CBG MEB

Public Assessment Report

Scientific discussion

Macrogol en electrolyten Naturel Tramedico Junior, powder for oral solution 6.9 g

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

NL License RVG: 119347

Date: 22 February 2018

This module reflects the scientific discussion for the approval of *Macrogol en electrolyten Naturel Tramedico Junior,* powder for oral solution 6.9 g. The marketing authorisation was granted on 14 February 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
EDQM	European Directorate for the Quality of Medicines
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 Naturel Tramedico Junior,* powder for oral solution 6.9 g from Tramedico B.V.

The product is indicated for:

- Treatment of chronic or habitual constipation in children aged 2-11 years;
- Resolving faecal impaction in children aged 2-11 years (defined as refractory constipation with faecal loading of the rectum and/or colon)
- Recurrence prevention of faecal impaction in children aged 2-11 years after successful disimpaction with macrogol and electrolytes.

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

This national procedure concerns a generic application claiming essential similarity with the innovator product Movicolon Junior Naturel 6.9 g powder for oral solution (NL License RVG 32357), which has been registered in the Netherlands by Norgine B.V. since 3 April 2006. The first marketing authorization was granted on 5 November 1996 for Movicolon 13.8 g, powder for oral solution (NL RVG 19006).

The 6.9 g formulation is a line extension to the MAH's formulation *Macrogol en elektrolyten Naturel Tramedico*, powder for oral solution 13.7 g (NL RVG 108115) which has been authorised in the Netherlands since 25 October 2010.

In line with the MAH's formulation *Macrogol en elektrolyten Naturel Tramedico* the marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Macrogol en electrolyten Naturel Tramedico Junior 6.9 g is a free-flowing white powder, which is packed in single-dose paper/LDPE/Al/LDPE sachets. The product is intended for oral administration after reconstitution in 70 ml of water. No accompanying diluent is supplied as water is employed as diluent.

Each sachet contains the following active ingredients:

Macrogol 3350	*6.563 g*
Sodium hydrogen carbonate	*89.3 mg*
Sodium chloride	*175.4 mg*
Potassium chloride	*25.1 mg*

The content of electrolyte ions per sachet when made up to 62.5 ml of solution is as follows:

Sodium	*65 mmol/l*
Chloride	*53 mmol/l*
Hydrogen carbonate	*17 mmol/l*
Potassium	*5.4 mmol/l*

The product does not contain any excipients.

II.2 Drug Substances

The product contains four active substances: Macrogol 3350, potassium chloride, sodium chloride and sodium hydrogen carbonate (sodium bicarbonate). All four substances are well known and described in the European Pharmacopoeia (Ph.Eur.). Macrogol 3350 is a white or almost white solid with a waxy

or paraffin like appearance, which is very soluble in water and in methylene chloride, very slightly soluble in alcohol, and practically insoluble in fatty oils and mineral oils. Potassium chloride is a white or almost white, crystalline powder which is freely soluble in water and practically insoluble in anhydrous ethanol. Sodium hydrogen carbonate is a white or almost white, crystalline powder which is soluble in water and practically insoluble in ethanol. Sodium chloride is a white, or almost white, crystalline powder which is freely soluble in water and practically insoluble in anhydrous ethanol.
For Macrogol 3350 and potassium chloride a CEP has been provided. For sodium chloride and sodium hydrogen carbonate full information has been provided in the dossier.

Under the official Certification Procedures (CEP) 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 European Pharmacopoeia.

Manufacturing process
The manufacturing process of Macrogol 3350 and potassium chloride is covered by their respective CEPs, therefore no details on the manufacturing process have been included.
Sodium chloride is a naturally occurring chemical. Sodium chloride is produced by evaporation of salt brine by steam. Sodium hydrogen carbonate is manufactured from refined sodium carbonate, purified water and food grade carbon dioxide. The sodium carbonate solution is reacted with food grade carbon dioxide to produce sodium hydrogen carbonate crystals.

Quality control of drug substances
The specifications of all four active substances are in line with their respective Ph.Eur. monographs and CEPs (where applicable), with additional in-house requirements for particle size for all four active substances to ensure a homogeneous blend during manufacture of the finished product. The specifications are acceptable in view of the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specifications have been provided for three batches of each drug substance.

Stability of drug substances
The re-test period of Macrogol 3350 is 3 years if stored at a temperature not exceeding 25°C. The re-test period of potassium chloride is 2 years. Assessment thereof was part of granting these CEPs and have been granted by the EDQM.
The re-test period for sodium chloride was set to 12 months. Retest data of one batch by the finished product manufacturer after 20 months storage under controlled room temperature (15-25°C) were provided to support the applied 12 months retest period. This retest period is justified based on the presented data and nature of the substance.
The re-test period for sodium hydrogen carbonate was set to 12 months. Retest data of two batches by the finished product manufacturer after 19 and 12 months storage under controlled room temperature (15-25°C) respectively, were provided to support the applied 12 months retest period. This retest period is justified based on the presented data and nature of the substance.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described. The product was developed as a line-extension to an already authorised 13.7 g sachet formulation and as a generic of the reference product Movicolon Junior Naturel 6.9 g, powder for oral solution. The pharmaceutical development of the product has been adequately performed.
Comparative dissolution data have been provided in the dossier demonstrating that the macrogol-electrolyte sachets (performed with the 13.7 g product versus Movicol 13.8 g sachets), in their powder form, dissolve at the same rate as the reference product. These data are also considered representative for the 6.9 g product applied for. A waiver for bioequivalence studies is considered justified in accordance with the Guideline on the investigation of bioequivalence. Both the test and reference products are aqueous solutions at the time of administration and contain the same active

substances in the same quantities. Besides the active substances no excipients are present in both the test and reference product.

Manufacturing process
All the ingredients, except macrogol 3350, are weighed out and passed through a sieve and mixed in a blender. Macrogol 3350 is then sieved, added and mixed in portions. After addition of the final portion of sieved macrogol the mixture is finally blended.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on a representative product has been presented on three full scaled batches.

Quality control of drug product
The product specification includes tests for appearance, pH, moisture content, uniformity of mass, uniformity of dosage units, assay of Macrogol 3350, sodium, potassium, bicarbonate and chloride, identification of Macrogol 3350, sodium, potassium, bicarbonate and chloride and microbial contamination. The release and shelf-life limits are identical and are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two production scaled batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided. Two full scaled batches were stored at 25°C/60% RH (12 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 paper/LDPE/Al/LDPE sachets. The stability results showed no clear trends or changes in any of the tested parameters at both storage conditions. The proposed shelf-life of 2 years and storage condition 'Store below 25°' are justified.

An in-use shelf-life of the product after reconstitution in water of 24 hours when stored covered in a refrigerator at 2-8°C has been justified.

Specific measures for 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 Naturel Tramedico Junior,* powder for oral solution 6.9 g 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 en electrolyten Naturel Tramedico Junior* 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 Junior Naturel 6.9 g powder for oral solution, 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.

IV.2 Pharmacokinetics

The product is an oral solution of highly water-soluble components. The absence of a bioequivalence study has been adequately justified in accordance with the Note for Guidance CPMP/EWP/QWP/1401/98, given that the proposed product is administered as an aqueous solution containing the same actives at the same concentration as the oral Movicolon Junior Naturel 6.9 g powder for oral solution currently approved. There are no other ingredients in the product which would affect gastrointestinal transit, absorption or *in-vivo* stability of the active substances.

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 Naturel Tramedico Junior.*

- Summary table of safety concerns as approved in RMP

Important identified risks	Off-label use Adverse effects related to shifts in fluid and electrolyte balance
Important potential risks	Potential to alter absorption and decrease efficacy of other medicinal products.
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 Junior Naturel. No new clinical studies were conducted. Equivalence to the reference product has been demonstrated based on quality data. 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 bridging report was submitted. The MAH refers to the successfully user tested PL for Laxido Orange, powder for oral solution (UK/H/1114/001). The key messages for safe use of the two leaflets are the same. The design and layout of the PLs are also comparable. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Macrogol en electrolyten Naturel Tramedico Junior powder for oral solution 6.9 has a proven chemical-pharmaceutical quality and is a generic form of Movicolon Junior Naturel 6.9 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, it is not possible to demonstrate equivalence by means of a bioequivalence study. The dosage form and 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.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for this generic medicinal product with the reference product, and have therefore granted a marketing authorisation. *Macrogol en electrolyten Naturel Tramedico Junior* was authorised in the Netherlands on 14 February 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Product Information affected	Date of end of the procedure	Approval/ non approval	Summary/ Justification for refuse