COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Macrogol and electrolytes naturel Sandoz 13.7 g, powder for oral solution

(macrogol 3350, sodium chloride, sodium hydrogen carbonate, potassium chloride)

NL/H/4382/002/DC

Date: 17 September 2019

This module reflects the scientific discussion for the approval of Macrogol and electrolytes Sandoz 13.7 g. The procedure was finalised on 4 July 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 Macrogol and electrolytes naturel Sandoz 13.7 g powder for oral solution from Sandoz B.V.

This medicine is indicated for the treatment of chronic constipation. It 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 generic application claiming essential similarity with the innovator product Movicol 13.8 g, powder for oral solution, which was registered in the UK on 18 December 1995 by Norgine Ltd. For each Member State the local national registration of Movicol is used as reference product.

The application for Macrogol and electrolytes naturel Sandoz 13.7 g concerns a new presentation under the same main MRP procedure number as Macrogol and electrolytes Sandoz 13.8 g (NL/H/4382/001). The difference in composition between the new formulation and the already registered product concerns only flavouring agents and sweetener: the new presentation does not contain flavouring agents nor sweetener.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC; this is in agreement with the legal basis for NL/H7/4382/001.

The concerned member states (CMS) involved in this procedure were Denmark and Sweden.

II. QUALITY ASPECTS

II.1 Introduction

Macrogol and electrolytes naturel Sandoz 13.7 g is a white crystalline powder for oral solution in sachet. The sachet is composed of paper, ethylene/methacrylic acid co-polymer and aluminium.

Each sachet contains the following active ingredients:

Macrogol 3350	13.125 g
Sodium Chloride	0.3507 g
Sodium Hydrogen Carbonate	0.1785 g
Potassium Chloride	0.0466 g

The content of electrolyte ions per sachet following reconstitution in 125 ml of water is equivalent to:

Sodium	65 mmol/l
Chloride	53 mmol/l
Hydrogen Carbonate (Bicarbonate)	17 mmol/l
Potassium	5 mmol/l

The product contains the excipient colloidal anhydrous silica.

II.2 Drug Substances

The product contains four active substances: macrogol 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride. All these are established substances described in the European Pharmacopoeia (Ph.Eur.). All the active substances are freely soluble in water. Macrogol 3350 is a white or almost white solid with a waxy or paraffin-like appearance. Sodium chloride is a white or almost white crystalline powder or colourless crystals or white or almost white pearls. Sodium hydrogen carbonate is a white or almost white, crystalline powder. Potassium chloride is a white or almost white, crystalline powder or colourless crystals.

The CEP procedure is used for each of 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

CEPs have been submitted; therefore no details on the manufacturing process of the active substances have been included.

Quality control of drug substances

The specification applied by the MAH is clearly presented for all substances and suppliers. Specifications are in line with the Ph. Eur. and CEP requirements. The specifications for all active substances are acceptable. The analysis methods are clearly described.

For the validation of analytical methods reference is generally made to the Ph.Eur. texts, which is generally acceptable. The suitability of the test for microbiological purity in the presence of all the active substances has been verified.

Batch analysis results have provided for three commercial-size batches of each active substance. All results comply with the specifications.

Stability of drug substances

The stability section is adequately covered by the CEP for all active substances, except for macrogol 3350 from one of the suppliers. For this manufacturer a stability study has been performed on three production-scale batches. Based on the provided stability data, a retest period of 36 months has been granted.

II.3 Medicinal Product

Pharmaceutical development

The aim of developing this additional formulation without flavours and without sweetener was to give a choice to patients who prefer not to ingest any "artificial" flavours and sweeteners. The formula without these excipients has a salty taste as a result of the electrolytes.

The application is based on *in-vitro* comparability with the already registered product containing flavours and sweeteners. No clinical studies were performed. As the product is administered as an oral solution, this is allowed, this is in accordance with the draft 'Guideline on equivalence studies for the demonstration of therapeutic equivalence for products that are locally applied, locally acting in the gastrointestinal tract', if the pharmaceutical similarity of the products is properly demonstrated.

The rationale of the manufacturing process steps and parameters and their impact on the quality of the finished product have been sufficiently discussed. The difference in composition between new formulation and the already registered product is minimal and concerns only flavouring agents, which amount for less than 1% of the total weight of a dosage unit. None of the excipients which differ between the products is expected to have any influence on the performance or bioavailability of the drug product. Moreover, the product is administered as a solution in water and all the components are freely soluble in water.

The physicochemical characteristics of the solutions (like pH, osmolality, electrolytes content) which are critical quality attributes of the products are expected to be similar. The MAH performed a comparative study of the properties of the ready-to-administer solutions made from batches of test product Macrogol and electrolytes naturel Sandoz 13.7 g, the registered product Macrogol and electrolytes Sandoz 13.8 g containing flavouring agents and sweeteners and the reference product, showing similarity of pH and osmolality. The pharmaceutical similarity is considered to be adequately proven.

Manufacturing process

The manufacturing process, including in-process controls, is described in a flow chart and in narrative form. The process comprises mixing of the components which results in a premix, then adding all other components and a part of the macrogol (obtaining filling blend 1). The sachets are then filled with blend 1 and the rest of the macrogol, and sealed.

No process validation for the drug product has been performed yet. A protocol for the proposed post-approval process validation is present in the dossier and has been found acceptable. The already registered product macrogol and electrolytes Sandoz 13.8 g is

produced at the same manufacturing sites following a similar process which has already been validated for similar products at the same batch size. This makes the proposed approach of post-approval validation acceptable. The applicant commits to perform the process validation on the first three produced full-size commercial batches at each manufacturing site.

Control of excipients

The only excipient, silica colloidal anhydrous, is controlled according to the appropriate Ph.Eur. monograph. This specification is acceptable.

Quality control of drug product

The specification at release and at shelf life is clearly proposed, the analysis methods refer, where possible, to the Ph. Eur. and are otherwise adequately described. The finished product is tested for appearance of powder and solution, dissolution time, pH of solution, loss on drying, uniformity of mass, content uniformity for potassium and hydrogen carbonate, identity and assay of all active substances, content of formaldehyde and microbiological purity. The specifications are set up in line with Guideline ICH Q6A.

Validation of in-house methods is performed on the already registered product; taking in consideration the small differences between the products it is acceptable to extrapolate the validation to the new formulation.

Stability of drug product

Stability studies have been performed on three full-size batches the formulation applied for and on several batches of similar drug products (including the already registered product Macrogol and electrolytes Sandoz 13.8 g) manufactured at the same sites. All the results are clearly presented and comply with the specification. The stability study design is in line with the 'Guideline on Stability Testing: Stability of existing active substances and related finished products'.

The stability study is completed on three batches of drug product with the same formulation but produced with a slightly different manufacturing process. The differences are described (mixing speed, sieves size) and are not expected to impact the stability of the finished product.

A shelf life of 36 months with a labelling statement 'this medicinal product does not require any special storage conditions' is granted based on the presented data, where no significant change was observed. The in-use stability of the solution after reconstitution has been investigated for the already registered product and can be applied for the new formulation as well. It is established at 24 hours in the refrigerator.

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 Macrogol and electrolytes naturel Sandoz 13.7 g powder for oral solution has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Macrogol and electrolytes naturel Sandoz 13.7 g 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 Movicol, 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

Macrogol 3350, potassium chloride, sodium chloride and sodium hydrogen carbonate 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

Bioequivalence studies between the reference medicinal product and the generic product are not required according to Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98). The medicinal product is an aqueous solution at the time of administration and contains active substances in the same concentrations as in the approved preparations. The excipients do not affect the gastrointestinal transit, the

absorption, solubility or *in-vivo* stability of the active substances. There are no significant differences in the amount of the excipients. The difference in composition between the new formulation and the already registered Sandoz product concerns only flavouring agents and sweetener, which amount for less than 1% of the total weight of a dosage unit. None of the excipients which differ between the products is expected to have any influence on the performance or bioavailability of the drug 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 Macrogol and electrolytes naturel Sandoz 13.7 g.

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

Important identified risks	• Hypersensitivity reactions including anaphylaxis • Fluid/electrolyte shifts, including hyperkalemia and hypokalemia
Important potential risks	• Drug interactions • Dehydration
Missing information	• Use in pregnancy and lactation

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 Movicol. No new clinical studies were conducted. Equivalence to the reference product has been demonstrated based on quality attributes. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has not been evaluated via a user consultation study. A satisfactory bridging report was submitted with a similar PL for an already approved product, containing Macrogol 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride. The PL is satisfactory.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Macrogol and electrolytes naturel Sandoz 13.7 g powder for oral solution has a proven chemical-pharmaceutical quality and is a generic form of Movicol 13.8 g powder for oral solution. Movicol is a well-known medicinal product with an established favourable efficacy and safety profile.

As the product is an oral solution at the time of administration and the active substances are not systemically absorbed but locally acting, it is not possible to demonstrate equivalence by means of a bioequivalence study. The dosage form, active substance composition and concentration are identical to the approved reference product. Equivalence has been adequately demonstrated based on chemical-pharmaceutical properties.

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 Macrogol and electrolytes naturel Sandoz 13.7 g with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 4 July 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