IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Wecol 6.9 g powder for oral solution
Sodium hydrogen carbonate
Potassium chloride
Sodium chloride
Macrogol 3350
PA23138/001/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/5695/001/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 01/05/2020 under procedure number IE/H/1130/001/DC.

Please note the following detail for the product in IE:
Marketing Authorisation Number: PA23138/001/001
Marketing Authorisation Holder: Stirling Anglian Pharmaceuticals Ireland Limited

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for CosmoCol Half & Paediatric 6.9 g, powder for oral solution (PL 42582/0007-0008; UK/H/5695 & 5696/001/DC) could be approved. CosmoCol Half 6.9 g, powder for oral solution is a pharmacy (P) medicine for the treatment of chronic constipation in adults, adolescents and the elderly and for resolving faecal impaction in adults, adolescents and the elderly. Faecal impaction is defined as refractory constipation with faecal loading in the rectum and/or colon confirmed by physical or radiological examination of the abdomen and rectum.
CosmoCol Paediatric 6.9 g, powder for oral solution is a prescription-only medicine (POM) for the treatment of chronic constipation in children aged 2 to 11 years and for the treatment of faecal impaction in children aged 5 years or above. Faecal impaction is defined as refractory constipation with faecal loading in the rectum and/or colon.

The applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Ireland as Concerned Member State (CMS). The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The reference medicinal products for these applications are Movicol Half 6.9g sachet, powder for oral solution which was originally granted in the UK on 16 October 2002 to Norgine Limited (PL 00322/0080) and Movicol Paediatric 6.9g sachet, powder for oral solution which was originally granted in the UK on 24 September 2003 to Norgine Limited (PL 00322/0082) and subsequently underwent a change of ownership procedure on 26 March 2008 to the current licence holder Norgine Pharmaceuticals Limited (PL 20011/0004).

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.

Macrogol 3350 is a large polymer with substantial osmotic activity. Macrogol 3350 binds molecules of water. When macrogol 3350 is administered by mouth, the resulting hydration of the colonic content facilitates transit and defaecation. Macrogol 3350 is chemically inert and cannot be metabolised by colonic bacteria, thus ingested macrogol 3350 is delivered quantitatively to the colon. Macrogol 3350 obligates intraluminal water and exerts its substantial osmotic activity, leading to modification of stool consistency and increased faecal bulk (*Schiller, Emmett et al. 1988; Attar, Lemann et al. 1999*). Due to little fluid exchange across the intestinal barrier (mucosa), the potential for systemic electrolyte disturbance is limited. Balanced electrolytes in the macrogol 3350 solution prevent net gain or loss of serum electrolytes across the mucosa and their loss through faecal water. As a result of the osmotic effect of the macrogol 3350 polymer, the electrolyte solution is retained in the colon. The mechanism of laxative action is accounted for by the osmotic activity of macrogol 3350 with balanced electrolytes. The non-absorption of macrogol 3350 together with its ability of water-binding due to hydrogen binding accounts for the dose-dependent effect of macrogol 3350 on stool weight, consistency, and colon transit time. The volume of non-absorbable fluid softens the hard stool. Dehydration does not occur, because the solution is isotonic.

No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

No new clinical data have been submitted and none are required for applications of this type. A bioequivalence study was not necessary to support these applications as both test and reference products are aqueous oral solutions at the time of administration and given that the products act locally in the gastrointestinal tract.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.
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 and CMS considered that the applications could be approved at the end of procedure (Day 210) on 11 January 2015. After a subsequent national phase, licences was granted in the UK on 03 February 2015.

II. QUALITY ASPECTS

II QUALITY ASPECTS

II.1 Introduction

One sachet of CosmoCol Half and Paediatric 6.9 g, powder for oral solution contains the following active ingredients:

- Macrogol 3350, 6.563 g
- Sodium chloride, 0.1754 g
- Sodium hydrogen carbonate, 0.0893 g
- Potassium chloride, 0.0233 g

The contents of electrolyte ions when one sachet is dissolved in 62.5 ml of water is:

- Sodium 65 mmol/l
- Chloride 53 mmol/l
- Hydrogen carbonate 17 mmol/l
- Potassium 5.0 mmol/l

Other ingredients consist of the following pharmaceutical excipients colloidal anhydrous silica, saccharin sodium, orange flavour and lemon lime flavour (consisting of sorbitol (E420) and alpha-tocopherol (E307)). The finished product is packed into a sachet comprised of a four-layer laminate film consisting of ionomer coex, aluminium, polyethylene and paper. The product is available in pack sizes of 6, 8, 10, 20, 30, 40, 50, 60 and 100 sachets. Not all pack sizes may be marketed. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2. Drug Substances

All aspects of the manufacture and control of the active substances, macrogol 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

Where appropriate, suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Where appropriate, stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, powder for oral solution containing 6.563 g of macrogol 3350, 0.1754 g of sodium chloride, 0.0893 g of sodium hydrogen carbonate and 0.0233 g of potassium chloride per sachet that was comparable in performance to the originator products Movicol Half 6.9g sachet, powder for oral solution (Norgine Limited) and Movicol Paediatric 6.9g sachet, powder for oral solution (Norgine Pharmaceuticals Limited). A satisfactory account of the pharmaceutical development has been provided.

Comparable *in-vitro* dissolution profiles have been provided for these products and the reference products.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the orange and lemon lime flavours which are controlled to suitable in-house specifications. In addition, confirmation has been provided that the orange and lemon lime flavours comply with Directive 88/388/EEC. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product
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 at commercial-scale batch size and shown satisfactory results.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years for the unopened sachet with the storage conditions 'Do not store above 25°C.'

The in-use shelf life for the reconstituted solution is as follows:
CosmoCol **Half** 6.9 g, powder for oral solution (once reconstituted):
Discard any solution not used within 6 hours and store at 2 - 8°C (refrigerated and covered).

CosmoCol **Paediatric** 6.9 g, powder for oral solution (once reconstituted):
The shelf life of the reconstituted solution is 24 hours with the storage conditions 'Store in a refrigerator (2 °C - 8 °C) and covered.'

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of these applications from a pharmaceutical viewpoint.

II.5 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.

III. NON-CLINICAL ASPECTS

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of macrogol 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride 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.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since CosmoCol Half and Paediatric 6.9 g, powder for oral solution are 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.6 Discussion on the non-clinical aspects

No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

There are no objections to the approval of these applications from a non-clinical viewpoint.

IV. CLINICAL ASPECTS

IV CLINICAL ASPECTS

IV.1 Introduction

As per the guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), "bioequivalence studies are generally not required if the test product is to be administered as an aqueous oral solution containing the same active substances as the currently approved product."
In addition, the excipients do not affect the gastrointestinal transit, the absorption, solubility or in-vivo stability of the active substances.
No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of macrogol 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride.

Based on the data provided, CosmoCol Half & Paediatric 6.9 g, powder for oral solution can be considered bioequivalent to Movicol Half 6.9g sachet, powder for oral solution (Norgine Limited) and Movicol Paediatric 6.9g sachet, powder for oral solution (Norgine Pharmaceuticals Limited).

IV.2 Pharmacokinetics

In line with the guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), the test product is to be administered as an aqueous oral solution containing the same active substance as the currently approved product. No bioequivalence study has been submitted with these applications and none are required.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for an application of this type.

IV.5 Clinical safety

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

IV.6 Risk Management Plan (RMP)

The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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 CosmoCol Half & Paediatric 6.9 g, powder for oral solution.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary table of safety concerns:

Summary of safety concerns	
Important identified risks	Immune system disorders • Hypersensitivity including anaphylactic reaction Metabolism and nutrition disorders • Imbalance of fluids or electrolytes (e.g. oedema, shortness of breath, increasing fatigue, dehydration, cardiac failure) Important interactions • Decreased efficacy with some concomitantly administered medicinal products, e.g. anti-epileptics <u>With regard to the lemon lime flavour of the product:</u> Congenital familial and genetic disorders • Risk in patients with hereditary fructose intolerance <u>With regard to CosmoCol Paediatric & CosmoCol Half:</u> Congenital familial and genetic disorders • Risk in patients with glucose-galactose malabsorption
Important potential risks	<u>With regard to CosmoCol Paediatric & CosmoCol Half:</u> • Risk in patients with impaired gag reflex • Risk in patients with reflux oesophagitis • Risk in patients with reduced levels of consciousness
Important missing information	<u>With regard to Cosmocol Orange Lemon and Lime):</u> • Use in pregnancy and lactation

Summary table of risk minimisation measures:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Hypersensitivity including anaphylactic reaction	1. Routine pharmacovigilance monitoring 2. Proposed text in SmPC 3. Proposed text in PIL	None proposed
Imbalance of fluids or electrolytes (e.g. oedema, shortness of breath, increasing fatigue, dehydration, cardiac failure)	1. Routine pharmacovigilance monitoring 2. Proposed text in SmPC 3. Proposed text in PIL	None proposed
Decreased efficacy with some concomitantly administered medicinal products, e.g. anti-epileptics	1. Routine pharmacovigilance monitoring 2. Proposed text in SmPC 3. Proposed text in PIL	None proposed
Risk in patients with glucose-galactose malabsorption	1. Routine pharmacovigilance monitoring 2. Proposed text in SmPC 3. Proposed text in PIL	None proposed
Important Potential risks		
Risk in patients with impaired gag reflex	1. Routine pharmacovigilance monitoring 2. Proposed text in SmPC 3. Proposed text in PIL	None proposed
Risk in patients with reflux oesophagitis	1. Routine pharmacovigilance monitoring 2. Proposed text in SmPC 3. Proposed text in PIL	None proposed
Risk in patients with reduced levels of consciousness	1. Routine pharmacovigilance monitoring 2. Proposed text in SmPC 3. Proposed text in PIL	None proposed
Missing information		
Not applicable	-	-

No new risks have been identified for these generic products, which are not recognised for the reference products. Overall, the proposed RMP has adequately captured the important identified and potential risks associated with the drug substances.

IV.7 Discussion on the clinical aspects

No new clinical studies were conducted, which is acceptable given that the applications were based on

being generic medicinal products of originator products that have been licensed for over 10 years.

A bioequivalence study was not necessary to support these applications as both test and reference products are aqueous oral solutions at the time of administration and given that the products act locally in the gastrointestinal tract.

The grant of marketing authorisations is recommended for these applications.

V User consultation

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 language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability, as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

V. OVERALL CONCLUSIONS

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 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride is considered to have demonstrated the therapeutic value of the compounds. The benefit-risk is, therefore, considered to be positive.

VI. REVISION DATE

28/02/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From UK/H/5695/001/DC to IE/H/1130/001/DC			
MAH transfer				18/12/2020