COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Movicolon Unidose 13.9 g/25 ml, oral solution in sachet

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

NL License RVG: 118570

Date: 23 October 2019

This module reflects the scientific discussion for the approval of Movicolon Unidose 13.9 g/25 ml, oral solution in sachet. The procedure was finalised at 12 September 2018. 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 Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Movicolon Unidose 13.9 g/25 ml, oral solution in sachet, from Norgine.

The product is indicated for the treatment of chronic constipation in adults and children above the age of 12. 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.

Movicolon is an iso-osmotic laxative. The active substances are macrogol 3350 and multiple electrolytes (sodium chloride, sodium hydrogen carbonate, potassium chloride). Macrogol is a biologically inert polymer. It is highly soluble in water, remains unchanged along the gut and is virtually unabsorbed from the gastrointestinal tract. It does not exert its activity through pharmacological means, but via an osmotic effect in the gut. The macrogol binds with water and retains it in the bowel. This allows the water to rehydrate and bulk the stool to trigger renewed colonic activity. Due to the electrolytes, this is achieved with an iso-osmotic effect, which allows a net balance of water and electrolytes between the gut and the body. The laxative process is based on rehydration of the stool, to achieve bowel movement.

This national procedure concerns a line extension to the registered product Movicolon 13.8 g, powder for oral solution (NL License RVG 19006) which has been registered since 5 November 1996. The differences with the original product are related to the new pharmaceutical form and flavour (excipients).

The line extension pertains to a change in form and flavour. The product form of Movicolon Unidose is a single dose sachet containing 25 mL of solution to be taken undiluted, with excipients of strawberry/banana flavour. The form and the flavour of the reference product is a powder for solution with excipients of lemon flavour.

The marketing authorisation is granted based on article 8(3) of Directive 2001/83/EC.

This application refers to a standalone dossier, which cross-refers to the non-clinical and clinical data approved for the existing product Movicolon. This information is not available in the public domain. The only new data provided concerns the new pharmaceutical form and the flavour.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a line extension.

II. QUALITY ASPECTS

II.1 Introduction

Movicolon Unidose is a clear, colourless to light yellow, free flowing, and oral solution.

Each 25 ml sachet contains:

Macrogol 3350	13.125 g
Sodium chloride	178.6 mg
Sodium hydrogen carbonate	350.8 mg
Potassium chloride	50.2 mg

The concentration of electrolyte ions in each 25 ml sachet is as follows:

Natrium	325 mmol/l
Chloride	267 mmol/l
Potassium	27 mmol/l
Bicarbonate	85 mmol/l

This corresponds to the following quantity of each electrolyte ion in each dose of 25 ml:

Natrium	8.125 mmol
Chloride	6.675 mmol
Potassium	0.675 mmol
Bicarbonate	2.125 mmol

The oral solution is packed in sachets made of polyethylene terephthalate, aluminium and polyethylene.

The excipients are: sucralose, purified water and strawberry/banana-flavour (containing natural flavour substances/preparations [including celery] and propylene glycol).

II.2 Drug Substances

The active drug substances are macrogol 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride. The main active ingredient is Macrogol 3350, also known as polyethylene glycol 3350, or PEG. All the drug substances are well known and described in the European Pharmacopoeia (Ph.Eur.). The substances are all soluble in water.

The CEP procedure is used for all 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
The manufacturing of the active substances is covered by the grant of the CEP by the EDQM. The CEPs for sodium chloride, potassium chloride and sodium hydrogen carbonate indicate that water is used in the last step of the synthesis. The suitability of the quality of the water used in the last step of the synthesis of these active substances has been stated and is acceptable for use in an oral solution.

Quality control of drug substance
Specifications and batch analytical data for control of the active substances by the MAH/drug product manufacturer are provided, as well as details on the analytical procedures and reference standards used. These are acceptable.

Stability of drug substance
The active substance macrogol is stable for up to 36 months when stored under the stated conditions. Sodium chloride is stable for 24 months, potassium chloride for 36 months and sodium hydrogen carbonate for 24 months when stored under the stated conditions. Assessment thereof was part of granting the CEPs 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 development has been described into sufficient detail, the choice of excipients is justified and their functions explained. The compatibility of the drug substances and excipients is demonstrated by the development studies. The formulation development studies support the choice of the strawberry-banana flavouring. Selection of the unit dose volume of 25 mL was determined with regard to the minimum volume in which the solutes will dissolve without risk of precipitation or affecting the manufacturing process. No clinical studies or bioavailability or bioequivalence studies are required for the proposed product as cross-reference is made to the non-clinical and clinical data approved for the existing product Movicolon. The choices of the packaging material and manufacturing process are supported by the development studies. The ease of opening of sachets has been shown to be satisfactory by the panel test method described in ISO 17480:2015 *Packaging – Accessible design – Ease of opening.*

Manufacturing process
The product is manufactured using conventional manufacturing techniques. The manufacturing process comprises dispensing, mixing, filtration and filling. Information on the filters used should be given. The manufacturing process including holding times of the bulk solution and packaging breaks has been adequately validated on three commercial scale batches.

Control of excipients
The 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 description, color of solution, pH, uniformity of content by mass variation, identification and assay of macrogol, sodium, potassium, chloride and hydrogen carbonate, microbial contamination. 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. Batch analytical data one full-scale and one pilot scale batch as well as for six commercial scale development batches 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 for one pilot scale and one production scale batches stored at 30°/65% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. On basis of the data provided a shelf life was granted of 24 months. The labelled storage conditions are: 'Store below 30°. Dot not store in a refrigerator or freezer.'

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 MEB considers that Movicolon Unidose 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)

The product is intended as a substitute for other macrogol 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride containing products on the market. The approval of this product will not result in an increase in the total quantity of these active substances released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

III.2 Discussion on the non-clinical aspects

This product is a line extension of Movicolon 13.8 g, powder for oral solution which is available on the Dutch market. No new preclinical data have been submitted. Therefore the application has not undergone additional pre-clinical assessment, which is acceptable for this type of application.

IV. CLINICAL ASPECTS

IV.1 Introduction

Macrogol 3350, sodium chloride, sodium hydrogen carbonate 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 MEB agrees that no further clinical studies are required.

For this application reference is made to the clinical data of Movicolon 13.8 g, powder for oral solution. No new clinical studies have been performed.

IV.2 Clinical efficacy and safety

The chemical composition of Movicolon Unidose is comparable to the composition of the already registered Movicolon. Therefore, no clinical differences in efficacy can be expected. Each sachet of both Movicolon and Movicolon Unidose contains 13.125 g macrogol.
A single dose of Movicolon requires 100 ml water more than a single dose of Movicolon Unidose (125 ml vs. 25 ml). Reference was made to the pharmacodynamic study by Flourié (1994)[1] performed in healthy subjects. This study showed that the weight and osmolality of the stool and frequency of bowel movement each day was comparable when 13.125 g macrogol was diluted in 31.25, 62.5, or 125 ml water. In addition, no clinical differences in adverse events when using these amounts were reported.

Unlike other Movicolon preparations (Movicolon and Movicolon Liquid), Movicolon Unidose contains a strawberry-banana flavour which consists of 0.025% celery oil. This amount (corresponding with 0.042 mg/25 ml) remains below the dose limit for causing a subjective reaction (700 mg) or where systematic reactions are observed (1900 mg and up; Ballmer-Weber et al. 2000[2]). Therefore, the proposed quantity of celery oil in Movicolon Unidose is acceptable from a safety point of view.

[1] Flourié B, Halphen M, Lémann M, Franchisseur C, Maurel M, Rambaud JC. (1994) 'Digestive effects of low doses of polyethylene glycol (PEG) in the healthy subjects', Gastroentérologie clinique et biologique;18:A108
[2] Ballmer-Weber BK, Vieths S, Luttkopf D, Heuschmann P and Wuthrich B. (2000) 'Celery allergy confirmed by double-blind, placebo-controlled food challenge: a clinical study in 32 subjects with a history of adverse reactions to celery root'. Journal of Allergy and Clinical Immunology; 106: 373-378

On basis of the comparability of chemical composition and the above mentioned findings, it can be expected that the efficacy and safety of Movicolon Unidose is comparable in comparison to Movicolon.

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 Movicolon Unidose.

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

Important identified risks	- Anaphylaxis - Fluid/electrolyte shifts
Important potential risks	- Reduced absorption of other medication - Dehydration
Missing information	- Use in pregnancy and lactation

The MEB 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 already approved product Movicolon 13.8 g, powder for oral solution. No new clinical studies were conducted. Risk management is adequately addressed.

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 Movicolon 13.8 g, powder for oral solution. 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

Movicolon Unidose 13.9 g/25 ml, oral solution in sachet has a proven chemical-pharmaceutical quality and is a legitimate line extension to Movicolon 13.8 g, powder for

oral solution. Movicolon is a well-known medicinal product with an established favourable efficacy and safety profile.

No new non-clinical or clinical studies were conducted. Risk management is adequately addressed.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, has therefore granted a marketing authorisation. Movicolon Unidose 13.9 g/25 ml, oral solution in sachet was authorised in the Netherlands on 12 September 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Variation type	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
Type IB: C.I.1.z	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a Union referral procedure	yes	01-04-2019	Approved	-
Type II: C.I.6.a	Change(s) to therapeutic indication(s); modification of an approved one	yes	02-10-2019	Approved	-
Type IA: B.III.1.a.2	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability; updated certificate from an already approved manufacturer	No	28-05-2019	Approved	-
Type IB: C.I.z	Safety, efficacy, pharmacovigilance changes; other	yes	17-07-2019	Approved	-