CBG MEB

Public Assessment Report

Scientific discussion

Macrogol en elektrolyten Alpex 13.8 g, powder for oral solution

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

NL License RVG: 113166

Date: 31 March 2015

This module reflects the scientific discussion for the approval of *Macrogol en elektrolyten Alpex 13.8 g*, powder for oral solution. The marketing authorisation was granted on 21 October 2013. For information on changes after this date please refer to the module 'Update'.

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 *Macrogol en elektrolyten Alpex 13.8 g*, powder for oral solution from Alpex Pharma (UK) Limited.

The product is indicated for:

- Treatment of chronic or habitual constipation in adults and children aged 12 years and older;
- Resolving faecal impaction (defined as refractory constipation with faecal loading of the rectum and/or colon) in adults and children aged 12 years and older.

A comprehensive description of the indications and posology is given in the SmPC.

Macrogol 3350 acts by virtue of its osmotic action in the gut, which induces a laxative effect. Macrogol 3350 increases the stool volume, which triggers colon motility via neuromuscular pathways. The physiological consequence is an improved propulsive colonic transportation of the softened stools and a facilitation of the defaecation. Electrolytes combined with macrogol 3350 are exchanged across the intestinal barrier (mucosa) with serum electrolytes and excreted in faecal water without net gain or loss of sodium, potassium and water.

This national procedure concerns a generic application claiming essential similarity with the innovator product Movicolon 13.8 g powder for oral solution (NL License RVG 19006), which has been registered in the Netherlands by Norgine B.V. since 5 November 1996 (original product).

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

II. QUALITY ASPECTS

II.1 Introduction

Macrogol en elektrolyten Alpex 13.8 g is a white to almost white powder, which is packed in single dose PET/PE/Al/LLDPE sachets. The product is intended for oral administration after reconstitution in 125 ml of water. No accompanying diluent is supplied as water is employed as diluent.

Each sachet contains the following active ingredients:

Macrogol 3350	*13.125 g*
Sodium hydrogen carbonate	*178.5 mg*
Sodium chloride	*350.7 mg*
Potassium chloride	*46.6 mg*

The content of electrolyte ions per sachet when made up to 125 ml of solution is as follows:

Sodium	*65 mmol/l*
Chloride	*53 mmol/l*
Potassium	*5 mmol/l*
Hydrogen carbonate	*17 mmol/l*

The excipients used are sucralose, silica colloidal anhydrous and orange flavour.

II.2 Drug Substances

The active substances are macrogol 3350, potassium chloride, sodium chloride and sodium hydrogen carbonate, which are well-known substances described in the European Pharmacopoeia (Ph.Eur.). Sodium chloride, potassium chloride and sodium hydrogen carbonate are all white or almost white crystalline powders, freely soluble in water and insoluble in anhydrous ethanol. Macrogol 3350 is a white to almost white solid substance with a waxy or paraffin-like appearance, which is very soluble in water, methylene chloride and alcohol and practically insoluble in fatty oils and mineral oils. Sodium

chloride, potassium chloride and sodium hydrogen carbonate are included in this formulation as actives, as per the innovator, to assist in the maintenance of electrolyte and water balance.

The MAH uses the CEP procedure 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 new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

As CEPs have been submitted for each of the active substances, no details on the manufacturing process have been included.

Macrogol 3350

Quality control of drug substance
The drug substance specification is in line with the two CEPs for macrogol 3350, with appropriate additional requirements. The specification is acceptable in view of the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches.

Stability of drug substance
The active substance of one CEP holder is stable for 3 years when stored under the stated conditions at a temperature below 25°C. Assessment thereof was part of granting the CEP and has been granted by the EDQM.
Stability data on the active substance obtained from the second CEP holder have been provided for three full-scale batches, demonstrating results that meet the requirements at 25°C/60% RH (24 months), 30°/65% RH (12 months) and 40°C/75% RH (6 months). A retest period of three years is justified based on these data.

Sodium hydrogen carbonate

Quality control of drug substance
The drug substance specification has been established in-house in line with the CEP. The specification is acceptable in view of the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three batches stored at 25°C/60% RH (24 months). All parameters tested remain relatively stable. Based on the stability data provided the proposed re-test period of 2 years when stored at 25°C/60% RH can be granted.

Sodium chloride

Quality control of drug substance
The specifications are set in line with the Ph.Eur. and include a limit for the particle size. Batch analysis data on two batches have been provided, showing compliance with the set limits.

Stability of drug substance
A declaration of conformity for the stability testing has been provided, claiming a retest period of three years. This is acceptable.

Potassium chloride

Quality control of drug substance

The drug substance specification is in line with the Ph.Eur.,with additional requirements for particle size. The specification is acceptable in view of the various European guidelines. Batch analytical data demonstrating compliance with the specification have been provided for two full-scale batches.

Stability of drug substance
The active substance is stable for 2 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 development of the product has been described, the choice of excipients is justified and their functions explained. Given the simplicity of the formulation (mainly of drug substances) and the manufacturing process, no particular formulation trials have been performed.
The drug product at issue is a locally applied, locally acting product. According to the 'Note for Guidance on the clinical requirements for locally applied, locally acting products containing known constituents', clinical trials are in principle necessary in order to demonstrate therapeutic equivalence with a reference product. The MAH has demonstrated therapeutic equivalence with the reference product solely by the submission of in-vitro data. The pharmaceutical development of the product has been adequately performed. Therapeutic equivalence with the reference product (Movicolon, Norgine B.V.) was shown on dissolution in different buffers (pH = 1.2, 4.5, 6.8), and on the following parameters after reconstitution: assay, osmolarity, viscosity, pH, and stability up to 24 hours (at 2 – 8°C), was shown. The reconstitution time is well below 2 minutes in both the test and the reference product. The comparison was done on three batches of both the test and reference product.

Manufacturing process
The manufacturing process consists of sieving of the components, blending and packaging. Process validation data on the product has been presented for three batches. The product is manufactured using conventional manufacturing techniques. Additional validation will be performed post registration.

Control of excipients
All excipients used comply with the requirements of their respective Ph.Eur. monographs, except for the orange flavour. The orange flavour complies with an in-house specification. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance of powder, pouches and solution, average weight, water content, uniformity of dosage units, identification, assay, seal, microbial quality, reconstitution time, pH and osmolarity. This is acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three pilot-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for three batches stored at 25°C/60% RH (6 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PET/white PE/Al/PE/LLDPE sachets.
Over six months the only trend that can be observed is a slight increase in water content, for the long term stability, that remains well within the limit. No photostability study has been performed. This is acceptable given the primary packaging. On the basis of these results a shelf-life of 12 months can be granted without special storage conditions. Post approval the shelf life was extended to 36 months.

The results of the stability studies after reconstitution, after 24 h (at 2 – 8°C), show that no significant modification of the physical characteristics and of the assay of the active substances were observed. Therefore a shelf life after reconstitution of 24 hours, when stored at 2 – 8°C, is acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalo-pathies

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 for *Macrogol en elektrolyten Alpex 13.8 g*, powder for oral solution has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment was made:

- The MAH committed to perform a validated study in order to determine homogeneity of sodium chloride and sodium bicarbonate.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since *Macrogol en elektrolyten Alpex* 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 Movicolon, 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 MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Macrogol 3350, potassium chloride, sodium chloride or 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 MEB agrees that no further clinical studies are required.

IV.2 Pharmacokinetics

Biowaiver
The drug product at issue is a locally applied, locally acting product. According to the 'Note for Guidance on the clinical requirements for locally applied, locally acting products containing known constituents', clinical trials are in principle necessary in order to demonstrate therapeutic equivalence with a reference product. As the drug product is a solution at the time of administration, the absence of a bioequivalence study is acceptable if differences in composition do not affect the efficacy and/or safety and relevant characteristics of the drug product are comparable to those of the reference product. Therapeutic equivalence with the reference product was demonstrated based on *in-vitro* data.
It is noted that the innovator has a lemon flavour, a different sweetener and does not contain silica. These differences in composition are not expected to influence the efficacy or safety of the product. In addition, absorption of macrogol, if any, is considered also not to be affected by these small differences. Therefore, a biowaiver is considered acceptable.

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 en elektrolyten Alpex.*

- Summary table of safety concerns as approved in RMP

Important identified risks	Intestinal perforation or obstruction Hypersensitivity Electrolyte imbalance
Important potential risks	Drug interactions: The absorption of other drugs may temporarily reduced due to a decrease in gastrointestinal transit time.
Important missing information	None

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 innovator product Movicolon. No new clinical studies were conducted. 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. The text of the PL is the same as the text already approved and in force for the reference medicinal product Movicolon 13.8 g, powder for oral solution. Bridging is considered acceptable; separate user testing is not required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Macrogol en elektrolyten Alpex 13.8 g, powder for oral solution has a proven chemical-pharmaceutical quality and is a generic form of Movicolon 13.8 g, powder for oral solution. Movicolon 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, a bioequivalence study is not required.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. *Macrogol en elektrolyten Alpex 13.8 g*, powder for oral solution was authorised in the Netherlands on 21 October 2013.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Extension of the shelf-life of finished product to 30 months.	IB	23-7-2014	14-8-2014	Approval	No
Extension of the shelf-life of finished product to 36 months.	II	30-10-2014	2-2-2015	Approval	No