COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Benlaxid 6.9 g and 13.7 g powder for oral solution (macrogol 3350/sodium chloride/sodium bicarbonate/potassium chloride)

NL/H/5457/001-002/DC

Date: 11 January 2023

This module reflects the scientific discussion for the approval of Benlaxid 6.9 g and 13.7 g powder for oral solution. The procedure was finalised at 31 August 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 Benlaxid 6.9 g and 13.7 g powder for oral solution from Italfarmaco, S.A.

Benlaxid 6.9 g powder for oral solution is indicated for:

- the treatment of chronic constipation in children 1 to 11 years of age.
- the treatment of faecal impaction in children from the age of 5 years, defined as refractory constipation with faecal loading of the rectum and/or colon.

Benlaxid 13.7 g powder for oral solution is indicated for:

- the treatment of chronic constipation. The product is also effective in resolving faecal impaction, defined as refractory constipation with faecal loading of the rectum and/or colon.

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 European Reference Product Movicol Junior Neutral 6.9 g sachet, powder for oral solution (SE/H/1799/003) and Movicol 13.8 g sachet, powder for oral solution (SE/H/1799/001). These products have been registered in Sweden by Norgine BV, since 5 April 2008.

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

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

II. QUALITY ASPECTS

II.1 Introduction

Benlaxid is a powder for oral solution, in the SmPC the powder is described as a free flowing white powder.

The products are packed in single-dose sachets of which the laminate consists of four layers: low density polyethylene (LDPE), aluminium, LDPE and paper.

Benlaxid 6.9 g

For this strength of product, each single-dose sachet of Benlaxid contains the following active ingredients:

Macrogol 3350	6.563 g
Sodium chloride	0.1754 g
Sodium bicarbonate	0.0893 g
Potassium chloride	0.0233 g

When the sachet is made up to 62.5 ml of solution, the content of electrolyte ions is as follows:

Sodium	65 mmol/l
Chloride	53 mmol/l
Potassium	5.0 mmol/l
Bicarbonate	17 mmol/l

The excipients are:
Orange flavour – maltodextrin (maize), arabic gum (E414), citric acid (E330), butylated hydroxy anisole (E320) and other flavouring substances.
Lemon flavour – maltodextrin (maize), flavouring preparations, flavouring substances, natural flavouring substances and alpha-tocophero (E307).
Aspartame (E951)
Sucralose

Each sachet contains 12.5 mg of aspartame (E951) which is an excipient with a known effect.

Benlaxid 13.7 g

For this strength of product, each single-dose sachet of Benlaxid contains the following active ingredients:

Macrogol 3350	13.125 g
Sodium chloride	0.3507 g
Sodium bicarbonate	0.1785 g
Potassium chloride	0.0466 g

When the sachet is made up to 125 ml of solution, the content of electrolyte ions is as follows:

Sodium	65 mmol/l
Chloride	53 mmol/l
Potassium	5.0 mmol/l
Bicarbonate	17 mmol/l

The excipients are:
Orange flavour – maltodextrin (maize), arabic gum (E414), citric acid (E330), butylated hydroxyanisole (E320) and other flavouring substances.
Lemon flavour – maltodextrin (maize), flavouring preparations, flavouring substances, natural flavouring substances and alpha-tocophero (E307).
Aspartame (E951)
Sucralose.

Each sachet contains 25 mg of aspartame (E951) which is an excipient with a known effect.

II.2 Drug Substance

The active substances are macrogol 3350, sodium chloride, sodium bicarbonate and potassium chloride. All four active substances are established active substances and described in the European Pharmacopoeia (Ph.Eur).

The CEP procedure is used for the active substances. 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 Ph.Eur.

Manufacturing process
Four CEPs have been submitted; therefore no details on the manufacturing processes have been included.

Quality control of drug substance
The active substance specifications are considered adequate to control the quality and meet the requirements of the monographs in the Ph.Eur. Batch analytical data demonstrating compliance with the specifications have been provided for three batches per drug substance.

Stability of drug substance
For macrogol 3350, no retest date was stated in the CEP. Therefore, stability data have been provided for three batches stored at 25°C/60% RH (long term conditions), 40°C/75% RH (accelerated conditions) and 30°C/65% RH (intermediate conditions) which is in accordance with applicable European guidelines. Although a slight increase in water content was observed at all conditions, all parameters stayed within the specification limit. No other trends were observed. Based on the data submitted, a retest period could be granted of two years when stored under the stated conditions.

For sodium chloride no retest date was stated in the CEP, hence stability studies were performed. Three batches were stored at 25°C/60% RH (long term conditions) which is in accordance with ICH guidelines. Based on the data submitted, a retest period could be granted of two years when stored under the stated conditions.

For sodium bicarbonate no retest date was stated in the CEP. Therefore, stability studies were performed. Three batches were stored at 25°C/60% RH (long term conditions) and 40°C/75% RH (accelerated conditions) which is in accordance with ICH guidelines. Based on the data submitted, a retest period could be granted of two years when stored under the stated conditions.

Potassium chloride is stable for two 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 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. In development several flavourings, sweeteners and combinations were tested. The rationale for the use of flavourings and sweeteners and safety concerns for the paediatric powder for oral solution have been adequately discussed.
The main development studies concerned the *in vitro* comparison of the test and reference product so that bioequivalence studies could be waived.

Manufacturing process

The manufacturing process is a standard process that consists of mixing a salt and flavour bulk mixture, filling the final packaging and separately filling the macrogol 3350 in the same sachet. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for three full scaled batches. The product is manufactured using conventional manufacturing techniques. A suitable risk evaluation on the formation of nitrosamine impurities has been provided.

Control of excipients

Aspartame and sucralose are in compliance with their Ph.Eur. monographs with an additional test for microbiological quality. The lemon and orange flavour comply with the requirements of European regulations on food additives. The control specifications used by the drug product manufacturer are considered adequate to control the materials for their intended use in the finished product and include appearance, identification by infrared light, water content and microbiological quality. 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, identity, reconstitution time, assay, formaldehyde, content uniformity and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

A forced degradation study was performed in order to demonstrate the stability indicating capabilities of the assay methods and the related substance method. Content uniformity and identification tests are not included in the shelf-life specifications all other parameters are included. For those parameters the release and shelf-life limits are identical.

Batch analytical data from three production scaled batches of both product strengths have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided on three production scaled batches per strength stored at 25°C/60% RH (24 months), 30°C/65% RH (24 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Under all conditions a decrease in formaldehyde was observed. On basis of the data submitted, a shelf life was granted of three years. The labelled storage conditions are to store in the original packaging.

No changes were observed in studies on the drug product following reconstitution in water prior to oral administration. Therefore, an in-use shelf life of 24 hours for the reconstituted product when stored at room temperature or in refrigerated conditions is acceptable.

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 Benlaxid 6.9 g and 13.7 g powder for oral 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 Benlaxid is intended for hybrid 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

The active substances are widely used, well-known active substances. Reference is made to the preclinical data obtained with the European reference 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

Macrogol 3350, sodium chloride, sodium bicarbonate and potassium chloride 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. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Benlaxid 6.9 g and 13.7 g powder for oral solution are locally acting products and they are not systematically absorbed, therefore bioequivalence cannot be demonstrated with bioavailability studies. The EMA Guideline on requirements for locally applied or locally acting products, containing known constituents (CPMP/EWP/239/95) states that in order to demonstrate therapeutic equivalence, clinical trials are in principle necessary, but other models may be used or developed.

In this case, essential similarity with the reference product is proven with comparative tests of qualitative attributes. For Benlaxid, the qualitative and quantitative composition is similar to that of the reference products Movicol Junior Neutral 6.9 g sachet, powder for oral solution and Movicol 13.8 g sachet, powder for oral solution. Differences in the excipients exist, but these are not expected to significantly impact bioavailability. In order to demonstrate physicochemical equivalence, the pH and osmolarity of both test and reference products were compared. In these comparisons, Benlaxid was found to be essentially similar to the reference product and thus the waiver for bioequivalence studies could be granted.

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 Benlaxid 6.9 g and 13.7 g powder for oral solution.

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

Important identified risks	-
Important potential risks	-
Missing information	-

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 European reference product Movicol. No new clinical studies were conducted. The MAH demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 language used for the purpose of user testing the PL was English.
The test consisted of: a pilot test with two participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Benlaxid 6.9 g and 13.7 g powder for oral solution have a proven chemical-pharmaceutical quality and are hybrid forms of products Movicol Junior Neutral 6.9 g sachet, powder for oral

solution and Movicol 13.8 g sachet, powder for oral solution. Movicol is a well-known medicinal product with an established favourable efficacy and safety profile.

Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of *in vitro* studies on the relevant quality attributes. A waiver for bioequivalence studies could be 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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Benlaxid with the reference products, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 31 August 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
N/A	N/A	N/A	N/A	N/A	N/A