IPAR

Public Assessment Report for a Medicinal Product for Human Use

Scientific discussion

Laxaclear 5.9g Powder for Oral Solution
MACROGOL 3350
PA0294/022/001

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.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy from Helsinn Birex Pharmaceuticals Ltd., the HPRA has granted a marketing authorisation for Laxaclear 5.9g Powder for Oral Solution, on 16th August 2013 as a short term laxative in cases of constipation in adults, adolescents and the elderly.

This application for a marketing authorisation was submitted in accordance with Article 10a of Directive 2001/83/EC and is referred to as a 'well established use' application. This means that the Marketing Authorisation Holder for Laxaclear has replaced the results of pre-clinical and clinical trials by detailed references to published scientific literature as it has been demonstrated that the active substance of the medicinal product has been in well established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety.

Laxaclear Powder for Oral Solution has been developed as a small-sachet presentation from the product Klean-Prep Powder for Oral Solution (PA 294/17/1 first authorised in Ireland in June 1988 and currently marketed) with the following proposed indication: For use as a short term laxative in cases of constipation in adults, adolescents and the elderly. Klean-Prep Powder for oral solution has been approved in Ireland since 1988 for the purpose of bowel cleansing prior to investigations or surgery and since 2002 for use as a short term laxative in cases of constipation .

The proposed indication for Laxaclear 5.9 g sachet, powder for oral solution is for the short term treatment of constipation. The active substance in Klean Prep Powder and Laxaclear is Macrogol 3350 with strength of 59 g for Klean-Prep and strength of 5.9 g for Laxaclear.

The applicant has applied for a classification of 'not subject to prescription' and for a supply designation of 'supply through pharmacies only' with promotion to the general public and healthcare professionals.

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

Name of the product	Laxaclear
Name(s) of the active substance(s) (INN)	MACROGOL 3350
Pharmacotherapeutic classification (ATC code)	A06AD65
Pharmaceutical form and strength(s)	5.9g Powder for Oral Solution
Marketing Authorisation Number(s) in Ireland (PA)	PA0294/022/001
Marketing Authorisation Holder	Helsinn Birex Pharmaceuticals Limited

II QUALITY ASPECTS

II.1. Introduction

This application is for Laxaclear 5.9g Powder for Oral Solution.

II.2 Drug substance

The active substance is Macrogol 3350, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Laxaclear Powder for Oral Solution is a white or almost white granular powder for oral solution which on reconstitution gives a clear colourless solution with a characteristic flavour of vanilla.

Each sachet contains 5.9g of Macrogol 3350, sodium sulphate anhydrous, sodium hydrogen carbonate, sodium chloride, potassium chloride, aspartame and vanilla flavour.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at a suitably qualified manufacturing site.

The manufacturing process has been validated according to relevant European and ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer’s specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for oral powders, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The product is packaged into sachets which are composed of coated paper, polyethylene, aluminium foil and surlyn. The sachets are then placed in a cardboard carton.

The surlyn portion of the laminate, which is in contact with the product, complies with the requirements for materials intended to come into contact with foodstuffs and is in compliance with Directive 10/2011/EC.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for 3 years when stored below 25°C.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Laxaclear 5.9g Powder for Oral Solution.

III NON-CLINICAL ASPECTS

III.1 Introduction

III.2 Pharmacology

The pharmacology of Macrogol 3350 is well characterised. Macrogol 3350 is an osmotic laxative. It increases stool frequency and accelerates the transit of intestinal contents through the large bowel. Macrogol 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 defecation. Electrolytes combined with macrogol 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.

III.3 Pharmacokinetics

The pharmacokinetics of polyethylene glycol 3350 (PEG 3350) have not been fully described because of lack of a sufficiently sensitive analytical method. It has generally been accepted that the absorption of (high molecular mass) PEG is negligible *(Brady et al, 1986)*. Macrogol is unchanged along the gut. It is virtually unabsorbed from the gastro-intestinal tract. Any macrogol that is absorbed is excreted via the urine.

III.4 Toxicology

No new information has been submitted

III.5 Ecotoxicity/environmental risk assessment

A formal ERA has not been submitted. This is acceptable.

III.6 Discussion on the non-clinical aspects

The non-clinical characteristics of macrogol are well defined. No new pre-clinical issues have been raised in the context of this assessment.

IV CLINICAL ASPECTS

IV.1 Introduction

Macrogol 3350 is a well known active substance with established efficacy and safety.

IV.2 Pharmacokinetics

The pharmacokinetics of polyethylene glycol 3350 (PEG 3350) have not been fully described because of lack of a sufficiently sensitive analytical method. It has generally been accepted that the absorption of (high molecular mass) PEG is negligible *(Brady et al, 1986)*. Macrogol is unchanged along the gut. It is virtually unabsorbed from the gastro-intestinal tract. Any macrogol that is absorbed is excreted via the urine.

IV.3 Pharmacodynamics

The pharmacology of Macrogol 3350 is well characterised. Macrogol 3350 is an osmotic laxative. It increases stool frequency and accelerates the transit of intestinal contents through the large bowel. 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 defecation. 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.

IV.4 Clinical Efficacy

Klean Prep (Macrogol 3350) was first licensed in Ireland in 1988. A number of other Macrogol products with an indication for constipation have been licensed since then. Therefore the efficacy of this osmotic laxative is well characterised. The applicant has submitted a clinical overview which provides information from three systematic reviews, a range of controlled (both placebo and active control) and open label non-controlled studies.
Two of the systematic reviews are further discussed below. One review was omitted as one of the authors worked for a manufacturer of a macrogol product. In addition it was felt that the Cochrane systematic review was more methodologically robust.
Lee-Robichaud[1] et al conducted a Cochrane systematic review of lactulose (another osmotic laxative) versus Polyethylene Glycol (including PEG 3350 and PEG 4000). The review included 10 randomised controlled trials which had enrolled a total of 868 participants who had been randomised to receive either lactulose or PEG either for chronic constipation or faecal impaction.
Participants ranged in age from 3 months to 70 years. Four studies recruited adults only.

Overall PEG was better than lactulose in terms of stool frequency per week, form of stool, relief of abdominal pain and the need for additional products.
Similar results on sub-group analysis (apart from relief of abdominal pain) were noted for children.
A systematic review of Macrogol laxatives in children with functional constipation and faecal impaction identified seven RCTs (of which five involved a comparison with lactulose, one with placebo and one with milk of magnesia).[2] Because of differences in study design, populations and treatment protocols a meta-analysis could not be carried out. Overall the five studies comparing Macrogol and lactulose concluded that the efficacy of Macrogol was at least as good as, if not better than lactulose or milk of magnesia over a wide range of doses and treatment durations.

The indication sought for this application is for the short term treatment of constipation (i.e. 5 days). Given the evidence of efficacy in chronic constipation and faecal impaction it is likely that Laxaclear will have efficacy in the short term treatment of chronic constipation.

IV.5 Clinical Safety

The applicant provided a review of safety in the Clinical Overview including a brief review of safety with non-prescription macrogol products.
As this is the first national application in Ireland for a non-prescription macrogol product and no macrogol non-prescription products are marketed in Ireland , the safety review will be considered in the context of the criteria for a

prescription medicine.
The safety of macrogol products is well characterised. The applicant reviewed 26 trials, including adults, elderly and children and adolescents. In these studies 1065 adult patients were treated in 13 studies, including at least 204 elderly (age ≥65) patients in 4 studies and 525 children or adolescents in 13 studies. Non-prescription products (Forlax, Transipeg, and Movicol) were used in 714 patients in 10 studies. Prescription-only products (Normopeg, MiraLAX [subsequently reclassified to OTC in 2006 by the FDA], Go-Lytely Lax, Isocolan, Colonsoft, and Pegorion) were used in 16 studies in 876 patients.

Long-term (2 weeks to 2 years) studies included 1315 patients in 20 studies; short-term (3 days to 2 weeks) studies included 275 patients in 6 studies. In adults (including elderly) the dosing ranged from 5.9 to 29.2 g/day, in children and adolescents from 0.25 to 1 g/kg body weight per day (dosing of non-prescription products: 5.9 to 23.6 g/day (133 ptyr); dosing of prescription-only products: 12 to 29.2 g/day (109 ptyr).

In clinical trials, the most frequent adverse effects of PEG were: abdominal pain, diarrhoea (being dose-dependent), nausea, vomiting, abdominal distension, flatulence and borborygmi. Mild and subclinical hyponatraemia were seen in preparations without electrolytes.
In rare cases, allergic reactions (pruritus, urticaria, dyspnoea), including anaphylaxis were seen. The overall safety profile of PEG in placebo-controlled trials was similar to that of placebo.
The safety data of PEG 3350 or 4000 in the elderly (≥65 years) was similar to those seen in other adult groups. The safety profile of PEG preparations was similar in children and adolescents. All reports concluded that PEG is safe for use as a laxative in these age groups.

Special considerations for non-prescription use.

Use without medical supervision
In general, constipation is a long-lasting problem for which patients seek medical advice infrequently. Although the ROME diagnostic criteria for constipation were developed to standardise the definition of constipation for enrolment in clinical trials, no widely accepted, clinically useful definition of constipation exists. Physicians typically define constipation on the basis of stool frequency, with fewer than 3 bowel movements per week considered abnormal. However, patients typically report other symptoms, such as straining, passage of hard stool, inability to defecate at will, unproductive urges, and sensation of incomplete evacuation *(Johanson, 2007).* Such symptoms are easily recognizable to the patient, and self-diagnosis of constipation is therefore not a problem.

The safety and efficacy profile of PEG-containing preparations is more favourable than those of other laxatives. While under medical supervision they can be used indefinitely; as non-prescription products, such preparations are indicated mainly for the short-term therapy of constipation. Although Macrogol 3350 5.9g is indicated for short-term treatment of constipation, in an open-label trial, *Di Palma* et al (2007) have found that polyethylene glycol (PEG 3350) laxative is safe and effective for treating constipation in adult and elderly patients for periods up to 12 months, with no evidence of tachyphylaxis.
Allergy to PEG or to the excipients may be a problem, but this happens only rarely and is unrelated to the method of sale (prescription-only or non-prescription).
No overdoses with PEG 3350 (or 4000) have been reported. Higher doses are not harmful, but a more pronounced laxative effect may be expected.

Masking deterioration of an underlying condition by symptomatic treatment
Constipation may be caused by a large number of diseases or drugs. Ulcerative colitis and/or Crohn's disease are severe conditions, and such patients are under medical supervision. Perforation is an acute condition with severe symptoms. Macrogol 3350 5.9 g is contraindicated in such conditions, in line with other osmotic laxatives. Patients with these conditions are either already under medical supervision, or due their nature the patients will seek medical, rather than pharmacist advice. An otherwise healthy individual with recurrent symptoms of constipation is likely to seek the pharmacist's advice first. If there is an underlying disease, there are either other symptoms, or the constipation will increase in severity over time, necessitating medical advice. It is very unlikely that in a healthy individual, without other symptoms, this laxative may mask an underlying disease.

However, colorectal cancers of the lower tract may change bowel habits and may present as constipation.
Bowel symptoms are often considered an indication to perform colonoscopy to identify or rule out colorectal cancer or

precancerous polyps. Investigation of bowel symptoms for this purpose is recommended by numerous clinical guidelines. However, the evidence for this practice is unclear.

According to a meta-analysis (*Adelstein et al, 2011),* current evidence suggests that the common practice of performing colonoscopies to identify cancers in people with bowel symptoms is warranted only for rectal bleeding (odds ratio [OR] 2.6) and the general symptom of weight loss (OR 2.9). The OR for constipation was only 1.1.

There is uncertainty as to whether constipation is associated with colorectal cancer. A study provided data from the largest single-centre experience so far reported in the literature and confirms that the yield of diagnostic colonoscopy in patients with constipation without 'high-risk' symptoms is low *(Obusez et al, 2011)*.
The patient information leaflets for non-prescription PEG laxatives advise the patient to seek medical advice should the product be ineffective after 5 days in order to prevent missed diagnosis.

Potential for misuse
The misuse of this product, similarly to other non-prescription (and prescription) laxatives, cannot be excluded. Abuse of laxatives is not an uncommon occurrence in the general population and is quite frequent among certain groups, such as in those with eating disorders. Both patients with anorexia nervosa and bulimia nervosa utilize laxatives in an attempt to reduce weight and remove unwanted calories, neither of which is possible with laxatives as the majority of calories from food intake are absorbed in the small intestine. Other groups that may utilize laxatives in an unhealthy way include athletes and the elderly. The motivation in the elderly group is often based on rigid and sometimes false conceptions about the need for daily bowel movements. This type of use can be difficult to identify as the individual may start out with legitimate constipation related to other disease states or concomitant medication use. However, when the frequency and duration of use exceeds the need, medical complications may occur *(Roerig et al, 2010)*.
The proportion of patients misusing PEG laxatives cannot be exactly estimated, although it is known that misuse of *stimulant* laxatives occurs more frequently *(Roerig et al, 2010)*. This may be related to the quick action of stimulants, many of which exert their effect overnight, compared to 24-48 hours required for onset of laxative effect with PEG. Patients may erroneously believe that they can avoid the absorption of calories with faster-acting laxatives. Furthermore, considering the widespread availability of laxatives for general sale (e.g. magnesium sulphate or magnesium hydroxide laxatives, herbal laxatives, laxatives purchased over the internet), any potential misuse of a product sold under the care of a pharmacist is expected to be low.

Conclusion on clinical aspects
Constipation is a condition which can be self-diagnosed and self managed. The indication sought in this application is for short term treatment of constipation (5 days). There is a low potential for the masking of a serious underlying condition and for potential misuse of macrogol. However these risks are unlikely to be higher than those associated with other non-prescription laxatives available in Ireland (e.g. lactulose another osmotic laxative).

Risk Management Plan
A risk management plan has not been submitted. The applicant's reasoning for not submitting an RMP are accepted.

Schedule for submission of Periodic Safety Update Reports (PSUR)
PSUR submissions are not required for this product as per the *List of EU reference dates and frequency of submission of PSURs.*

The Marketing Authorisation Holder submitted a set of documents describing the Pharmacovigilance System, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

IV.6 Discussion on the clinical aspects
The pharmacodynamics, efficacy and safety of Macrogol are well characterised. Macrogol products have been approved on a prescription only basis in Ireland since 1988.

Constipation is a condition which can be self-diagnosed and self managed. The indication sought in this application is for the short term treatment of constipation (5 days). There is a low potential for the masking of a serious underlying condition and for potential misuse of macrogol. However these risks are unlikely to be higher than those associated with other non-prescription laxatives available in Ireland (e.g. lactulose another osmotic laxative).

No objections have been raised by the Prescription Status Advisory Group of the HPRA to this switch application.

Therefore it is concluded that the benefit risk profile for Laxaclear 5.9g is positive in the non-prescription pharmacy only setting.

V OVERALL CONCLUSIONS

Laxaclear Powder for Oral Solution has been developed as a small-sachet presentation from the product Klean-Prep Powder for Oral Solution (PA 294/17/1 first authorised in Ireland in June 1988 and is currently marketed) with the following proposed indication: for use as a short term laxative in cases of constipation in adults, adolescents and the elderly.

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

The HPRA, on the basis of the data submitted, considered that Laxaclear 5.9g Powder for Oral Solution demonstrated adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

Following MRP/DCP procedure:
Discussion in CMD(h), specific obligations, follow-up measures, if applicable

References

1. Lee-Robichaud H, Thomnas K, Morgan J, Nelson RL. Lactulose versus Polyethylene Glycol for Chronic Constipation (Review) Cochrane Database of Systematic Reviews 2010, Issue 7. Art. No. :CD007570. DOI 10.1002/14651858.CD007570.pub2.
2. Candy D, Belsey J. Macrogol (polyethylene glycol) laxatives in children with functional constipation and faecal impaction: a systematic review. Arch Dis Child 2009; 94: 156-160

VI REVISION DATE

December 2014

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	Approval/ non approval
Type IB – category A.2.B Change in the (invented) name of the medicinal product in Ireland from Birapeg to Laxaclear - change to SPC sections 1, 2, 4.2, 4.3, 4.4, 4.7, 4.8	Case reference number 2153312	SPC, Labels, Package leaflet and Braille declaration	7th November 2014	12th December 2014	Approval