

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Macrogol en elektolyten CF 13.7 g and 6.9 g, powder for oral
solution
Centrafarm 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/1866/001-002/DC
Registration number in the Netherlands: RVG 108092-108093

22 December 2011

Pharmacotherapeutic group:	Osmotically acting laxatives
ATC code:	A06AD65
Route of administration:	oral
Therapeutic indication:	13.7 g - chronic constipation; faecal impaction, defined as refractory constipation with faecal loading of the rectum and/or colon; 6.9 g - chronic constipation in children 2 to 11 years of age; faecal impaction in children 2 to 11 years of age; prevention of re-impaction after successful disimpaction in children 2 to 11 years of age.
Prescription status:	prescription only (in NL)
Date of authorisation in NL:	29 November 2011
Concerned Member States:	Decentralised procedure with AT (13.7 g), IT (6.9 g) and BE, DE, IE and LU (13.7 g and 6.9 g)
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 en elektolyten CF 13.7 g and 6.9 g, powder for oral solution, from Centrafarm B.V. The date of authorisation was on 29 November 2011 in the Netherlands.

Macrogol en elektolyten CF 13.7 g is indicated for:

- Treatment of chronic constipation
- Resolving faecal impaction, defined as refractory constipation with faecal loading of the rectum and/or colon.

Macrogol en elektolyten CF 6.9 g is indicated for:

- Treatment of chronic constipation in children 2 to 11 years of age.
- Treatment of faecal impaction in children 2 to 11 years of age, defined as refractory constipation with faecal loading of the rectum and/or colon.
- Prevention of re-impaction after successful disimpaction in children 2 to 11 years of age.

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 Movicol/Movicolon. Movicol was first registered in 1995 in the UK by Norgine Ltd, UK. In the Netherlands, Movicolon 13,8 g and Movicolon Junior 6,9 g (MAH: Norgine BV, the Netherlands, NL license RVG 19006 and 29318, respectively) have been registered through national procedures since 1996 and 2006 respectively. In addition, reference is made to Movicolon authorisations in the individual member states (reference product).

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

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 aqueous oral solution at the time of administration and the active substance 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 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 for the 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 sodium hydrogen carbonate 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.

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 another supplier, 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 drug product is a white crystalline powder which is packed in single dose sachets (laminated 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 water. No accompanying diluent is supplied as water is employed as diluent.

Each sachet of Macrogol en elektolyten CF 13.7 g contains the following active ingredients:

<i>Macrogol 3350</i>	<i>13.125 g</i>
<i>Sodium chloride</i>	<i>350.7 mg</i>
<i>Sodium hydrogen carbonate</i>	<i>178.5 mg</i>
<i>Potassium chloride</i>	<i>46.6 mg</i>

Each sachet of Macrogol en elektolyten CF 6.9 g contains the following active ingredients:

<i>Macrogol 3350</i>	<i>6.563 g</i>
<i>Sodium chloride</i>	<i>175.4 mg</i>
<i>Sodium hydrogen carbonate</i>	<i>89.3 mg</i>
<i>Potassium chloride</i>	<i>23.3 mg</i>

The content of electrolyte ions per sachet when made up to 125 ml respectively 62.5 ml of solution is as follows:

<i>Sodium</i>	<i>65 mmol/l</i>
<i>Chloride</i>	<i>53 mmol/l</i>
<i>Hydrogen carbonate</i>	<i>17 mmol/l</i>
<i>Potassium</i>	<i>5.4 mmol/l</i>

The excipients are acesulfame potassium (E950), and lemon flavour (contains acacia gum (E414) and 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 a stable, robust and reproducible Macrogol sachets (powder for oral solution), equivalent to the reference medicinal product Movicol 6.8 g and 13.8 g sachets, Powder for Oral Solution, held by Norgine Limited. A comparison has confirmed the same active ingredients in the same concentrations for both Movicol sachets and Macrogol sachets, with Movicol containing a lime and lemon flavor, whilst Macrogol contain only a lemon flavor. Both Movicol sachets and Macrogol 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 are shown.

Excipients

Acesulfame potassium is contained as sweetening agent (at a level of 0.07%). This excipient is described in the Ph.Eur. 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 mix 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 with two sizes, one size for both 6.86 g and 13.72 g sachets and one size only for 13.72 g sachets, and on four batches of of another size for both 6.86g and 13.72g sachets. Validation data of a third batch will be provided post-approval. Although the manufacturing process is deemed a non-standard process, these batches are considered representative for the proposed commercial batch size. Validation data will be performed in support of the bulk holding time, results will be sent as soon as available.

Container closure system

It can be assumed that the outer LDPE layer is the only layer in contact with the drug product. Compliance to Directive 2002/72/EC, Directive 1935/2004, EC Regulation 2023/2006 and Ph.Eur. monographs 3.2.2 and 3.1.3 as well as compliance to European Guideline on Plastic Immediate Packaging Materials (CPMP/QWP/4359/03) and corresponding Ph.Eur. monographs is provided. 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 shelf-life limit for water content will be re-evaluated once more data is available. 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 24-month storage at long term and 12-month storage at 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 sachets and reconstituted solution seems to be 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 36 months can be granted. No special storage conditions are required. A shelf-life of 24 hours can be accepted for the reconstituted product. Photostability studies have been

conducted on Macrogol sachets as per guideline CPMP/ICH1279/95. The product was found to be photostable.

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.

Several commitments have been made with regard to the drug product; these can be found on page 8 of this PAR.

II.2 Non clinical aspects

These products are a generic formulation of Movicolon 13.8 g and Movicolon Junior 6.9 g, which are 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 in adults and children 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.

Risk management plan

This combination of active substances was first approved in 1995, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of these active substances can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

For the 13.7 g strength, the content of the SPC approved during the decentralised procedure is in accordance with that accepted during procedure NL/H/1862-65/01/DC, which was finalised on 2 November 2010 with the same CMS's (among others). The MAH has amended the SPC in line with the SPC of the above mentioned procedures.

The SPC proposal for children (6.9 g strength) is in line with the innovator SPC and with the current guidelines. The SPC is agreed upon.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

The MAH submitted the user text for Macrogol en elektolyten CF 6.9 g. This is the junior version of the macrogol in the present procedure. In the user test 26 questions were asked divided over the several headings of the PIL. Three general questions were asked. In a pilot phase 3 professionals (who had knowledge of the guidelines) gave their opinion. Further on two rounds with each 10 participants were tested. The findability and understanding was categorised in: very easy, easy, slightly difficulty and lots of difficulty. Almost every person scored each question in "very easy", sometimes "easy" and only once "slightly difficulty" was scored.

The MAH did supply a bridging report, which presents the differences between the user-tested PIL of Macrogol en elektolyten CF 6.9 g, powder for oral solution (parent PIL) and the PIL of Macrogol en elektolyten CF 13.7 g, powder for oral solution (daughter PIL). The bridging report presents a side by side comparison of the leaflet text for the parent and daughter PILs. Textual differences are represented for each section, together with the key questions related to this section. Overall, the leaflet content of parent and daughter PIL 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 PIL's.

Conclusion

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

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Macrogol en elektolyten CF 13.7 g and 6.9 g, powder for oral solution have a proven chemical-pharmaceutical quality and are a generic form of Movicolon 13.8 g and Movicolon Junior 6.9 g. 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 en elektolyten CF 13.7 g and 6.9 g with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 25 August 2011. Macrogol en elektolyten CF 13.7 g and 6.9 g, powder for oral solution were authorised in the Netherlands on 29 November 2011.

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 first 5 commercial batches will be tested for microbial control and reconstitution time to support the proposed non-routine testing schedule.
- The first 5 commercial batches will be tested for pH and clarity and colour of the reconstituted solution to support the proposed non-routine testing schedule.
- The first three commercial scale batches will be placed on stability at long term conditions for the proposed shelf-life and at accelerated conditions for 6 months.
- Validation will be conducted on an additional batch(es) of the drug product with three different batch sizes (when additional batches are planned).
- Results with respect to confirmation of the holding time of the bulk blend will be presented once available.
- The water content shelf-life specification will be re-evaluated once additional stability data is available.
- The stability studies will be continued up to the proposed shelf-life. The authorities will be informed in case out of specification results are observed in the mean time.

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 _{1/2}	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