrhythmias and syncope
Missing information	• Safety in pregnant women • Safety in patients with severe hepatic impairment • Safety in patients with severe/unstable cardiovascular disease

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 Resolor. No new clinical studies were conducted. Risk management is adequately addressed. A BCS class I biowaiver has been granted. 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 been performed on the basis of a bridging report making reference to Resolor 1 mg and 2 mg, film-coated tablets for content and Areston 12.5 mg film-coated tablets for layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Stercore 1 mg and 2 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic form of Resolor 1 mg and 2 mg film-coated tablets. Resolor is a well-known medicinal product with an established favourable efficacy and safety profile.

A BCS class I biowaiver has been granted.

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 Stercore 1 mg and 2 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 6 April 2022.

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