COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Macrogol en Electrolyten Auro 13.8 g, powder for drink

(macrogol 3350
potassium chloride
sodium chloride
sodium hydrogen carbonate)

NL License RVG: 124472

Date: 18 January 2023

This module reflects the scientific discussion for the approval of Macrogol en Electrolyten Auro. The marketing authorisation was granted on 12 April 2021. 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 Macrogol en Electrolyten Auro, powder for drink, from Aurobindo Pharma B.V.

The product is indicated for the treatment of chronic or habitual constipation and faecal impaction (defined as persistent constipation with faecal filling of the rectum and/or colon) in adults and children from 12 years of age.

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

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

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Macrogol en Electrolyten Auro, powder for drink, is a white powder and contains the following active substances: macrogol 3350 (13.125 grams), potassium chloride (0.0466 grams), sodium chloride (0.3507 grams) and sodium hydrogen carbonate (0.1785 grams). The concentration of the electrolytes after dissolving one sachet in 125 ml water is as follows: sodium (65 mmol/liter), chloride (53 mmol/liter), potassium (5 mmol/liter) and hydrogen carbonate (17 mmol/liter).

The powder is packed in sachets (paper – polyethylene – aluminium – ionomer) and boxes.

The excipients are: orange aroma (contains flavourings, maltodextrin, acacia (E414) and alpha-tocopherol (E307)), lemon/lime aroma (contains flavourings, maltodextrin, mannitol (E421), gluconolactone (E575), sorbitol (E420), acacia (E414) and colloidal silica dioxide, anhydrous (E551)), colloidal silica dioxide anhydrous (E551) and sodium saccharine (E954).

II.2 Drug Substance

The active substances are macrogol 3350, potassium chloride, sodium chloride and sodium hydrogen carbonate, established active substances described in the European Pharmacopoeia (Ph.Eur.). The drug substances are freely soluble in water. The active substances do not exhibit polymorphism and are not chiral.

The CEP procedure is used for the active substance. 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

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monographs in the Ph.Eur. for all of the active substances present in the drug product with additional limits in accordance with the requirements stated on the CEPs. For macrogol, one drug substance specification which applies to the drug substance obtained from each supplier has been provided. Batch analytical data demonstrating compliance with this specification have been provided for seven batches of macrogol 3350 coming from three different suppliers and three batches of potassium chloride, sodium chloride and sodium hydrogen carbonate.

Stability of drug substance

This section is covered by the CEP for all drug substances except for macrogol 3350 from one supplier and for sodium hydrogen carbonate.

Stability data of five batches of macrogol 3350 have been provided under the following conditions: 25°C/60% RH, 30°C/65% RH and 40°C/75% RH for 36 (three batches), 24 (two batches), 12 (two batches), nine (three batches) and six months (five batches). This is in accordance with applicable European guidelines demonstrating the stability of the active substance for 36 months. Based on the data submitted, a retest period could be granted of 36 months when stored with storage conditions 15 – 25°C. This is acceptable based on the provided stability data and the Guideline on Stability testing of existing active substances and related finished products.

No stability study has been performed for sodium hydrogen carbonate as it is chemically stable. Eventual decomposition (known to take place only at very high temperature) produces no toxic compounds, but only sodium carbonate, carbon dioxide and water. Assay is tested before use if the material is stored for more than one month.
The active substances potassium chloride and sodium chloride are stable for 24 months and 36 months respectively. 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 development of the drug product has been described, the choice of excipients is justified and their functions are explained. The objective was to develop a powder, free of agglomerates, that is pleasant in taste when dissolved in water. No bioequivalence study has been carried out. A waiver has been claimed and is acceptable. The proposed limit for particle size of macrogol 3350 and electrolytes has been adequately justified.

Manufacturing process

The manufacturing takes place at two manufacturing sites. The process consists of blending, sieving, filling and packaging. It is considered to be a standard process. Process validation has been presented for three production scale batches at both manufacturing sites. The MAH has confirmed that for the determination of the shelf-life of the finished product, the MAH follows the Note for Guidance on "Start of shelf-life of the finished dosage form (i.e. CPMP/QWP/072/96).

Control of excipients

The excipients comply with the Ph.Eur. requirements. These specifications are acceptable.

Quality control of drug product

The drug product specification includes tests for appearance and odour of powder, dissolution, appearance and pH of solution, loss on drying, uniformity of mass, identity and assay of the drug substances, formaldehyde and microbiological quality. The tests for uniformity of mass and identity of the drug substances are not performed during stability studies. The drug product specification is considered to be acceptable. Non-routing testing of microbiological quality has been substantiated and is acceptable. Batch analytical data of three batches manufactured at both manufacturing locations have been provided, demonstrating compliance with the proposed drug product specification.

Stability of drug product

Stability data on the product have been provided for three production scale batches of each manufacturing site in accordance with applicable European guidelines demonstrating the stability of the product for 36 months. The drug product was stored in paper aluminium foil sachets for 36 months at 25°C/60% RH and for 12 months at 40°C/75% RH. Batches manufactured at one of the two sites were also stored for 12 months at 30°C/65% RH. On basis of the data submitted, a shelf life was granted of 36 months. There are no special storage conditions for this medicinal product. Results of an in-use stability of a solution after reconstitution with a slightly different composition with regard to the flavouring agents have been provided and can be applied for the proposed drug product as well. The in-use shelf life and storage conditions for the reconstituted product is 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 MEB considers that Macrogol en Electrolyten Auro 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 Macrogol en Electrolyten Auro 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

This product is a hybrid 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 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 MEB agrees that no further clinical studies are required.

To support the application, the MAH compared the composition, solubility and osmolarity of the solution.

IV.2 Pharmacokinetics

To support the application, the MAH compared the composition, solubility and osmolarity of the solution. Regarding the composition, Macrogol en Electrolyten Auro and the reference Movicolon contain the same active ingredient in the same amounts (see table 1). The excipients in both formulations are shown in table 2.

Table 1. The quantitative and qualitative composition of the active ingredients in Macrogol en Electrolyten Auro and Movicolon.

Composition per sachet (in mg)	**Macrogol en Electrolyten / 13.8 g sachet**	**Movicolon 13.8 g poeder voor drank (RVG 19006)**
Macrogol 3350	13 125 mg	13 125 mg
Sodium chloride	350.7 mg	350.70 mg
Sodium hydrogen carbonate	178.5 mg	178.50 mg
Potassium chloride	46.6 mg	46.60 mg
Concentration after dissolution in 125 ml water	**Macrogol en Electrolyten / 13.8 g sachet**	**Movicolon 13.8 g poeder voor drank (RVG 19006)**
Sodium	65 mmol/l	65 mmol/l
Chloride	53 mmol/l	53 mmol/l
Hydrogen carbonate	17 mmol/l	17 mmol/l
Potassium	5.4 mmol/l	5.4 mmol/l

Table 2. The excipients in Macrogol en Electrolyten Auro and Movicolon.

	Macrogol en Electrolyten Auro, powder for drink	**Movicolon 13.8 g, powder for drink**
Excipients		
Sweetener	Saccharin sodium	Acesulfame K (E950)
Flavouring agent	Orange flavour, consisting of: Flavouring substances, maltodextrin, acacia (E414) and a-tocopherol (E307). Lemon-Lime flavour, consisting of: Natural lemon oil, natural powder flavour lemon, powder flavour lime, maltodextrin, mannitol (E421), gluconolactone (E575), sorbitol (E420), acacia (E414) and silica colloidal anhydrous (E551).	Lemon flavour, consisting of: Lemon oil, lime oil, citric acid, dextrin and vegetable gum.
Anti-caking agent	Silica colloidal anhydrous (E551)	-

In order to provide evidence that both test and reference drug products are truly solutions at the time of administration the aqueous solutions obtained after dissolving one sachet of test and reference formulation in water in line with SmPC posology were investigated to verify the claim of solution. Solubility was evaluated by comparative determination of the assay content of macrogol 3350 in the liquids obtained after dissolving one sachet of the test and reference drug products in tap water (=determination of batch specific total amount of macrogol 3350 considered as reference) in comparison to the liquid obtained after subsequent filtration(=determination of actually dissolved amount of macrogol 3350). The dissolved fraction is expressed as the ratio of actually dissolved vs batch specific theoretically dissolvable amount analysed. The determinations were performed in triplicate. The results are provided in table 3.

Table 3. Fraction of actually dissolved vs. batch specific total amounts (i.e. theoretically dissolvable amount) of Macrogol 3350 obtained after dissolving one sachet Macrogol en Electrolyten, powder for drink (test product) and Movicolon 13.8 g, powder for drink (reference product) within tap water by triplicate determination of assay in filtered vs. unfiltered liquids.

Test product (Macrogol en Electrolyten, powder for drink)

Batch	Average (n=3) dissolved fraction of macrogol 3350 (actually/theoretically dissolvable) [%]	Standard deviation (n=3)	Range of dissolved fraction of macrogol 3350 (± standard deviation) [%]
1	97.1	0.2	96.9 – 97.3
2	97.0	0.4	96.6 – 97.4
Total mean	97.1	0.3	96.8 – 97.4

Reference product (Movicolon 13.8 g, powder for drink)

Batch	Average (n=3) dissolved fraction of macrogol 3350 (actually/theoretically dissolvable) [%]	Standard deviation (n=3)	Range of dissolved fraction of macrogol 3350 (± standard deviation) [%]
1	98.3	1.4	96.9 – 99.7
2	98.8	1.1	97.7 – 99.4
Total mean	98.5	1.3	97.2 – 99.8

Both drug products contain as excipients a sweetener and flavouring system. The hybrid formulation additionally contains colloidal anhydrous silica as anti-caking agent at a very low amount only. Moreover, both flavouring systems share the presence of essential oils from lemon and lime, gums (acacia, vegetable gum) and a mixture of saccharides (maltodextrin, dextrin). As expected for flavouring agents, there are some differences in their qualitative compositions across both drug products. However, considering the very small amounts of flavouring systems within this type of drug products in general and the correspondingly very

low amounts in the drug product under discussion (flavour orange: 56 mg, flavour lemon-lime: 50 mg), there is no relevant impact on gastrointestinal motility or gastro-intestinal transit likely. In addition, any meaningful interaction regarding the absorption, solubility or *in vivo* stability of the active substances is deemed improbable to be exerted by the flavouring system or sweetener used.

In order to determine the overall effect of the slightly different qualitative compositions in excipients of test and reference drug products the osmolality of the oral solutions obtained after dissolving one sachet of test and reference formulation in water (both tap and deionised) (actually eight sachets were dissolved in tap and deionised water) in line with SmPC posology was investigated on three test and two reference product batches. Osmolality was determined according to general Ph.Eur. monograph 2.2.35. The results are provided in table 4.

Table 4. Comparison of total osmolality of dissolved test (Macrogol en Electrolyten, powder for solution) and reference (Movicolon 13.8 g, powder for solution) drug product (one sachet within tap water and deionised water).

Osmolarity (mOsm/kg)					
Test			**Reference**		
Batch number	Deionised water	Tap water	Batch number	Deionised water	Tap water
1	302	313	1	299	316
2	313	322	2	302	314
Mean	308	318	Mean	301	315

The osmolality of the test and reference drug products dissolved in both tap and deionised water is very similar and indicates thereby comparable properties in this regard for both formulations at the time of administration regardless of slight differences in the excipients' compositions. Moreover, the osmolality relevant for the clinical efficacy and safety is expected to be even more similar across both drug products because at the site of action (lower parts of intestine and rectum) the starch/saccharides (dextrin, maltodextrin) components as well as the essential oils contained in the flavouring systems will be already digested and/or absorbed and no longer be present in the gut so that the primary driving force for the intended pharmacodynamics effect will be exerted by the osmolality of the remaining active substances (i.e. macrogol and electrolytes moieties) which are fully identical for test and reference drug products.

Biowaiver

No bioequivalence studies are submitted. Macrogol en Electrolyten Auro 13.8 g, powder for drink, is an powder for oral solution containing the active ingredients Macrogol 3350, sodium chloride, potassium chloride and sodium hydrogen carbonate. The purpose of the pharmaceutical development was to obtain an powder for oral solution of active ingredients which should be essentially similar to the reference product, Movicolon and should meet Ph.Eur. requirements for such a kind of pharmaceutical formulation.

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 intends to demonstrate therapeutic equivalence with the reference product solely by the submission of *in vitro* data.

To support this, the MAH applied the "Guideline on equivalence studies for the demonstration of therapeutic equivalence for products that are locally applied, locally acting in the gastrointestinal tract as addendum to the guideline on the clinical requirements for locally applied, locally acting products containing known constituents." For oral solutions acting locally in the intestine/rectum (CHMP 2017), following decision trees for products acting locally in the intestine and in the rectum on how to establish therapeutic equivalence.

Based upon the results provided and in accordance with the decision tree, the small difference observed in excipients between test and reference Movicolon 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, the waiver for bioequivalence studies 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 Electrolyten Auro.

Tablet 5. Summary of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
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. The MAH demonstrated through dissolution and osmolarity studies that the dissolution and osmolarity profiles of the product are 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

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Macrogol en Electrolyten Sandoz 13.8 g powder for oral solution (NL/H/4382/001/MR). The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Macrogol en Electrolyten Auro, powder for drink has a proven chemical-pharmaceutical quality and is a hybrid form of Movicolon. Movicolon is a well-known medicinal product with an established favourable efficacy and safety profile.

No bioequivalence has been shown to be in compliance with the requirements of European guidance documents. However, as Macrogol en Electrolyten Auro is a locally acting drug without systemic absorption a pharmacokinetic bioequivalence study is not suitable to test therapeutic equivalence, nor necessary for a safety evaluation of comparable systemic absorption. This conclusion is supported and the reasoning behind the lack of bioequivalence studies is acceptable.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Macrogol en Electrolyten Auro with the reference product, and have therefore granted a marketing authorisation. Macrogol en Electrolyten Auro was authorised in the Netherlands on 12 April 2021.

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
Type C.I.8.a	Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use* - Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location	No	27-05-2021	Approved	N/A
Type A.5a	Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites) - The activities for which the manufacturer/importer is responsible include batch release	Yes	26-07-2021	Approved	N/A
Transfer of MAH + Type A.2.b	Transfer of MAH from Apotex Europe B.V. to Aurobindo Pharma B.V. + Change in the (invented) name of the medicinal product - for Nationally Authorised Products	Yes	25-1-2022	Approved	N/A
Type C.I.2.a	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product - Implementation of change(s) for which no new additional data are submitted by the MAH	Yes	23-3-2022	Approved	N/A