COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Macrogol and electrolytes Sandoz 13.8 g powder for oral solution

NL/H/4382/001/MR

Date: 7 May 2018

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, it is considered that Macrogol and electrolytes Sandoz 13.8 mg powder for oral solution could be approved.

Macrogol and electrolytes Sandoz is indicated for the treatment of chronic constipation.

The application is submitted as abridged application according to Article 10(1) of Directive 2001/83/EC, claiming to be a generic medicinal product of Movicol 13.8 g sachet Powder for Oral Solution, first authorised in the UK to Norgine Limited in December 1995.

No new non-clinical studies were conducted, which is acceptable given that the products contain a widely-used, well-known active substance. No clinical studies have been performed and none are required for these applications as the pharmacology of macrogol 3350, sodium chloride, sodium hydrogen carbonate, potassium chloride is well-established.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a Risk Management Plan.

Following a Change of Ownership procedure, the Marketing Authorisation Hermalax Powder for oral solution, sachet was granted to Sandoz Limited on 10 November 2011 (UK/H/4219/001/DC).

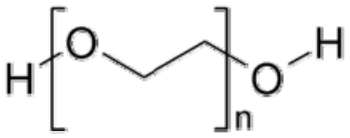
The product name of Hermalax Powder for oral solution, sachet was changed to Compound Macrogol 13.8 g Powder for Oral Solution on 14 June 2012, and subsequently to Macrogol and electrolytes Sandoz 13.8 g powder for oral solution during the RMS change on 3 May 2018.

II. QUALITY ASPECTS

II.1 Introduction

II.2 Drug substances

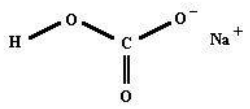
Macrogol 3350
INN/Ph.Eur name: Macrogol 3350
Structural formula:



Molecular formula: $H-(OCH_2-CH_2)_n-OH$

Appearance: White or almost with solid with a waxy or paraffin-like appearance.
Solubility: Very soluble in water and in methylene chloride, very slightly soluble in alcohol, practically insoluble in fatty oils and in mineral oils.

Sodium Hydrogen Carbonate
INN: Sodium hydrogen carbonate
Structure:



Physical form: A white powder (crystalline)
Solubility: Sparingly soluble in water

Molecular formula: $NaHCO_3$
Molecular weight: 84.01

Sodium chloride
INN/Ph.Eur name: Sodium chloride
Molecular formula: NaCl

Appearance: White, crystalline powder or colourless crystals or white pearls
Solubility: Freely soluble in water, practically insoluble in ethanol.

Molecular weight: 58.4

Potassium chloride
INN/Ph.Eur name: Potassium chloride
Molecular formula: KCl

Appearance: White or almost white crystalline powder or colourless crystals.
Solubility: Freely soluble in water, and practically insoluble in anhydrous ethanol.

Molecular weight: 74.6

Macrogol 3350, sodium hydrogen carbonate, sodium chloride and potassium chloride comply with their relevant European Pharmacopoeia monographs.

All aspects of the manufacture of the active substances macrogol 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride from its starting materials are controlled by Certificates of Suitability.

An appropriate retest period has been proposed based on stability data submitted for the active substances.

Appropriate specifications are provided for the active substances, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specifications.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredients. All potential known impurities have been identified and characterised. Suitable Certificates of Analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substances to be physically and chemically stable drugs, and supporting appropriate retest periods.

II.3 Medicinal Product

Other Ingredients
Other ingredients are pharmaceutical excipients colloidal anhydrous silica, saccharin sodium, orange flavour (containing flavouring substances and flavouring preparations, maltodextrin, acacia gum and alpha-tocopherol) and lemon lime flavour (consisting of flavouring preparations, maltodextrin, mannitol, gluconolactone, sorbitol (E420), acacia gum, colloidal anhydrous silica).

None of the excipients used contain material of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development
The objective of the development programme was to produce products that could be considered generic medicinal products of Movicol 13.8 g sachet Powder for Oral Solution.

The applicant has provided suitable product development sections. Justifications for the use and amounts of each excipient have been provided and are valid.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial-scale batches of each strength have been provided.

Finished Product Specification
The finished product specifications proposed for the products are acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have

been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container-Closure System
These products are packaged in sachets composed of paper, ethylene/methacrylic acid co-polymer and aluminium then packed in a carton box.
Pack sizes are 2, 6, 8, 10, 20, 30, 50, 60 (2x30) and 100 (2x50) sachets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with EU legislation regarding contact with food.

Stability of the product
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 36 months with storage instructions, 'Do not store above 25°C'.

For the reconstituted solution the shelf-life is 24 hours with storage conditions 'Store covered in a refrigerator (2°C to 8°C)'.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of this application from a pharmaceutical viewpoint.

No user testing results have been submitted for the PL for this product. 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.

III. NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of macrogol 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride are well-known. As these are widely used, well-known active substances, the applicant has not provided any additional studies and none are required.

The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment

IV. CLINICAL ASPECTS

IV.1 Introduction

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier.

IV.2 Pharmacokinetics and IV.3 Pharmacodynamics

No new pharmacokinetic or pharmacodynamic data were submitted with this application and none were required, as per the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, if the test product is an aqueous oral solution at the time of administration and contains an active substance in the same concentration as an approved oral solution, bioequivalence studies may be waived, if the excipients contained in it do not affect gastrointestinal transit, absorption, solubility or in-vivo stability of the active substance.

IV.4 Clinical efficacy

No new efficacy data were submitted with this application and none were required.

IV.5 Clinical safety

No new safety data were submitted with this application and none were required.

IV.7 Discussion on the clinical aspects

SUMMARY OF PRODUCT CHARACTERISTICS (SPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPCs, PLs and labelling are medically satisfactory and consistent with those for the reference product, where appropriate.

CLINICAL EXPERT REPORT
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

MAA FORM
The MAA Forms are medically satisfactory.

CONCLUSIONS
It is recommended that Marketing Authorisations are granted for these applications.

V. USER CONSULTATION

No user testing results have been submitted for the PL for this product. 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.

IV. OVERALL CONCLUSION, BENEFIT/ RISK ASSESSMENT AND RECOMMENDATION

QUALITY

The important quality characteristics of Macrogol are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY

No bioequivalence studies have been performed and none are required for these applications, given the composition of the products and its intended route of administration.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PLs and labelling are satisfactory and consistent with that for the reference product.

BENEFIT/RISK ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with macrogol 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride is considered to have demonstrated the therapeutic value of the compounds. The risk benefit is, therefore, considered to be positive.

STEPS TAKEN AFTER INITIAL PROCEDURE – SUMMARY

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
Updated certificate from an already approved manufacturer.	UK/H/4219/ 001/IB/025		01/12/2017	02/01/2018	Approved	No
Updated certificate from an already approved manufacturer.	UK/H/4219/ 001/IB/024		01/12/2017	31/12/2017	Approved	No
Updated certificate from an already approved manufacturer.	UK/H/4219/IB/026/G		22/11/2017	07/12/2017	Approved	No
Change of the address in Spain of the MAH	UK/H/4219/ 001/IA/023/ G		16/03/2017	14/04/2017	Approved	No
Implementation of change(s) for which no new additional data is required to be submitted by the MAH.	UK/H/4219/ 001/IB/022		21/02/2016	28/06/2016	Approved	No
Change outside the approved specifications limits range for the active substance.	UK/H/4219/ 001/II/021		24/07/2015	19/02/2016	Approved	Yes
Change in the name of a manufacturer	UK/H/4219/ 001/IA/020/ G		10/01/2015	23/02/2015	Approved	No
Renewal procedure	UK/H/4219/ 001/R/001		06/11/2017	06/12/2017	Approved	Yes
To register the replacement of Ph. Eur. 2.9.40 (Potassium, Sodium, Hydrogen Carbonate, Macrogol 3350) with Ph. Eur. 2.9.6 (Potassium,	UK/H/4219/ 001/IA/019		30/10/2014	26/11/2014	Approved	No

Hydrogen carbonate) and to Ph. Eur. 2.9.5., for the finished product.						
To update of the SmPC and consequentially the leaflet as the result of a repeat use procedure UK/H/4219/001 /E01 (EOP, Day 90: 03/06/2013) as a fulfilment of the commitment made by the MAH within Responses to Day 60 comments from CMSs: NL, ES and IE and also in line with the QRD template	UK/H/4219/ 001/II/018	SmPC, PL	17/10/2014	21/04/2015	Approved	Yes
Change in the address of the MAH	UK/H/4219/I A/017/G		28/08/2014	27/09/2014	Approved	No
1) To register replacement of Excipient Flavour Lemon-Lime 2) To register replacement of Flavour Orange Evogran. 3) To register minor changes to the manufacturing process.	UK/H/4219/I A/016/G		21/08/2014	11/09/2014	Approved	No
1) To register replacement of Excipient Flavour Lemon-Lime 2) To register replacement of	UK/H/4219/I A/014/G		17/05/2014	26/06/2014	Approved	No

Flavour Orange Evogran. 3) To register minor changes to the manufacturing process.						
To delete tests from specification of lemon lime and orange flavour and to delete non-significant specification parameters.	UK/H/4219/ 001/IB/015		28/05/2014	29/09/2014	Approved	No
To submit the risk management plan, (RMP).	UK/H/4219/ 001/II/013		09/04/2013	29/08/2013	Approved	Yes
To add a secondary packaging site, to the licence.	UK/H/4219/ 001/IA/012		06/11/2013	27/11/2013	Approved	No
Repeat use procedure to register the product in Spain, Italy, Ireland and Portugal.	UK/H/4219/ 001/E/001		05/03/2013	03/06/2013	Approved	No
To register the introduction of the Pharmacovigilance System Master File (PSMF) of Sandoz according to the CMDh recommendation for classification variations according to Art. 5 of commission Regulation (EC} No 1.23412008.	UK/H/4219/ 001/IA/011		31/10/2012	26/11/2012	Approved	No
To change the name of the medicinal	UK/H/4219/ 001/IB/010		08/11/2012	09/01/2013	Approved	No

product in Luxembourg from 'Macrolax poudre pour solution buvable' to 'Macrogol + elektrolytes Sandoz poudre pour solution buvable' due to marketing reasons.						
To update the frequency of testing for uniformity of dosage units (Content uniformity) to Skip testing: every 10th batch.	UK/H/4219/001/IB/009		09/07/2012	06/09/2012	Approved	No
To extend the shelf life of the finished product to 36 months and to extend the shelf life of the reconstituted solution to 24 hours.	UK/H/4219/IB/008/G		09/07/2012	30/07/2012	Approved	No
To add a finished product manufacturer, primary and secondary packager, batch release site and QC site, To also add a 'leak test' as an alternative the in-process test procedure to the 'Tightness of seals' test.	UK/H/4219/IB/005/G	PL	21/06/2012	17/08/2012	Approved	No
B.II.b).2.b). 1 Not including batch control/testing	UK/H/4219/IA/006/G		21/05/2012	21/06/2012	Approved	No

B.II.d).2. a) Minor changes to an approved test procedure B.III.1.a). 2 Updated certificate from an already approved manufacturer B.III.1.a). 3 New certificate from a new manufacturer (replacement or addition)						
To change the name of the medicinal product from "Laxmac, poeder voor orale oplossing" to "Macrogol + elektrolytes Sandoz poeder voor drank" in Belgium only.	UK/H/4219/ 001/IB/003	SmPC, PL and labelling	11/05/2012	07-06-2012	Approved	No
PL 17740/0008-0018	N/A	Licence cancellation	N/A	Licence was cancelled on 17/12/2014	Approved	No
Change of ownership procedure for PL 17740/0009 to PL 04416/1319 (Sandoz Limited)	N/A	Change of ownership	N/A	Change of ownership procedure from Hermes Arzneimittel GmbH to Sandoz Limited on 10/11/2011	Approved	No
For PL 04416/1319-0002; To change the name of the product in the UK from Hermalax, powder for oral solution to Compound Macrogol	UK/H/4219/ 001/IB/003	SmPC, PIL and labelling	29/02/2012	30/03/2012	Approved on 14/06/2012	No

13.8g Powder for Oral Solution						
For PL 04416/1319-0022: To update sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8 and 5.3 of the SmPC and consequentially the leaflet as the result of a repeat use procedure UK/H/4219/001/E01 (End of procedure, Day 90: 03/06/2013) as a fulfilment of the commitment made by the applicant also in line with the QRD template.	UK/H/4219/001/II/018	SmPC and PIL.	17/10/2014	08/04/2015	Approved on 21/04/2015	Yes-see annex 1

ANNEX 1

Product:	Compound Macrogol 13.8g Powder for Oral Solution
Marketing Authorisation Holder:	Sandoz Limited
Active Ingredient(s):	macrogol 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride
Type of Procedure:	Mutual Recognition
Submission Type:	Variation
Submission Category:	Type II
Submission Complexity:	Standard
EU Procedure Number (if applicable):	UK/H/4219/001/II/018

Reason:
To update sections 4.1 (Therapeutic indications), 4.2 (Posology and method of administration), 4.4 (Special warnings and precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction), 4.6 (Fertility, pregnancy and lactation), 4.8 (Undesirable effects), 5.1 (Pharmacodynamic properties) and 5.3 (Preclinical safety data) of the SmPC and consequentially the leaflet to fulfil a regulatory commitment agreed during the mutual recognition procedure NL/H/4382/001/E01 (concluded on 03/06/2013). The product information (SmPC and PIL) has also been revised in line with the QRD template.

Supporting Evidence
Revised SmPC fragments and PL.

Evaluation
The proposed changes to the SmPC and PL are acceptable. The updated SmPC fragments and PIL have been incorporated into the Marketing Authorisation.

Conclusion
Approved on 28 April 2015.