Public Assessment Report

National Procedure

Macrogol 10 g powder for oral solution

Macrogol 4000

PL 16363/0562

Milpharm Limited
LAY SUMMARY

Macrogol 10 g powder for oral solution
macrogol 4000

This is a summary of the Public Assessment Report (PAR) for Macrogol 10 g powder for oral solution. It explains how Macrogol 10 g powder for oral solution was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Macrogol 10 g powder for oral solution.

This product will be referred to as Macrogol in this lay summary for ease of reading.

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?
This application is for a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised in the UK called Dulcobalance powder for oral solution in sachet (PL 34926/0018).

Macrogol is used for the treatment of constipation in adults and children aged 8 years and over.

How does Macrogol work?
Macrogol contains the active substance macrogol 4000 and belongs to a group of medicines called osmotic laxatives. Macrogol carries water to the stool, which loosens and increases stool volume, helping to overcome sluggish bowels. Macrogol is not absorbed into the bloodstream or broken down in the body.

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

Adults and children over 8 years
The recommended dose is one to two sachets per day, preferably taken as a single dose in the morning.

The patient should start by taking one sachet each day and if needed increase to two sachets each day.

The daily dose can be adjusted according to the effect obtained and may range from one sachet every other day (especially in children) up to a maximum of two sachets per day.

The contents of the sachet should be dissolved in a glass of water (at least 50 ml) immediately before drinking the liquid.

For further information on how Macrogol is used, refer to the package leaflet and Summary/Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can be obtained without a prescription.
What benefits of Macrogol have been shown in studies?
Macrogol is a generic medicine that fulfills criteria meaning that no additional studies are required. Macrogol has been considered a generic medicine of the reference medicine based on a comparison of their physical and chemical characteristics. Further information is provided in the main body of the PAR.

What are the possible side effects of Macrogol?
Because Macrogol is a generic medicine, its benefits and possible side effects are considered to be the same as for the reference medicine.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the Summary of Product Characteristics (SmPC) available on the MHRA website.

Why was Macrogol approved?
It was concluded that, in accordance with EU requirements, Macrogol has been shown to be comparable to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Macrogol?
A Risk Management Plan (RMP) has been developed to ensure that Macrogol is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet, 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 and reviewed continuously.

Other information about Macrogol
A Marketing Authorisation for Macrogol was granted in the UK on 15 February 2019.

The full PAR for Macrogol follows this summary.

This summary was last updated in April 2019.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Macrogol 10 g powder for oral solution (PL 16363/0562) could be approved.

The product is indicated for the symptomatic treatment constipation in adults and children aged 8 years and above. An organic disorder should have been ruled out before initiation of treatment.

Macrogol should remain a temporary adjuvant treatment to appropriate lifestyle and dietary management of constipation, with a maximum 3-months treatment course in children. If symptoms persist despite associated dietary measures, an underlying cause should be suspected and treated.

High molecular weight (4000) macrogols are long linear polymers which retain water molecules by means of hydrogen bonds. When administered by the oral route, they lead to an increase in volume of intestinal fluids. The volume of unabsorbed intestinal fluid accounts for the laxative properties of the solution.

This application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, for a generic medicine. The reference medicinal product is Dulcobalance (PL 34926/0018) which was granted a product licence in the UK to Ipsen Limited, UK on 18 January 2002.

No new non-clinical studies were conducted, which is acceptable given that the application is based on being a generic medicinal product of a reference product that has been licensed for over 10 years.

A biowaiver was submitted with this application, which was accepted. No bioequivalence study was required, and no new clinical studies were provided with this application.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A Marketing authorisation was granted for this product on 15 February 2019.
II QUALITY ASPECTS

II.1 Introduction
This product consists of sachets containing 10 g of macrogol 4000. In addition to macrogol 4000, this product also contains the excipients saccharin sodium, Orange Grape Fruit Flavour (contains orange oil, grape fruit oil, orange juice, citral, acetaldehyde, linalool, ethyl butyrate, alpha terpeniol, octonal, beta & gamma hexenol, maltodextrin, gum arabic, sorbitol (E420), butylated hydroxyanisole (E320)).

The finished product is packed in paper/polyethylene/aluminium/polyethylene sachets and supplied in pack sizes of 10, 20 and 30 sachets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE
rINN: macrogol 4000
Chemical Name: Macrogols
Molecular Formula: H-[OCH₂-CH₂]ₙ-OH
Molecular Weight: 4000 (average)
Appearance: white or almost white solid with a waxy paraffin like appearance
Solubility: very slightly soluble in alcohol and practically insoluble in fatty oils and in mineral oils.

Macrogol 4000 is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCT
Pharmaceutical development
A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the manufacture of the final product.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.
Finished Product Specification
The finished product specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf life of 2 years, without special storage conditions, is acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of macrogol 4000 are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided, and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology
No new toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of macrogol 4000 are well-known. According to the regulatory requirements, the applicant has provided a suitable biowaiver and a bioequivalence study is not required for this product. An overview based on a literature review is, thus, satisfactory.

IV.2 Pharmacokinetics
No new pharmacokinetic data have been submitted for this application and none were required.

IV.3 Pharmacodynamics
No new pharmacodynamic data have been submitted for this application and none were required.
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. The safety profile for this product is considered to be the same as Dulcobalance (PL 34926/0018).

IV.6 Risk Management Plan (RMP)
The Applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. The Applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects
The grant of a marketing authorisation is recommended for this application.

V USER CONSULTATION
A user consultation with target patient groups on the PIL has been performed on the basis of a bridging report making reference to Dulcosoft 10 g powder for oral solution (PL 04425/0725) in terms of content and metoprolol in terms of layout. The bridging report submitted by the MAH is acceptable.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with macrogol 4000 is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.
Macrogol 10 g powder for oral solution

Each sachet contains 10 g of macrogol 4000.
Each sachet contains 4 mg of amylase.
Oral use.
Swallow the contents of the sachet whole.

Macrogol powder for oral solution
30 sachets

MILPHARM

The recommended dose is 1 to 2 sachets daily, preferably taken as a single dose in the morning.
Dissolve the contents of the sachet in a glass of water (at least 50 ml) just before use.

Batch Details

10 g

PL 16363/0562

MILPHARM

MILPHARM Limited

Amadeus Business Park

Rutland Way (B2) Limited

United Kingdom

Code: A09K12/14/7015

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Code: A09K12/14/7015
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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the product licence are recorded in the current SmPC and/or PIL available on the MHRA website.

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