CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Macrogol and Electrolytes 13,7 g powder for oral solution Pharmachemie B.V., the Netherlands

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

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1865/001/DC
Registration number in the Netherlands: RVG 105943

22 April 2011

Pharmacotherapeutic group:	Osmotically acting laxatives
ATC code:	A06AD65
Route of administration:	oral
Therapeutic indication:	chronic constipation; faecal impaction, defined as refractory constipation with faecal loading of the rectum and/or colon
Prescription status:	prescription only (in NL)
Date of authorisation in NL:	21 March 2011
Concerned Member States:	Decentralised with BE, DE, ES, HU, IE, IT, LU, SE, and UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Macrogol And Electrolytes 13,7 g powder for oral solution, from Pharmachemie B.V. The date of authorisation was on 21 March 2011 in the Netherlands. The product is indicated:

- for the treatment of chronic constipation
- 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 SPC.

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 decentralised procedure concerns a generic application claiming essential similarity with the innovator product Movicolon 13,8 mg (NL license RVG 19006) which has been registered in the Netherlands by Norgine BV since 1996 (original product). In addition, reference is made to equivalent products in the individual member states (reference product).
For Member state HU the MAH refers to the European Reference product: Movicol 13,8 g from Norgine Ltd (UK).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

The MAH requested as legal status of the proposed product "*Not subject to medical prescription*". In the Netherlands however, the innovator product is subject to medical prescription and therefore the request of the MAH was not granted in the Netherlands.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired.
As the product is an oral solution at the time of administration and the active is not systemically absorbed but locally acting, a bioequivalence study is not presented in line with Note for Guidance on Bioavailability and Bioequivalence – CPMP/EQP/QWP/1401/98.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

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 generic medicinal products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substances are macrogol 3350, potassium chloride, sodium chloride and sodium hydrogen carbonate, which are well-known substances, described in the 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. Sodium chloride may also exist as colorless crystals of white to almost white pearls, and potassium chloride may also be present as colorless crystals. 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. 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 macrogol 3350 and potassium chloride. In addition one of the suppliers of sodium hydrogen carbonate has also been issued a CEP. 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.

Manufacture
For macrogol 3350 and potassium chloride and for one of the sodium hydrogen carbonate suppliers, the manufacturing process is covered by the CEP's.
For both sodium chloride and sodium hydrogen carbonate from a second supplier the manufacturers have been provided.

Quality control of drug substance
Macrogol 3350, potassium chloride and sodium hydrogen carbonate are adequately controlled by the respective CEP's. Additional requirements specified are that water be employed as solvent in the last step of synthesis of potassium chloride and that for macrogol, formaldehyde is limited to a certain value. This limit is in line with the current Ph.Eur. monograph for macrogol 3350. Both sodium chloride and sodium hydrogen carbonate are typically used as excipients in pharmaceutical products and are suitably controlled by the relevant Ph.Eur monographs. The MAH has set particle size requirements for all components.

Stability of drug substance
A re-test period of 3 years is approved for macrogol manufactured by one manufacturer when adequately stored below 25°C. A re-test period of three years when adequately stored is accepted for the drug substance macrogol. For a second macrogol supplier a re-test period of 3 years or 1 year is approved depending on the container closure, with no specific storage conditions. A re-test period of 2 years has been declared for potassium chloride, with no specific storage conditions. For sodium hydrogen carbonate (CEP grade) a re-test period of 2 years has been declared, with no special storage conditions. For sodium chloride and sodium hydrogen carbonate from a second suppiler respectively, a re-test period of 4 years with no specific storage conditions has been proposed, when stored unopened in the proposed packaging. This is deemed acceptable based on the fact that these drug substances are inorganic and not susceptible to change when stored in the applied packaging and storage conditions. The MAH adopts the

same packaging and re-test period as indicated on the CEP or employed by the respective suppliers of the active substances.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
The product is formulated as a powder for oral solution which is packed in sachets (laminate consisting of four layers (inner to outer): low density polyethylene, aluminium, low density polyethylene and paper). 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 chloride	*350.7 mg*
Sodium hydrogen carbonate	*178.5 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*
Hydrogen carbonate	*17 mmol/l*
Potassium	*5.4 mmol/l*

The excipients are acesulfame potassium (E950), and lemon flavour (contains acacia gum (E414) + flavouring).

The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The aim of the development work was to develop stable, robust and reproducible Macrogol and Electrolyte Sachets (powder for oral solution), equivalent to the reference medicinal product Movicol 13.8 g sachets, Powder for Oral Solution, held by Norgine Limited. A comparison has confirmed the same active ingredients in same concentrations for both Movicol sachets and Macrogol and Electrolytes sachets, with Movicol containing a lime and lemon flavor, whilst Macrogol and Electrolytes contain only a lemon flavor. Both Movicol sachets and Macrogol and Electrolytes sachets contain the sweetening agent acesulfame potassium. Particle size and dissolution time were investigated during the development. A rapid dissolution time of 3 minutes was observed for the test product and compared well with the dissolution time of the UK reference product. Reconstitution time of the test product in the proposed diluent (water) was also tested and found to be rapid and comparable to that of the reference product (≤ 1 minute). No bioequivalence study has been performed, since the product in question is in aqueous oral solution at the time of administration. The MAH compared the pH and osmotic values of both test and reference product. Similarity between the generic product and the reference product with respect to osmolality and pH was shown.

Excipients
Sweetening agent lemon flavour DC 210 PH is controlled by in-house procedures. The MAH has confirmed that the ingredients of the lemon flavour comply with Directive 88/388/EEC for flavours. The composition of the flavourant is provided. The MAH has justified the concentration of the sweetening agent, acesulfame potassium. The type of excipients and packaging are usual for this type of dosage form.

Manufacturing process

Dry pre-mixing and blending is employed. The process is simple. All active ingredients are sieved together, followed by the flavor and sweetening agents which are each sifted separately. The following critical steps are controlled: speed of blender and blending time, fill weight, uniformity of fill weight, leak test and integrity of sachets and for the blend, moisture content and particle size testing is performed when applicable. Yields are also recorded for the filled and sealed sachets. Process validation has been performed on two batches of three sizes (2 batches each). Validation data of a third batch will be provided post-approval. For larger commercial batch sizes, validation data should be submitted by Variation application. Validation data have been supplied in support of the bulk holding time, but a holding time will be established for each batch size, once data of the third batches are available.

Container closure system

It can be assumed that the outer LDPE layer is the only layer in contact with the drug product. The LDPE layer in contact with the drug product complies with Ph Eur 3.1.1 polyolefines and the EU Food Directive 2002/72/EG. As the drug product concerns a blend of dry powder, leaching of additives from the packaging to the product is not considered relevant.

Quality control of drug product

The following parameters are controlled: description including odour, identification of the actives, average fill weight, uniformity of fill weight, moisture content, reconstitution time, clarity and color of the reconstituted solution, pH of the reconstituted solution, uniformity of dosage units by weight variation, uniformity of content for hydrogen carbonate, sodium, potassium and chlorides, assay of the four actives, and microbial limit test. The methods have been adequately described and, where relevant, validated. Assay of macrogol is adequately determined. The specifications are acceptable. The first 5 commercial batches will be tested for microbial control and reconstitution time, pH and clarity and colour of the reconstituted solution to support the proposed non-routine testing schedule.

Microbiological attributes

The test for microbial contamination is included as a part of finished product specification to check the microbiological quality of the drug product, since some excipients may tend to support microbial growth. Microbial purity testing is included as a parameter in the finished product and shelf-life specifications

Compatibility

Compatibility of the finished product, once reconstituted in the proposed diluent (water) has been shown up to 24 hours, which is the maximum in-use storage period.

Stability tests on the finished product

Stability data has been submitted for 18-month storage at long term and intermediate storage conditions and 6-month accelerated storage conditions. At each time point also the reconstituted solution was tested after zero, nine, and twelve hours (and 24 hours in one batch) of storage at 5°C and 25°C. The unopened and reconstituted solution is stable at all tested conditions. Assay results showed some changes over time; however, no specific patterns or trends are noted. Based on the provided data, a shelf-life of 30 months can be granted. No special storage conditions are required. A shelf-life of 24 hours can be accepted for the reconstituted product, when stored between 2 and 8°C.
The MAH has committed to place the first three commercial scale batches on stability at long term conditions for the proposed shelf-life and at accelerated conditions for 6 months.

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.2 Non clinical aspects

This product is a generic formulation of Movicolon 13,8 mg, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of macrogol 3350, potassium chloride, sodium chloride or sodium hydrogen carbonate 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.

II.3 Clinical aspects

Macrogol 3350, potassium chloride, sodium chloride or sodium hydrogen carbonate are well-known active substances with established efficacy and tolerability.

The safety and efficacy of the constituents of this product in the treatment of constipation and faecal impaction are well established and have been reviewed by a Clinical Expert. 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 an oral solution currently approved, there being no other ingredients in the product which would affect gastrointestinal transit, absorption or *in-vivo* stability of the active.

Product information

SPC
The SPC is largely in line with the SPC of the Dutch innovator and another generic of Movicolon (DK/H/1199/001, which is in line with the innovator text) approved in CMS: AT, BE, CY, CZ, DE, DK, EL, ES, FI, FR, HU, IE, IS, IT, LU, NL, NO, PL, PT, SE, SI, SK, UK.
Furthermore some text proposals are adapted in line with the European recently approved innovator text Movicol UK/H/131 (4.1, 4.2, 4.4 and 4.8) and the national Dutch innovator text Movicolon (4.6 and 5.3). The new text proposal is agreed with all CMS.
The MAH committed to amend the text in 4.6 and 5.3 when these sections may differ much from the Movicol SPC after finalising the variation UK/131/001/II/42. Since NL is not involved in UK/131/001/II/42, DE is asked to inform the Member states and MAH in case of significant differences.

Readability test
The MAH submitted the user text for Macrogol plus electrolytes 6.9 g. This is the junior version of the macrogol in the present procedure.
The user test was assessed by the UK in the ongoing procedures for Macrogol plus electrolytes 6.9 g UK/H/2440, 4009, 3983/DC. The following was concluded: "*The proposed PIL has been subjected to appropriate user testing and passed the defined success criteria*".
The MAH did supply a bridging report, which presents the differences between the user-tested PL of Macrogol plus electrolytes 6.9 g, powder for oral solution (parent PL) and the PL of Macrogol and electrolytes 13.7g, powder for oral solution (daughter PL).

Content
The bridging report presents a side by side comparison of the leaflet text for the parent and daughter PLs. Textual differences are represented for each section, together with the key questions related to this section. Overall, the leaflet content of parent and daughter PL is considered to be sufficiently similar to allow bridging.

Layout and style
The mock-ups of the user-tested parent leaflet and daughter leaflet are provided in the bridging report. The bridging report states that the design and layout are identical for both PL's.

Conclusion
The Member states consider that bridging between the PL of Macrogol plus electrolytes 6.9 g, powder for oral solution (parent PL) and the PL of Macrogol and electrolytes 13.7g, powder for oral solution (daughter PL) is acceptable. The PL fulfils the requirements of patient consultation as meant in the Guideline on readability.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Macrogol and Electrolytes 13,7 g powder for oral solution has a proven chemical-pharmaceutical quality and is a generic form of Movicolon 13,8 mg. Movicolon is a well-known medicinal product with an established favourable efficacy and safety profile.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Macrogol and Electrolytes 13,7 g powder for oral solution with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 3 November 2010. Macrogol and Electrolytes 13,7 g powder for oral solution is authorised in the Netherlands on 21 March 2011.

A European harmonised birth date has been allocated, 15 April 1991, and subsequently the first data lock point for macrogol 3350 is May 2013. The first PSUR will cover the period from the date of approval to May 2013, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be 31 January 2014.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product
- The MAH has committed to place the first three commercial scale batches on stability at long term conditions for the proposed shelf-life and at accelerated conditions for 6 months.
- The MAH has committed to conduct validation on an additional batch(es) of the drug product with three specific batch sizes (when additional batches are planned).
- The MAH has committed to test the first 5 commercial batches for microbial control and reconstitution time to support the proposed non-routine testing schedule.
- The MAH has committed to test the first 5 commercial batches for pH and clarity and colour of the reconstituted solution to support the proposed non-routine testing schedule.
- The MAH has committed to continue the stability studies up to the proposed shelf-life.

SPC
- The MAH committed to amend the text in 4.6 and 5.3 when these sections may differ much from the Movicol SPC, after finalising the variation UK/131/001/II/42. Since NL is not involved in UK/131/001/II/42, DE is asked to inform the Member states and MAH in case of significant differences.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached