# Public Assessment Report

# Decentralised Procedure

COMPOUND MACROGOL 13.8G POWDER FOR ORAL SOLUTION

**UK/H/4219/001/DC**
**UK Licence No: PL 04416/1319**

**Sandoz Limited**

# LAY SUMMARY

**Macroherm Powder for oral solution, sachet**

**Compound Macrogol 13.8g Powder for Oral Solution (previously called Hermalax Powder for oral solution, sachet).**

(13.125 g macrogol 3350 per sachet, 0.3507 g sodium chloride per sachet, 0.1785 g sodium hydrogen carbonate per sachet and 0.0466 g potassium chloride per sachet, powder for oral solution)

This is a summary of the Public Assessment Report (PAR) for Macroherm Powder for oral solution, sachet (PL 17740/0008; UK/H/4218/001/DC; this licence was cancelled on 17 December 2014) and Compound Macrogol 13.8g Powder for Oral Solution; (PL 04416/1319; UK/H/4219/001/DC) [Compound Macrogol 13.8g Powder for Oral Solution was previously called Hermalax Powder for oral solution, sachet; PL 17740/0009; UK/4219/001/DC]. It explains how Macroherm Powder for oral solution, sachet and Compound Macrogol 13.8g Powder for Oral Solution were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Macroherm Powder for oral solution, sachet and Compound Macrogol 13.8g Powder for Oral Solution.

These products will be collectively referred to as Macrogol throughout the remainder of this public assessment report.

For practical information about using Macrogol, patients should read the package leaflet or contact their doctor or pharmacist.

**What is Macrogol and what is it used for?**
Macrogol is a ‘generic medicine’. This means that Macrogol is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Movicol 13.8 g sachet Powder for Oral Solution (Norgine Limited, UK).

Macrogol is a laxative used for the treatment of long term constipation

**How does Macrogol work?**
Macrogol contains the active ingredients macrogol 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride. Macrogol 3350 belongs to a group of medicines known as osmotically acting laxatives which work by making the patient’s faeces softer and easier to pass, giving the patient relief from constipation. The electrolytes or salts (sodium chloride, sodium hydrogen carbonate and potassium chloride) help maintain the patient’s normal levels of sodium, potassium and water whilst the patient is being treated for constipation.

**How is Macrogol used?**
The pharmaceutical form of this medicine is a powder for oral solution and the route of administration is via the mouth (oral).

For adults, children (aged 12 years and above) and the elderly, the usual dose for constipation is one sachet taken one to three times daily.

**How to mix:**
Open the sachet and pour the contents into a glass. Add about 125 ml or a quarter pint of water to the glass. Stirr well until the powder has dissolved and then drink it.

**Duration of treatment**
This course of treatment for constipation should not normally last longer than 2 weeks. Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

This medicine can be obtained without a prescription.

**What benefits of Macrogol have been shown in studies?**
No additional studies were needed as Macrogol is a generic medicine that is given as an oral solution and contains the same active substance as the reference medicine, Movicol 13.8 g sachet Powder for Oral Solution (Norgine Limited, UK).

**What are the possible side effects of Macrogol?**
Because Macrogol is a generic medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of all side effects reported with Macrogol, see section 4 of the package leaflet available on the MHRA website.

**Why was Macrogol approved?**
It was concluded that, in accordance with EU requirements, Macrogol has been shown to have comparable quality and to be comparable to Movicol 13.8 g sachet Powder for Oral Solution (Norgine Limited, UK). Therefore, the MHRA decided that, as for Movicol 13.8 g sachet Powder for Oral Solution (Norgine Limited, UK), the benefits are greater than their risk and recommended that they can be approved for use.

**What measures are being taken to ensure the safe and effective use of Macrogol?**
Safety information has been included in the Summary of Product Characteristics, healthcare professional leaflet and the package leaflets for Macrogol including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

**Other information about Macrogol**
Austria, Belgium, Germany, Denmark, Finland, Luxemburg, Poland, Sweden and the UK agreed to grant Marketing Authorisations for Macroherm Powder for oral solution, sachet (PL 17740/0008; UK/H/4218/001/DC) and Hermalax Powder for oral solution, sachet (PL 17740/0009; UK/4219/001/DC) to Hermes Arzneimittel GmbH on 20 September 2010. Marketing Authorisations were granted in the UK on 12 October 2010.

Subsequent to a Change of Ownership procedure, the Marketing Authorisation Hermalax Powder for oral solution, sachet (PL 17740/0009; UK/4219/001/DC) was granted to Sandoz Limited on 10 November 2011 (PL 04416/1319; UK/4219/001/DC).

The product name of Hermalax Powder for oral solution, sachet was changed to the current product name, Compound Macrogol 13.8g Powder for Oral Solution on 14 June 2012.

**The marketing Authorisation for Macroherm Powder for oral solution, sachet (PL 17740/0008; UK/H/4218/001/DC) was cancelled on 17 December 2014.**

The full PAR for Macrogol follows this summary.

For more information about treatment with Macrogol read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in May 2015.

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# Scientific discussion during initial procedure

## I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, Austria, Belgium, Germany, Denmark, Finland, Luxemburg, Poland, Sweden and the UK considered that the applications for Macrogol could be approved. These products have a general public licence (P) to be supplied through non-pharmacy outlet and pharmacies. Macrogol are indicated for the treatment of chronic constipation.

These applications for Macrogol are submitted as abridged applications according to Article 10(1) of Directive 2001/83/EC, claiming to be generic medicinal products of Movicol 13.8 g sachet Powder for Oral Solution, first authorised in the UK to Norgine Limited in December 1995.

No new non-clinical studies were conducted, which is acceptable given that the products contain a widely-used, well-known active substance. No clinical studies have been performed and none are required for these applications as the pharmacology of macrogol 3350, sodium chloride, sodium hydrogen carbonate, potassium chloride is well-established.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan.

Subsequent to a Change of Ownership procedure, the Marketing Authorisation Hermalax Powder for oral solution, sachet (PL 17740/0009; UK/4219/001/DC) was granted to Sandoz Limited on 10 November 2011 (PL 04416/1319; UK/4219/001/DC).

The product name of Hermalax Powder for oral solution, sachet was changed to the current product name, Compound Macrogol 13.8g Powder for Oral Solution on 14 June 2012.

**The marketing Authorisation for Macroherm Powder for oral solution, sachet (PL 17740/0008; UK/H/4218/001/DC) was cancelled on 17 December 2014.**

# SCIENTIFIC OVERVIEW AND DISCUSSION

## II QUALITY ASPECTS

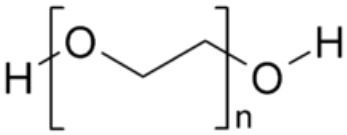
### II.1 Introduction

### II.2 Drug substances

**Macrogol 3350**

INN/Ph.Eur name: Macrogol 3350

Structural formula:



Molecular formula: $H-(OCH_2-CH_2)_n-OH$

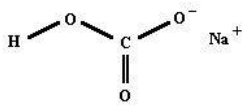
Appearance: White or almost with solid with a waxy or paraffin-like appearance.

Solubility: Very soluble in water and in methylene chloride, very slightly soluble in alcohol, practically insoluble in fatty oils and in mineral oils.

**Sodium Hydrogen Carbonate**

INN: Sodium hydrogen carbonate

Structure:



Physical form: A white powder (crystalline)

Solubility: Sparingly soluble in water

Molecular formula: $NaHCO_3$

Molecular weight: 84.01

**Sodium chloride**

INN/Ph.Eur name: Sodium chloride

Molecular formula: NaCl

Appearance: White, crystalline powder or colourless crystals or white pearls

Solubility: Freely soluble in water, practically insoluble in ethanol.

Molecular weight: 58.4

**Potassium chloride**

INN/Ph.Eur name: Potassium chloride

Molecular formula: KCl

Appearance: White or almost white crystalline powder or colourless crystals.

Solubility: Freely soluble in water, and practically insoluble in anhydrous ethanol.

Molecular weight: 74.6

Macrogol 3350, sodium hydrogen carbonate, sodium chloride and potassium chloride comply with their relevant European Pharmacopoeia monographs.

All aspects of the manufacture of the active substances macrogol 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride from its starting materials are controlled by Certificates of Suitability.

An appropriate retest period has been proposed based on stability data submitted for the active substances.

Appropriate specifications are provided for the active substances, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specifications.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredients. All potential known impurities have been identified and characterised. Suitable Certificates of Analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substances to be physically and chemically stable drugs, and supporting appropriate retest periods.

## II.3 Medicinal Product

### Other Ingredients

Other ingredients are pharmaceutical excipients colloidal anhydrous silica, saccharin sodium, orange flavour (containing flavouring substances and flavouring preparations, maltodextrin, acacia gum and alpha-tocopherol) and lemon lime flavour (consisting of flavouring preparations, maltodextrin, mannitol, gluconolactone, sorbitol (E420), acacia gum, colloidal anhydrous silica).

None of the excipients used contain material of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these products.

### Pharmaceutical Development

The objective of the development programme was to produce products that could be considered generic medicinal products of Movicol 13.8 g sachet Powder for Oral Solution.

The applicant has provided suitable product development sections. Justifications for the use and amounts of each excipient have been provided and are valid.

### Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial-scale batches of each strength have been provided.

**Finished Product Specification**
The finished product specifications proposed for the products are acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

**Container-Closure System**
These products are packaged in sachets composed of paper, ethylene/methacrylic acid co-polymer and aluminium then packed in a carton box.
Pack sizes are 2, 6, 8, 10, 20, 30, 50, 60 (2x30) and 100 (2x50) sachets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with EU legislation regarding contact with food.

**Stability of the product**
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 36 months with storage instructions, 'Do not store above 25 °C'.

For the reconstituted solution the shelf-life is 24 hours with storage conditions 'Store covered in a refrigerator (2 °C to 8 °C)'.

## II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of this application from a pharmaceutical viewpoint.

No user testing results have been submitted for the PIL for this product. A satisfactory bridging report was submitted with a similar PIL for an already approved product, containing Macrogol 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride. The PIL is satisfactory.

## III. NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of macrogol 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride are well-known. As these are widely used, well-known active substances, the applicant has not provided any additional studies and none are required.

The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment

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# IV CLINICAL ASPECTS

## IV.1 Introduction

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier.

## IV.2 Pharmacokinetics and IV.3 Pharmacodynamics

No new pharmacokinetic or pharmacodynamic data were submitted with this application and none were required, as per the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, if the test product is an aqueous oral solution at the time of administration and contains an active substance in the same concentration as an approved oral solution, bioequivalence studies may be waived, if the excipients contained in it do not affect gastrointestinal transit, absorption, solubility or in-vivo stability of the active substance.

## IV.4 Clinical efficacy

No new efficacy data were submitted with this application and none were required.

## IV.5 Clinical safety

No new safety data were submitted with this application and none were required.

## IV.7 Discussion on the clinical aspects

SUMMARY OF PRODUCT CHARACTERISTICS (SPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING

The SmPCs, PILs and labelling are medically satisfactory and consistent with those for the reference product, where appropriate.

CLINICAL EXPERT REPORT

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

MAA FORM

The MAA Forms are medically satisfactory.

## CONCLUSIONS

It is recommended that Marketing Authorisations are granted for these applications.

# V User consultation

No user testing results have been submitted for the PIL for this product. A satisfactory bridging report was submitted with a similar PIL for an already approved product, containing Macrogol 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride. The PIL is satisfactory.

# IV OVERALL CONCLUSION, BENEFIT/ RISK ASSESSMENT AND RECOMMENDATION

## QUALITY

The important quality characteristics of Macrogol are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

## NON-CLINICAL

No new non-clinical data were submitted and none are required for an application of this type.

## EFFICACY

No bioequivalence studies have been performed and none are required for these applications, given the composition of the products and its intended route of administration.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PILs and labelling are satisfactory and consistent with that for the reference product.

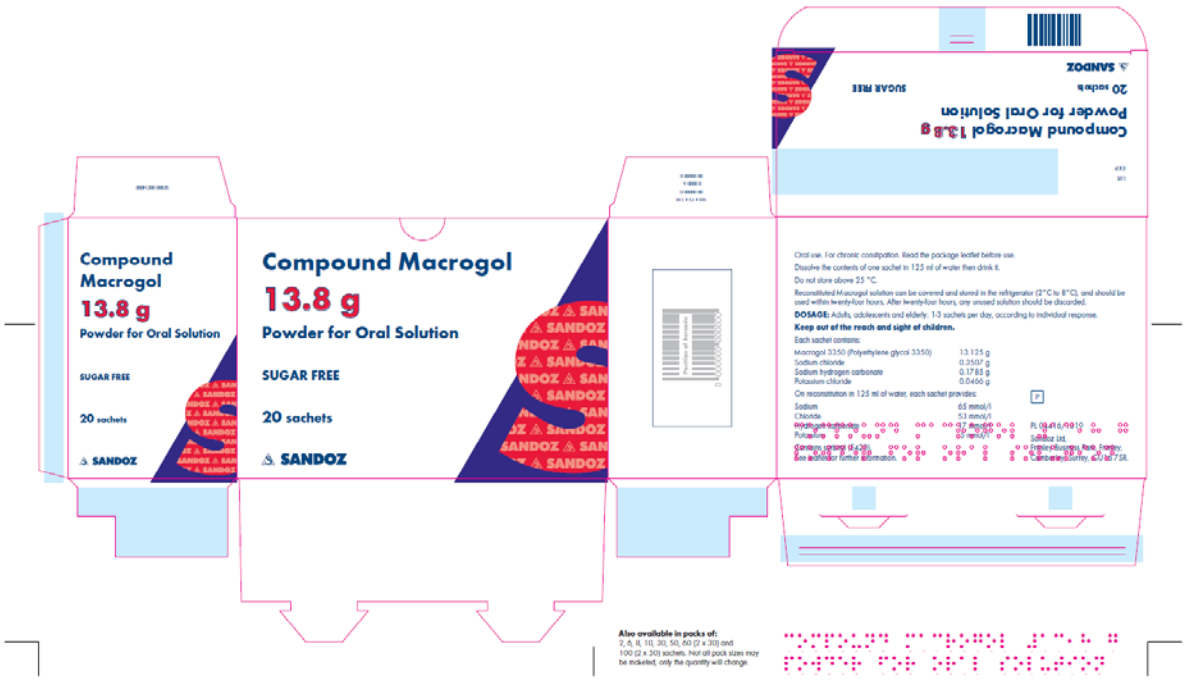
## BENEFIT/RISK ASSESSMENT

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with macrogol 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride is considered to have demonstrated the therapeutic value of the compounds. The risk benefit is, therefore, considered to be positive.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**

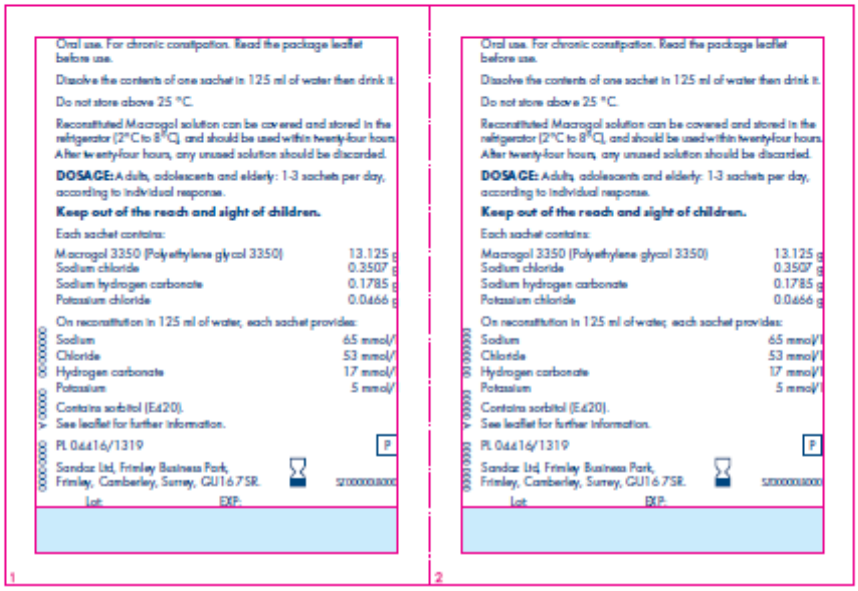
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Macrogol is presented below:





Compound
Macrogol
13.8 g
Powder for Oral Solution
SUGAR FREE
1 sachet
SANDOZ
Compound
Macrogol
13.8 g
Powder for Oral Solution
SUGAR FREE
1 sachet
SANDOZ


Oral use. For chronic constipation. Read the package leaflet before use.
Dissolve the contents of one sachet in 125 ml of water then drink it.
Do not store above 25 °C.
Reconstituted Macrogol solution can be covered and stored in the refrigerator (2°C to 8°C), and should be used within twenty-four hours. After twenty-four hours, any unused solution should be discarded.
DOSAGE: Adults, adolescents and elderly: 1-3 sachets per day, according to individual response.
Keep out of the reach and sight of children.
Each sachet contains:
Macrogol 3350 (Polyethylene glycol 3350) 13.125 g
Sodium chloride 0.3507 g
Sodium hydrogen carbonate 0.1785 g
Potassium chloride 0.0466 g
On reconstitution in 125 ml of water, each sachet provides:
Sodium 65 mmol/l
Chloride 53 mmol/l
Hydrogen carbonate 17 mmol/l
Potassium 5 mmol/l
Contains sorbitol (E420).
See leaflet for further information.
PL 04416/1319
P
Sandoz Ltd, Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR.
Lot
EXP:
1
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# STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

| Scope | Procedure number | Product Information affected | Date of start of the procedure | Date of end of procedure | Approval/ non approval | Assessment report attached |
|---|---|---|---|---|---|---|
| PL 17740/0008-0018 | N/A | Licence cancellation | N/A | Licence was cancelled on 17/12/2014 | Approved | No |
| Change of owenership procedure for PL 17740/0009 to PL 04416/1319 (Sandoz Limited) | N/A | Change of ownership | N/A | Change of ownership procedure from Hermes Arzneimittel GmbH to Sandoz Limited on 10/11/2011 | Approved | No |
| For PL 04416/1319-0002; To change the name of the product in the UK from Hermalax, powder for oral solution to Compound Macrogol 13.8g Powder for Oral Solution | UK/H/4219/ 001/IB/003 | SmPC, PIL and labelling | 29/02/2012 | 30/03/2012 | Approved on 14/06/2012 | No |
| For PL 04416/1319-0022: To update sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8 and 5.3 of the SmPC and consequentially the leaflet as the result of a repeat use procedure UK/H/4219/001 /E01 (End of procedure, Day 90: 03/06/2013) as a fulfilment of the commitment made by the applicant also in line with the | UK/H/4219/ 001/II/018 | SmPC and PIL. | 17/10/2014 | 08/04/2015 | Approved on 21/04/2015 | Yes-see annex 1 |

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|---|---|---|---|---|---|---|
| QRD template. | | | | | | |

## ANNEX 1

**Our Reference:** PL 04416/1319-0022

**Product:** Compound Macrogol 13.8g Powder for Oral Solution

**Marketing Authorisation Holder:** Sandoz Limited
**Active Ingredient(s):** macrogol 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride

**Type of Procedure:** Mutual Recogniton
**Submission Type:** Variation
**Submission Category:** Type II
**Submission Complexity:** Standard
**EU Procedure Number (if applicable):** UK/H/4219/001/II/018

**Reason:**
To update sections 4.1 (Therapeutic indications), 4.2 (Posology and method of administration), 4.4 (Special warnings and precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction), 4.6 (Fertility, pregnancy and lactation), 4.8 (Undesirable effects), 5.1 (Pharmacodynamic properties) and 5.3 (Preclinical safety data) of the SmPC and consequentially the leaflet to fulfil a regulatory commitment agreed during the mutual recognition procedure UK/H/4219/001/E01 (concluded on 03/06/2013). The product information (SmPC and PIL) has also been revised in line with the QRD template.

**Supporting Evidence**
Revised SmPC fragments and PIL.

**Evaluation**
The proposed changes to the SmPC and PIL are acceptable. The updated SmPC fragments and PIL have been incorporated into the Marketing Authorisation.

**Conclusion**
Approved on 28 April 2015.