Public Assessment Report

Decentralised Procedure

TRANSISOFT 8.5 g powder for oral solution in sachet

(Macrogol 3350)

Procedure number: UK/H/6021/001/DC

UK Licence Number: PL 19549/0006

Laboratoires MAYOLY SPINDLER
LAY SUMMARY
TRANSISOFT 8.5 g powder for oral solution in sachet
(macrogol 3350)

This is a summary of the Public Assessment Report (PAR) for TRANSISOFT 8.5 g powder for oral solution in sachet (PL 19549/0006; UK/H/6021/001/DC). It explains how TRANSISOFT 8.5 g powder for oral solution in sachet 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 TRANSISOFT 8.5 g powder for oral solution in sachet.

The product will be referred to as TRANSISOFT 8.5 g powder throughout the remainder of this lay summary.

For practical information about using TRANSISOFT 8.5 g powder, patients should read the package leaflet or contact their doctor or pharmacist.

What is TRANSISOFT 8.5 g powder and what is it used for?
TRANSISOFT 8.5 g powder is used for the treatment of chronic constipation in adults. It is not recommended for children below 17 years of age.

How does TRANSISOFT 8.5 g powder work?
The active ingredient in TRANSISOFT 8.5 g powder contains the active ingredient macrogol 3350, which belong to a group of medicines called laxatives. This medicine carries water to the stool, which loosens and increases stool volume, helping to overcome sluggish bowels. It is not absorbed into the blood stream or broken down in the body.

How is TRANSISOFT 8.5 g powder used?
The pharmaceutical form of this medicine is powder for oral solution. This medicine should be taken as a single dose, preferably in the morning.

The recommended dosage is 2 sachets per day.

The content of the sachets should be dissolved in a half glass of water (100 ml) and patients should drink the liquid immediately. This medicine usually takes 24 to 48 hours to work. However, patients should talk to their doctor if symptoms do not improve after 5 days of using TRANSISOFT 8.5 g powder.

The patient should always take this medicine exactly as described in the package leaflet or as their doctor or pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

For further information on how TRANSISOFT 8.5 g powder is used, refer to the package leaflet and Summary 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 TRANSISOFT 8.5 g powder have been shown in studies?
The company provided data from available studies as well as from literature references to support the efficacy and safety of the product.
These studies have shown that TRANSISOFT 8.5g powder is effective in treating chronic constipation in adults.

**What are the possible side effects of TRANSISOFT 8.5 g powder?**
The most common side effects with TRANSISOFT 8.5 g powder (which may affect more than 1 in 10 people) is diarrhoea.
The common side effects with TRANSISOFT 8.5 g powder (which may affect up to 1 in 10 people) are abdominal pain, swollen abdomen (abdominal distention), wind (flatulence), vomiting, feeling sick (nausea) and abnormal liver function tests.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with TRANSISOFT 8.5 g powder, see section 4 of the package leaflet available on the MHRA website.

**Why was TRANSISOFT 8.5 g powder approved?**
The MHRA decided that the benefits of this medicine are greater than its risks and recommended that it be approved for use.

**What measures are being taken to ensure the safe and effective use of TRANSISOFT 8.5 g powder?**
A risk management plan (RMP) has been developed to ensure that TRANSISOFT 8.5 g powder is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for TRANSISOFT 8.5 g powder 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 TRANSISOFT 8.5 g powder**
Belgium, France, Republic of Ireland and the UK agreed to grant a Marketing Authorisation for TRANSISOFT oral solution in sachet on 22 June 2016. A Marketing Authorisation was granted in the UK on 20 July 2016.

The full PAR for TRANSISOFT 8.5 g powder follows this summary. For more information about treatment with TRANSISOFT 8.5 g powder, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in September 2016.
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I. INTRODUCTION

Please note that the below scientific discussion consists of the original assessment of this product licence, plus a summary of key post approval changes at the end of this introduction section to improve the accuracy of this Public Assessment Report.

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for TRANSISOFT 8.5 g powder for oral solution in sachet (PL 19549/0006; UK/H/6021/001/DC) is approvable. The product is a pharmacy (P) medicine indicated for the symptomatic treatment of chronic constipation in adults.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Belgium, France and Republic of Ireland as Concerned Member States (CMS). The application was submitted under Article 8(3) of Directive 2001/83/EC, as amended, for a new product with known active substance.

The applicant has provided available clinical studies and literature references in support of this product. The dossier refers to a United States (US) Marketing Authorisation for MiraLAX®, which was first approved in the USA in 1999 (NDA 20-698) as a prescription only product. Following three further clinical trials, over the counter (OTC) status was obtained in the USA in 2005. The applicant has adequately justified the applicability of clinical trials conducted in the USA to the EU population according to ICH E5 and no bridging study is required.

The draft EMA guideline on the evaluation of medicinal products for the treatment of chronic constipation (EMA/CHMP/336243/2013) was released for consultation in February 2014. The submitted studies were conducted in 2003/2004 prior to the development of the CHMP guidance document and their design is considered acceptable.

TRANSISOFT 8.5 g powder for oral solution contains the active substance macrogol 3350 which is a long linear polymers that retain water molecules by means of hydrogen bonds. When administered by the oral route, this leads to an increase in volume of intestinal fluids. The volume of unabsorbed intestinal fluid accounts for the laxative properties of the solution.

A summary of the pharmacovigilance system and a detailed risk management plan have been provided with this application and these are satisfactory.

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 CMSs considered that the application could be approved at the end of procedure on 22 June 2016. After a subsequent national phase, a licence was granted in the UK on 20 July 2016.

Summary of key post-approval changes:

The following post-approval variations have been granted for these licences:

1. The shelf life has been extended of the finished product as packaged for sale (supported by real time data) from 24 to 36 months (UK/H/6021/001/IB/003; PL 19549/0006 – 0008)
II QUALITY ASPECTS

II.1 Introduction
The product is a white powder for oral solution, presented in single-dose sachets and contains 8.5 g of macrogol 3350 as an active substance. The product only consists of the active substance packed into sachets with no excipients.

The finished product is packed into a sachet comprised of paper/polyethylene and low density/aluminum foil/polyethylene. The product is available in pack sizes of 14 or 28 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
Macrogol 3350
INN: Macrogol 3350
Chemical name(s): (α-hydro-ω-hydroxypoly(oxy-1,2-ethanediyl)
Structure:

\[
\begin{array}{c}
H \\
\left[ \begin{array}{c}
O \\
\left[ \text{CH}_2 \right]_{n} \\
O \\
\end{array} \right] \\
\end{array}
\]

Molecular formula: \( H\left[\text{OCH}_2\text{CH}_2\right]_n\text{OH} \)
Molecular weight: 3000 to 3700g/mol
Appearance: Macrogol 3350 is a white or almost white solid.
Solubility: It is very soluble in water and in dichloromethane; very slightly soluble in ethanol; and practically insoluble in mineral oils.

All aspects of the manufacture and control of the active substance, macrogol 3350, 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

Suitable pharmaceutical development data have been provided for this application.

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. The test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. 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 the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years with no special storage conditions is set. Once the solution is reconstituted the product must be used immediately.

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 this application from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of macrogol 3350 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. In addition to the published literature, the Applicant has supplemented the non-clinical dossier with summaries of a number of studies.

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
PEG 3350 is considered to be pharmacologically inert, as it is not absorbed or metabolized and does not interact with specific receptors. Greater than 99.5% of the ingested dose remains in the gastrointestinal tract. The laxative effect of PEG 3350 appears to be through its properties as an osmotic agent within the colon, which increases stool mass, hydration and volume, as well as increasing stool lubrication. The increased colonic mass appears to stimulate peristalsis and thus increases gastric motility.

III.2.1 Primary pharmacodynamics
Non-clinical studies have confirmed that the administration of PEG 3350 results in an increase in stool frequency, volume and/or softness in mice, rats, rabbits and dogs. PEG 3350 exerts a greater effect on osmotic pressure greater than would be predicted from its molecular weight, which may indicate interactions between PEG and water molecules to alter the physical chemistry of solutions. As PEG is not metabolised, there are no associated increases in intestinal gas, a common phenomenon with other metabolised laxatives, such as lactulose and certain fibres. In addition, administration of PEG does not appear to affect clinical chemistry and electrolyte balance, associated with sodium phosphate laxatives.

III.2.2 Secondary pharmacodynamics
In addition to its laxative effect, a number of secondary pharmacological effects of PEG 3350 have been reported in the literature.

The primary osmotic mode of action of PEG 3350 increases faecal dry and wet weight, faecal water output and faecal volume without increasing the percent of faecal water. The increase in volume of faecal matter in the intestines is believed to stimulate gastro-intestinal motility. In vitro experiments using rabbit isolated distal colon muscle strips indicated that this effect was not due to stimulation of the gut enteric nervous system. However, an increase in the duration of peristaltic waves was observed when then PEG 3350 was administered directly to the lumen of the colon segments. Addition of muscarinic and tachykinin receptor blockers appeared to attenuate this response. However, as an effect of the hypotonocity of the PEG 3350 solution itself used in these experiments could not be ruled out, it is not known whether PEG exerts a direct effect on neuronal receptors in the intestine.
III.2.3 Safety pharmacology

The effect of a single dose of PEG 3350 on renal function was evaluated in dogs at doses up to 24 mg/kg. Renal function was assessed by evaluating changes in glomerular filtration rate; tubular reabsorption; and distal and convoluted tubular regulation of free water reabsorption.

At the high dose (85-fold above the intended human dose), administration of PEG 3350 resulted in profuse diarrhoea and mild emesis. However, renal changes were consistent with compensatory mechanisms to handle the fluid and osmotic overload, and were considered non-adverse. All effects were reversible at 36 hours post-dose. The NOAEL was considered to be >24 mg/kg.

Repeated dose toxicity studies of up to 9 months duration in dogs (discussed below) confirmed the absence of renal adverse effects.

The only safety pharmacology study described relates to renal safety. No studies or references relating to the cardiovascular, respiratory and central nervous system safety pharmacology of PEG 3350 have been provided. Considering that PEG 3350 is considered to be pharmacologically inert and is not absorbed or metabolised, this is considered acceptable.

III.2.4 Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies of PEG 3350 were performed, and no specific pharmacodynamic drug interactions have been reported in the literature.

The absence of pharmacodynamic drug interaction studies is considered acceptable, considering PEG 3350 is pharmacologically inert.

Overall conclusions on pharmacology

The pharmacology of PEG is well known and described in the literature. The Applicant has provided an adequate review of the available literature, and available supporting non-clinical pharmacology studies. Apart from renal safety, there is very limited discussion of safety pharmacology. However, as PEG 3350 is considered to be pharmacologically inert and is not absorbed or metabolised, this is considered acceptable.

III.3 Pharmacokinetics

- Pharmacokinetic studies

The lack of sufficiently sensitive and specific methods have historically limited the ability to generate data on the levels of PEG in biological matrices, particularly in relation to kinetics in plasma, due to the limited systemic absorption of PEG. Detection of PEG in urine and faeces following oral administration confirm that high-molecular weight PEG is poorly absorbed with less than 0.2% of the administered dose recovered in the urine, and 90-100% of the dose excreted in faeces. Intravenous administration of PEG showed rapid excretion in the urine.

III.3.1 Methods of analysis

A highly sensitive analytical method was developed in order to detect PEG 3350 in biological matrices, including plasma.

III.3.2 Absorption

Studies with unlabelled PEG 3350

Systemic absorption of PEG 3350 was demonstrated to be low, as only ng/mL levels were detected in blood after administration of doses in the g/kg range. In mice, rats and rabbits, blood levels appeared to peak 1-2 hours after dosing and were below the LLOQ by 24 hours after dosing in most animals and at
most dose levels. In summary, PEG 3350 appears to be systemically absorbed at a very low level in all species examined.

In mice, the systemic exposures (AUC\textsubscript{0-24}) following oral administration of PEG 3350 generally increased with dose over the 1.5- to 6-g/kg/day dose range. T\textsubscript{max} ranged from 1 to 2 hours post-dosing.

In rats, systemic exposure following oral administration of PEG 3350 increased in a dose-proportional manner. T\textsubscript{max} after oral dosing ranged from 1 to 2 hours.

In dogs, systemic exposure typically increased in a dose proportional manner over the dose range of 0.75 to 3 g/kg/day. There was no evidence of accumulation following dosing for up to 38 weeks.

Studies with radiolabeled PEG 3350

In spite of the experimental difficulties encountered, the radiolabeled studies confirm the data from the unlabelled studies. The T\textsubscript{max} in rat plasma was between 0.5-2 hours. 74-80% of the administered dose was eliminated in the faeces and 7.5%-11% was eliminated in the urine.

The amount of radioactivity that was found in expired air or volatiles was similar to the amount of low molecular weight non-PEG radioactivity in the starting material, suggesting that the metabolism of PEG 3350 was very low.

III.3.3 Distribution

Organ distribution studies were not performed. The absence of tissue distribution studies is considered acceptable, considering the low absorption of PEG 3350.

III.3.4 Metabolism

There is no evidence to suggest that PEG 3350 is metabolised, and the absence of metabolism studies is therefore considered acceptable.

III.3.5 Excretion

In a pharmacokinetic and mass balance study in rats conducted with \textsuperscript{14}C-PEG 3350, recovery of the administered radioactivity was generally low and extremely variable (57.2, 84.5, and 62 % in three experiments), and the cause was not determined. Faeces was the major route of elimination (60-70% of the dose). Mean urinary elimination ranged from approximately 10-20% of dose.

A second pharmacokinetic and mass balance study (Covance 7496-100) was conducted in rats after a single dose of \textsuperscript{14}C-PEG 3350 (6000 mg/kg). The main route of excretion was via faeces, and most of the elimination occurred over the first 24 hours after dosing. A smaller amount of radioactivity was excreted in urine (7.46 and 10.7% over 72 hours in males and females, respectively). A small amount (about 3.7%) of radioactivity was recovered in expired air.

The total mass balance of radioactivity was 96.7 ± 2.6% in males and 95.8 ± 2.2% in females.

These results indicate that most of the high molecular weight PEG fractions are not absorbed after oral administration and are eliminated unchanged in the faeces.

III.3.6 Pharmacokinetic drug interactions

No non-clinical pharmacokinetic drug interaction studies have been conducted.

Overall conclusions on pharmacokinetics

The Applicant has summarised the available supporting non-clinical pharmacokinetic studies, and the data provided are considered acceptable. Systemic absorption following oral administration of PEG
3350 is minimal, and as such distribution and metabolism studies are not considered necessary. The primary route of PEG 3350 excretion is via the faeces. However, any absorbed PEG 3350 appears to go through renal excretion. PEG 3350 may impact the absorption of poorly water-soluble drugs, due to its effect on gastric transit time.

III.4 Toxicology
The Applicant has provided a full range of supportive and pivotal toxicology studies with PEG3350. The pivotal studies were conducted under GLP conditions. For practical reasons, related to the viscosity of the PEG 3350 solution, the maximum dose that could be administered to rodents was 6 g/kg/day, which is 8.5 times more concentrated than the intended human dose.

III.4.1 Single dose toxicity
A single dose of PEG 3350 was administered via oral gavage to dogs at dose levels of 6, 12 and 24 g/kg to investigate the effects on renal function. Observed changes in renal function included decreased creatinine and free water clearance and decreased sodium excretion rates. The observed changes were within normal physiological ranges were not of significant magnitude to be considered adverse.

III.4.2 Repeat-dose toxicity
Repeat dose studies were conducted with PEG 3350 in mice, rats and dogs for up to 9 months duration.

In mice, PEG 3350 was dosed for up to three months at dose levels of up to 6 g/kg/day. In the 3 month study, PEG 3350-related effects in the 1.5 and 3 g/kg/day dose groups included soft faeces and microscopic findings in the small intestine (duodenum, jejunum and ileum) and in the large intestine (cecum, colon and rectum). The findings were not considered adverse and the NOAEL in this study was 6 g/kg/day.

In rats, PEG 3350 was administered for 3 months and 6 months at dose levels of 1.5, 3 and 6 g/kg/day. In the three month study, there were no PEG 3350-related effects, and the NOEL was 6 g/kg/day. In the six month study, soft faeces and changes in serum chemistry and urinalysis parameters were considered related to treatment with PEG 3350. These clinical chemistry effects and the subsequent acidosis were most likely the result of water/electrolyte loss via the gastrointestinal tract. Microscopic lesions in the kidney (cytoplasmic vacuolation of cortical tubular epithelial cells) were noted in 5/12 males examined in the 6 g/kg/day group, graded as minimal in severity. In addition, there was no evidence of inflammation or necrosis, and no change in renal function evidenced by renal clearance of creatinine and electrolytes.

In dogs, PEG 3350 was administered for 28 days and 9 months. In the 28 day study, PEG 3350 was administered at dose of 3, 6 and 9.3 g/kg/day. In the 6 and 9.3 g/kg/day dose groups, emesis, diarrhoea, soft and/or mucoid faeces was observed, which was of sufficient severity to be considered to be adverse (although other in-life parameters were not adversely affected). Based on these findings, the NOAEL in this study was considered to be 3 g/kg/day. In the 9 month study, the dose levels were 0.75, 1.5 and 3 g/kg/day. The NOAEL in this study was considered to be 3 g/kg/day.

III.4.3 Genotoxicity
The genotoxicity of PEGs has been reported in the literature. For example, no evidence of genotoxicity for PEG 6000 in a mouse Lymphoma model, or for PEGs 300-400 in a sister chromatid exchange method in Chinese hamster ovary (CHO) cultured cells, in an unscheduled DNA synthesis assay, or in a rat bone marrow cytogenetic assay.

In the study reports provided by the Applicant, there was no evidence of genotoxicity in standard tests with PEG 3350.
III.4.4 Carcinogenicity
2-year carcinogenicity studies with PEG 3350 were conducted in mice and rats at doses up to 6 g/day.

In both mouse and rat studies, there was no increased incidence of neoplastic findings at any dose level. The no observed effect level (NOEL) for carcinogenicity in both species was 6 g/kg/day. In mice, non-neoplastic changes included an increased incidence of renal amyloidosis in females in the 6 mg/kg/day dose group. In rats, renal changes consisting of hyperplastic proximal convoluted tubules affected both males and females at all dose levels in the 104-week carcinogenicity phase. These effects may be related to those seen with other hyperosmolar substances.

III.4.5 Reproductive and developmental toxicity

III.4.5.1 Fertility and early embryonic development
A fertility and early embryonic development study was conducted with PEG 3350 in rats at dose levels up to 2 g/kg/day.

Males received a minimum of 28 daily doses prior to mating, and were dosed throughout the mating period through one day prior to euthanasia. Females received a minimum of 14 daily doses prior to pairing and were dosed through gestation day 7. A laparohysterectomy was performed on gestation day 15 for each female with evidence of mating.

Male and female survival was unaffected and there were no PEG 3350-related effects.

In rats, the NOAEL for male and female reproductive toxicity and for early embryonic development until implantation was considered to be 2 g/kg/day.

III.4.5.2 Embryo-fetal development
In rats, PEG 3350 was administered once daily from gestation day (GD) 6-17 at dose levels of 0.5, 1, and 2 g/kg/day. On gestation day 20, a laparohysterectomy was performed.

There were no PEG 3350-related effects on survival, clinical condition, body weights and food consumption, and intrauterine growth and survival were unaffected. No fetal malformations or developmental variations were observed, and the NOEL was considered to be 2 g/kg/day for both maternal and development toxicity.

In the embryo-fetal development study in rabbits, PEG 3350 was administered to groups of 25 artificially inseminated female rabbits from GD 7 through to GD 20 at dose levels of 0.5, 1 and 2 g/kg/day. On GD 29, a laparohysterectomy was performed.

No PEG 3350-related effects on survival and internal findings were observed. In addition, there were no effects on intrauterine growth and survival observed, and no fetal malformations or developmental variations were observed. Maternal effects noted predominantly in the 2 g/kg/day group included decreased food consumption and clinical signs. Soft stool and wet or dry brown material on the tail were attributed to local effects on the gastrointestinal tract. Based on these findings, the NOAEL for maternal toxicity was considered to be 1 g/kg/day, and the NOAEL for developmental toxicity was 2 g/kg/day.

III.4.5.3 Prenatal and postnatal development, including maternal function
A pre- and postnatal development study was conducted in rats dosed with PEG 3350 from GD 6 through to lactation day 20 (weaning) at dose levels of 0.5, 1 and 2 g/kg/day. Females were allowed to deliver and rear their offspring to lactation day 21. On gestation day 20, F1 females were necropsied, and fetuses were examined externally for malformations and developmental variations. The F1 males were necropsied following the last laparohysterectomy.
No PEG 3350-related effects were observed in this study, and the 2 g/kg/day dose level was considered the NOEL and the NOAEL for F0 maternal toxicity, F1 developmental/neonatal toxicity, F1 parental systemic toxicity and F1 reproductive toxicity.

III.5 Ecotoxicity/environmental risk assessment (ERA)
The Applicant has conducted an ERA, primarily based on literature data available on the monomer, ethylene glycol. PEG 3350 was not considered likely to bio-accumulate, or to pose a risk to the aquatic environment and microorganisms.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS
IV.1 Introduction
The applicant has provided eight clinical studies. There were five clinical studies with a pharmacokinetic endpoint (851-PK-001, 851-PK-002, 851-PK-004, 851-PK-005 and 851-CR3-PK), one pivotal efficacy study (851-CR1) and two supportive studies (851-ZCC and 851-CR3).

IV.2 Pharmacokinetics
Four clinical studies were conducted with a primary pharmacokinetic (PK) endpoint (Table 1) and one (851-CR3-PK) examined PK in the long term safety study.

Table 1: Tabular Summary of PK Studies

<table>
<thead>
<tr>
<th>Study identifier</th>
<th>Objective(s) of the study</th>
<th>Study design and type of control</th>
<th>Test product(s); Dosage regimen; Route of administration</th>
<th>Number of subjects</th>
<th>Healthy subjects or diagnosis of patients</th>
<th>Duration of treatment</th>
<th>Study status; Type of report</th>
</tr>
</thead>
<tbody>
<tr>
<td>851-PK-001</td>
<td>Evaluate PK of PEG 3350 after a single dose</td>
<td>Unblinded, no control</td>
<td>MiraLAX 17 g/day oral</td>
<td>6</td>
<td>Healthy subjects</td>
<td>Single dose</td>
<td>Complete; Full</td>
</tr>
<tr>
<td>851-PK-002</td>
<td>Evaluate PK of PEG 3350 during 7 days</td>
<td>Unblinded, no control</td>
<td>MiraLAX 17 g/day oral</td>
<td>14</td>
<td>Healthy subjects</td>
<td>7 daily doses</td>
<td>Complete; Full</td>
</tr>
<tr>
<td>851-PK-004</td>
<td>Examine the effects of end stage renal disease on the PK of PEG 3350</td>
<td>Unblinded</td>
<td>MiraLAX 17 g/day oral</td>
<td>12</td>
<td>6 patients with end-stage renal disease and 6 matched healthy controls</td>
<td>7 daily doses</td>
<td>Complete; Full</td>
</tr>
<tr>
<td>851-PK-005</td>
<td>Examine the effect of age on the PK of PEG 3350</td>
<td>Unblinded, young and elderly patients</td>
<td>MiraLAX 17 g/day oral</td>
<td>12</td>
<td>elderly, 11 young</td>
<td>7 daily doses</td>
<td>Complete; Full</td>
</tr>
<tr>
<td>851-CR3-PK</td>
<td>Examine the PK of PEG 3350 in a dosing chronic study</td>
<td>Unblinded, no control</td>
<td>MiraLAX 17 g/day oral</td>
<td>24</td>
<td>Adults with at least three months’ history of constipation</td>
<td>Up to 207 daily doses</td>
<td>Complete; Full</td>
</tr>
</tbody>
</table>
Study 851-PK-001
This was a single dose PK evaluation of 17g oral dose of PEG 3350 powder for solution in 250mL of water in 6 fasted adult (less than 65 years of age) volunteers (3 male, 3 female). Blood samples were collected at hour 0 (pre-dose) and at 1, 2, 4, 6, 8, 9, 12, 18, 24, 30, 36, 42 and 48 hours post-dose. Urine was collected prior to dosing (a single void) and then over intervals of 0-6, 6-12, 12-24 and 24-48 hours post-dose. Samples for each individual for each interval were mixed prior to removal of two aliquots (15mL each). Plasma PK parameters AUC_0-1, C_max and T_max were determined from plasma concentration versus time profiles. AUC_0-inf, K_el and T_{1/2} could not be calculated from the plasma data due to a limited number of points in the elimination phase, most likely due to limitations of assay sensitivity. From the urine data, amount excreted (Ae), cumulative amount excreted (Cum. Ae), cumulative percent of dose excreted (Cum. % dose) and excretion rate were calculated for each collection interval. T_{1/2} and K_el were calculated from the excretion rate-time data. The percent of dose excreted from time 0 to infinity [Cum. %Dose (0-inf)] was estimated.

Study 851-PK-002
This was a multiple dose PK evaluation in 14 normal volunteers (7 males and 7 females) receiving 17g of PEG 3350 powder for solution dissolved in 250mL of water per day for 7 days. Blood samples were collected at Hour 0 (pre-dose) and at 1, 2, 4, 6, 8, 10, 12, 15 and 24 hours postdose on Days 1, 5 and 7 of a 7 day regimen of 17g PEG 3350 once daily. Urine was collected prior to dosing (single void) and over intervals of 0-24 hours postdose on Days 1 and 5. On Day 7, urine was collected over the intervals of 0-6, 6-10, 10-16, 16-24, 24-30 and 30-36 hours. Standard plasma PK parameters were calculated as were AUC_0-inf following the first dose and the accumulation ratio [AUC(0-tau)_{Day 7}/AUC(0-tau)_{Day 1}]. Excretion amounts and rates were calculated from the urine data and the T_{1/2} and K_el were calculated from the excretion rate-time data following the dose on Day 7.

Study 851-PK-004
This study compared the levels of PEG 3350 in the blood of 6 dialysis patients with End Stage Renal Disease (creatinine clearance CrCl <15mL/min) to 6 healthy adult volunteers (CrCl ≥80mL/min) matched to the patients in terms of age, sex and weight. Subjects received 7 days of oral PEG 3350 powder for solution at a dose of 17g per day.

PK blood and urine sampling (healthy controls only) were conducted after the 7th dose. Blood samples for analysis of PEG 3350 were taken before administration of test article on Day 1 and before dosing on Days 5 and 7. The pre-dose blood sample on day 7 was taken after dialysis and before study medication. On day 7, PK blood samples were taken at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours post-dose. The next dialysis occurred after the 48 hour blood sample had been collected. Urine collection from subjects not on haemodialysis were collected prior to dose on Day 7 and over intervals of 0-24 and 24-48 hours after the Day 7 dose.

Study 851-PK-005
This study assessed the effect of age on the plasma and urine PKs of PEG 3350 powder for solution in healthy adult subjects; 17g PEG 3350 powder for solution was administered once daily for 7 days in young (Group A) and elderly (Group B) subjects. Faecal excretion of PEG 3350 was determined in the young subjects (≥18 and ≤ 40 years of age).

Plasma samples were collected on Day 1 (predose only) and Day 7 of the 7 day regimen (pre dose and at 1, 2, 4, 6, 8, 10, 12, 15, 18 and 24 hours post dose). Plasma PK parameters AUC_0-t, AUC_{0-tau}, T_{1/2}, K_el, C_max, C_min and T_max were determined from the plasma concentration-time data following the dose on Day 7. Urine samples for PK analysis were taken at the following intervals: Day 1 – pre-dose and Day 7 - 0-6, 6-10, 10-16, 16-24, 24-30, 30-36, 36-40, 40-48, 48-54 and 54-60 hours post-dose. The amount excreted, cumulative amount excreted [Cum.Ae(0-24)], cumulative percent of dose excreted, excretion...
rate and renal clearance (CLr) of PEG 3350 were calculated from the urine data following the dose on Day 7. The PEG 3350 amount excreted, cumulative amount excreted and cumulative percent of dose excreted in the faeces were determined in young subjects at 24-hour intervals from Day 1 post-dose until Day 11.

In addition, samples for PK assessment were taken from a subset of patients in Study 851-CR3, a long term open label multicentre safety study of PEG 3350 powder for solution in constipated adults at a nominal daily dose of 17 g for up to 12 months. Investigators could half the dose if patients persistently experienced loose stools and/or discomfort. Patients returned to the study centre for follow-up at approximately 2, 4, 6 and 9 months and for a termination visit at 12 months. Blood and urine samples were taken at these visits and stored for PEG analysis. Patients were asked to provide the time of their last dose.

**Conclusion**

Systemic absorption was low and fell in most subjects to undetectable levels by 18-24 hours. The half-life (T1/2) was variable, with a range of 3.6 to 8.0 hours. Based on this half-life, little accumulation would be expected with single daily doses and steady state would be expected after 2-3 days. The amount of PEG 3350 recovered in urine gave an indicator of systemic absorption and in these two studies this was around 0.17%. PEG is excreted predominantly in faeces, with 93% of the dose excreted in faeces in one study. The small amount of PEG absorbed systemically is excreted in the urine. Excretion is prolonged with PEG 3350 detected at 60 hours post dose in the urine and 96 hours post dose in faeces. The urinary PK data in this study with a t1/2 of 20 hours was attributed to continued absorption of small amounts of PEG 3350 from the intestines that were not detected in plasma with an assay LLOQ of 100ng mL. Persistence in the gut has been attributed to delayed transit times. Standard PK assessment was performed on blood and urine samples. The limitations of assay sensitivity meant that plasma half-life could not be calculated for several subjects. Faecal samples were analysed in a single study. The above studies were conducted in normal volunteers after a 10 hour fast. Systemic exposure was low and unlikely to be influenced to any clinically relevant extent by food. Plasma and urine PEG 3350 concentrations were very variable. All plasma levels and the majority of urine levels (54/55) were within the range seen in formal single and multiple dose PK studies. There were no statistically significant effects of demographic parameters (gender, age and race) or duration of dosing on PEG 3350 levels in plasma and urine.

**Special populations**

- **Impaired renal function**

  **Study 851 – PK-004**

  PEG 3350 analyses were performed in 12 patients, 6 with ESRD and 6 matched controls. Plasma levels ranged from non-detectable to 5567 ng/mL and were significantly elevated in ESRD patients compared to normal volunteers. AUC and t1/2 were significantly higher in ESRD patients compared to healthy volunteers, whilst T_{max} did not differ. Plasma levels prior to dosing were <LLOQ in all normal volunteers and <LLOQ in 5/6 at 24 hours after dosing. In contrast, PEG 3350 was detectable in ESRD patients prior to dosing and for up to 48 hours post dose. The mean pre-dose levels before the fifth daily dose in ESRD patients did not differ from the pre-dose levels before, or 48 hours, after the 7th dose suggesting that there was no additional accumulation of PEG 3350 in plasma following repeated doses.

  Urinary PEG 3350 concentrations in healthy adult volunteers ranged from 33.47µg/mL to 83.81µg/mL. The mean cumulative amount of the administered dose that was excreted in urine in the first 24 hours after dosing on Day 7 was 0.58%. The exposure values [C_{max} (1426 ng/mL) and AUC_{0-tau} (11082.4 ng*h/mL)] and 24 hour urine excretion (0.58%) were higher in these normal volunteers compared to normal subjects in other PK studies. Inspection of the analytical results, study conduct and subject demographics failed to yield an explanation for this anomaly.
The $C_{\text{max}}$ and AUC in ESRD patients were reportedly lower than in dogs or rats exposed to PEG 3350 powder for solution in chronic toxicity and carcinogenicity studies which failed to show significant toxicity.

A single dialysis session, as observed from one protocol violator, appeared to partially clear plasma PEG 3350.

**Study 851 – PK – 005**

Eight out of twelve elderly subjects had mildly impaired renal function (CrCL 50 – 80 mL/min). All subjects had a serum creatinine within the normal range (0.5 to 1.3 mg/dL) at screening so the lower creatinine clearance values was considered to be due to age-related decline in renal function. PK and urinary excretion of PEG 3350 in these individuals did not differ significantly from young healthy adult volunteers. No relationship between PEG 3350 exposure and renal function was observed. Although the p value for the slope from the linear regression was statistically significant (test of hypothesis slope = 0), the $r^2$ value ($r^2=0.23$) showed a very poor correlation between the variables.

A second stage had been planned for study 851-PK-004 to include 6 patients with mild, 6 with moderate and 6 with severe renal disease and 18 healthy adult volunteers. As Stage I showed a significant effect of ESRD on PEG 3350 PK and study PK-005 showed no effect of mild renal impairment on PEG 3350 PK, it was decided not to proceed with Stage II.

**Impaired hepatic function**

No data in subjects with impaired hepatic function was presented. As PEG 3350 is minimally absorbed and not metabolised, impaired hepatic function is unlikely to be of clinical significance from a PK view point.

- **Gender**

PEG 3350 exposure, based on $C_{\text{max}}$ and AUC, appeared numerically higher in females than males after a single dose in Study 851-PK-001 and on all days tested following multiple doses in Study 851-PK-002.

No statistically significant difference was found in the comparison of Day 7 data between females and males from the ANOVA of ln-transformed parameters. The 90% CI for $C_{\text{max}}$ was 101.61-312.53 (p=0.0917), for AUC$_{0-4}$ was 80.73 – 320.73 (p=0.2426) and for AUC$_{0-tau}$ was 107.40-265.88 (p=0.0615). Variability was high and the sample size was small (n=7) which contributed to the wide 90% confidence intervals.

Urinary excretion appeared similar in males and females on Days 1 and 5 and numerically higher in males on Day 7.

In Study 851-PK-005, $C_{\text{max}}$ was higher in young females (542 ng/mL) versus young males (353 ng/mL); this was a statistically significant difference (p<0.05). Otherwise, no statistically significant difference ($\alpha=0.05$) in PEG 3350 PK parameters were shown between females and males, young or elderly.

There was only 1 female in each group in the renal study (851 – PK-004) so analyses by gender were not performed. In the pop PK assessment (851-CR3-PK), mean plasma concentration was higher in males compared to females (189.06 vs. 87.02 ng/mL), the opposite of what was seen in the formal PK studies.

Higher $C_{\text{max}}$ and AUC were usually seen for females but this difference did not generally reach statistical significance. The % of administered dose excreted in urine over 24 hours was independent of gender.

- **Race**
In the pop PK study, there were no differences in plasma PEG levels according to race. Mean levels of urine PEG were higher in 19 black patients (21271 ng/ml) compared to 33 white patients (15741ng/mL) but median levels were similar (9260 and 9133 ng/mL respectively).

There was no strong evidence of an influence of race on PK parameters; however the data is limited.

- **Weight**
  No information regarding weight was provided. In studies 851- PK-004 and 005, plasma PK parameters were normalised by body weight prior to log-transformation.

- **Elderly**
  **Study 851 – PK – 005**
  24 healthy subjects were enrolled; 6 males and 6 females aged 18 – 40 [young population] and 6 males and 6 females over the age of 65 [elderly population]. 22 subjects completed the study. Subject 3 withdrew following Day 2 dosing and was excluded from the PK analysis. Subject 17 was discontinued following the 160-168 hour urine collection interval and was not included in the calculations of $K_{el}$ and $T_{1/2}$ obtained from urine data.
  Exposure parameters ($C_{max}$ and AUC) were variable and exhibited substantial overlap between the two groups. Mean systemic exposure was higher in the elderly than younger subjects but the difference was not statistically significant. The results were influenced by Subject 5 in the young group, with a very low systemic absorption of PEG 3350 and undetectable plasma concentrations at each time point, except 1 hour post dose. The mean plasma half-life was about 5 hours in both groups and median $T_{max}$ (2 hours) was not different between the groups.

  Mean renal clearance of PEG was lower (20%) in elderly subjects. Again there was overlap in individual values between the 2 age groups and no statistically significant difference was shown. Mean cumulative urinary excretion over 24 hours was similar and the cumulative % of administered dose excreted in urine did not differ between young and elderly subjects (0.23 - 0.25%).

  Exposure was higher in the elderly but it was within the range seen in other studies and the difference was not statistically significant. The data is limited; normally a discussion of exposure in age groups, 65-74, 75-84, and 85+ would be expected. If data is very limited in those over 75, this should be reflected in the SmPC.

**Interactions**
No PK interaction studies were conducted.

**Exposure relevant for safety evaluation**
The product acts locally and systemic exposure is very low. The majority of adverse effects are in the GI tract. Exploration of the effect on the systemic exposure in different sub-populations is in some cases limited. In ESRD the exposure is seen to increase 5 fold.

**Overall conclusions on pharmacokinetics**
PEG 3350 is minimally absorbed and almost completely eliminated in the faeces. Literature reviews indicate that PEG 3350 is not metabolised in vivo and is not a substrate for bacterial growth with the usual enteric organisms. The small amount absorbed is excreted in urine (about 0.25% of the total dose).
Plasma levels were evident at 1 hour after dosing with $T_{max}$ at 2-3 hours; they fell in most subjects to undetectable levels by 18-24 hours. The half-life ($T_{1/2}$) was variable, with a range of 3.6 to 8.0 hours.
The median accumulation ratio (Day 7/ Day 1) in a multiple dose study was 1.7. Excretion is prolonged with PEG 3350 detected at 60 hours post dose in the urine and 96 hours post dose in faeces.
Study 851-PK-005 evaluated plasma and urine PK in the elderly in comparison to young patients and faecal excretion in the young cohort. PEG is excreted predominantly in faeces with an average of 93% of the total PEG dose excreted in faeces over the 10 day measurement period. Excretion was prolonged with PEG 3350 detected at 60 hours post dose in the urine and 96 hours post dose in faeces. The urinary PK data in this study with a t1/2 of 20 hours was attributed to continued absorption of small amounts of PEG 3350 from the intestines that were not detected in plasma with an assay LLOQ of 100ng/mL. Persistence in the gut has been attributed to delayed transit times.

Literature evidence and PK data support a lack of in vivo metabolism of PEG 3350.

Considerable inter-individual variability (>48% CV) was observed in the PK parameters in Study 851-PK-002. It was postulated that individual differences in GI transit time could lead to differing amounts of PEG absorbed from the intestinal lumen and the observed variability in systemic exposure. Intra-individual variability was also high; the statistical mixed model provides estimates of the PK parameters taking into account intra-subject variability. As Macrogol is not a narrow therapeutic index drug this variability is less likely to be a concern.

Exposure was non-significantly higher in females in the formal PK studies and in males in the PK subset analysis of study 851-CR3. Overall there was no consistent difference between males and females in PK parameters. Systemic exposure was higher in the elderly (Study 851-PK-005) but the difference was not statistically significant; the mean C\textsubscript{max} was 9.31 ng/mL/kg (SD 5.39) in the elderly compared to 6.89 ng/mL/kg (SD 3.68) in the young subjects and the mean AUC\textsubscript{(0-t)} was 66.73 ng.hr/mL/kg (SD 40.85) compared to 39.68 ng.hr/mL/kg [respective % mean ratio 134.9 (90% CI 84.12-216.48, p=0.2875) and 210.3 (90% CI 100.12-441.80, p=0.0995)]. Exposure was significantly (five fold higher) higher in subjects with ESRD (Study 851-PK-004). It appears that PEG is partially cleared by renal dialysis (Study 851-PK-006). The C\textsubscript{max} (mean 3286.2 ng/mL, SD 1664.1) and AUC (60858.4 ng*hr/mL, SD 36653.4) in ESRD patients were reportedly lower than in dogs or rats exposed to PEG 3350 powder for solution in chronic toxicity and carcinogenicity studies which failed to show significant toxicity. No dose adjustment is required in renal impairment.

No POPPK model containing information from all studies is available. Plots of C\textsubscript{max} and AUC versus weight from Studies PK001, PK002 and PK005 were presented. There appeared to be no relationship between weight and exposure.

**IV.3 Pharmacodynamics**

PEG is a linear polymer consisting of repeating two-carbon length hydrocarbons joined by an ether linkage which allows hydrogen bonding to oxygen in the surrounding water molecules. The temporal pattern of elimination and excretion supports a local, direct effect on faecal water content as the mechanism of action. The pharmacodynamic mode of action, namely an influence on bowel motility and water secretion, means that a potential to influence absorption of other compounds exists. This has been largely unexplored and hence there is limited data available. The applicant had described this potential interaction in the summary of product characteristics (SmPC) with the associated risk of decreased efficacy of concomitantly administered medicinal products.

**IV.4 Clinical efficacy**

Macrogol 3350 powder for solution is a laxative composed of polyethylene glycol 3350 (PEG 3350). The product was first approved in the USA in 1999 as prescription only product. In support of the original US NDA 20-698, the applicant performed Phase 3 double-blind, placebo-controlled, clinical studies of PEG 3350 without electrolytes in normal constipated outpatients to demonstrate safety and efficacy with a 2 week course of treatment.

Braintree Protocol 851-3 confirmed the minimum effective dose as 17g PEG 3350 per day. Diarrhoea occurred at the higher dose (34g). No further dose response studies were described in adults.
The applicant provided full reports of three studies (851-ZCC, 851-CR3 and one long term study on safety (851-CR1)) conducted for the over the counter (OTC) application in the USA.

Table 2 – Summaries of studies 851-ZCC, 851-CR3 and 851-CR1

<table>
<thead>
<tr>
<th>Study ID</th>
<th>No. of study centres / locations</th>
<th>Design</th>
<th>Study Posology</th>
<th>Study Objective</th>
<th>Subjs by arm entered/compl.</th>
<th>Duration</th>
<th>Gender M/F</th>
<th>Median Age</th>
<th>Diagnosis Incl. criteria</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>851-CR1</td>
<td>50</td>
<td>Randomised, double blind placebo controlled</td>
<td>PEG3350 17 g/day oral Placebo</td>
<td>Efficacy and safety during 6 months use</td>
<td>207/127</td>
<td>6 months</td>
<td>46/258</td>
<td>53 (75 elderly)</td>
<td>Adults with at least 3 month history of constipation % patients successfully treated acc. to Modified ROME criteria</td>
<td></td>
</tr>
<tr>
<td>851-ZCC</td>
<td>25</td>
<td>Randomised, open label parallel</td>
<td>Zelnorm 6mg bid oral</td>
<td>Compare safety and efficacy of 4 weeks PEG3350 to Zelnorm</td>
<td>120 (106/14)</td>
<td>4 weeks</td>
<td>24/213</td>
<td>46 (31 elderly)</td>
<td>Adults with at least 3 month history of constipation % patients successfully treated acc. to Modified ROME criteria</td>
<td></td>
</tr>
<tr>
<td>851-CR3</td>
<td>50</td>
<td>Open -label, single arm</td>
<td>PEG3350 17g/day oral</td>
<td>Evaluate safety of 12 months use of PEG3350 daily in constipated patients</td>
<td>311/184</td>
<td>12 months</td>
<td>63/248</td>
<td>57 (116 elderly)</td>
<td>Adults with at least 3 month history of constipation Global efficacy assessment question in symptom questionnaire</td>
<td></td>
</tr>
</tbody>
</table>

All studies were conducted at sites in the USA. The population with functional constipation is sufficiently similar for clinical trials conducted in the US to apply to EU patients.

Main study: 851-CR1 – Extended Use of Miralax laxative in constipated patients
This randomised, double-blind placebo controlled trial conducted over 6 months (851-CR1) is considered to be the main efficacy study in adults. The open label studies 851-ZCC and 851-CR3 are regarded as supportive. Six months is an adequate duration for the efficacy assessment. The draft EMA guideline on chronic constipation (EMA/CHMP/336243/2013) recommends an additional study period of at least 4 weeks to evaluate withdrawal/rebound, which can be best addressed with a randomised withdrawal phase. Withdrawal/ rebound on discontinuing macrogol 3350 were not assessed but a sensitivity analysis where patients who discontinued early were considered as failure showed maintenance of treatment effect.

- Objectives
  To evaluate the safety and efficacy of extended (chronic) use of PEG 3350 laxative compared to placebo in constipated patients.

Methods
Inclusion criteria
Study entry was based on at least a 3 month history of constipation meeting the ‘Modified Rome’ criteria of less than 3 satisfactory bowel movements per week and 1 or more of the following:
[a] Straining in more than 25% of defecations
[b] Lumpy or hard stools in more than 25% of defecations
[c] Sensation of incomplete evacuation in more than 25% of defecations
Exclusion criteria included:
Haem positive stool
History of inflammatory bowel disease, bowel resection or colostomy
Known organic cause for constipation
Taking medications known to affect bowel habits (e.g. Zelnorm, anticholinergics, macrolide antibiotics).
Hypo/hyperthyroidism
Patients who are breastfeeding, pregnant or intend to become pregnant during the study
Loose stools and sufficient criteria for irritable bowel syndrome (IBS) (at least 12 weeks in the preceding 12 months of abdominal discomfort/pain with 2 of the following – relieved with defecation/onset associated with a change in stool frequency or form)

Patients were allowed the use of non-constipating medications but fibre was prohibited

Criteria for functional constipation have evolved since the study was conducted with the ROME III guidance published in 2006. This stipulates that digital rectal examination (DRE) should be conducted prior to trial inclusion to exclude individuals with defaecation disorders. This was not performed but otherwise inclusion/exclusion criteria were considered appropriate.

Treatments
PEG 3350 or placebo (maltodextrin) was provided to patients in identically labelled single dose packets. Patients were instructed to mix the contents of 1 packet (approximately 17g) with 8oz. juice or other beverage and take once daily for up to 180 days. The time of the dose was not specified.
Patients were allowed the use of bisacodyl 5mg tablets as rescue medication and were instructed to take 10mg of bisacodyl if they experienced severe discomfort due to their constipation or if they had not had a BM in 4 days. Rescue medication was provided by the study centre. The dose of study drug could not be increased above 1 packet.

PEG 3350 and placebo appeared appropriately similar. A placebo-controlled study is considered appropriate to conclude on the benefit-risk balance of a product in this indication. Standardisation of rescue medication is endorsed.

Outcomes/endpoints
The primary efficacy endpoint was assessed on the basis of a binary outcome of overall treatment success (responder) or failure (non-responder). Treatment success was defined according to the “Modified ROME” criteria as 3 or more satisfactory stools per week and a maximum of 1 of the 3 additional Rome criteria [a-c] above.

A successful treatment week was defined as a patient having ≥3 satisfactory bowel movements and no more than 1 of the remaining 3 ROME symptoms, without the aid of rescue medication or prohibited laxatives. To be successfully treated a patient had to have 50% or more of their treatment weeks rated as successful (i.e. the ratio of successful treatment weeks to total number of weeks of treatment was ≥0.50). Patients who received less than 8 weeks of active treatment were classified as overall treatment failures. Only days in which data were reported were counted towards the success calculation for that particular week. Missed days were treated as if no bowel movement occurred and no alternative laxative was used.

Secondary endpoints included “Super Efficacy” where the patient had at least 3 satisfactory bowel movements and no Rome symptoms and successful treatment weeks in terms of no rescue medication or prohibited laxative.

The primary efficacy endpoint is considered appropriate in terms of ≥3 satisfactory stools per week and a maximum of 1 out of 3 ROME symptoms. However, to only require 50% of treatment weeks to be successful appears low. The EMA guideline recommends 75% response rate related to the total duration
of the study in weeks, including “sustained response” defined as fulfilling these criteria for the last 4 weeks of treatment. The applicant represented data calculated with the number of responders as those with 75% of treatment weeks successful and the last 4 weeks of treatment all successful. It is noted that for patients who prematurely discontinue treatment (unless they have less than 8 weeks of treatment where they are counted as failures) only the time on treatment is counted for the assessment of the primary endpoint. An alternative definition of overall treatment success considering the full planned treatment period would be to classify patients as a responder if at least 50% (or 75%) of the weeks in the planned 6 months treatment period were successful. Weeks after discontinuation would be considered as unsuccessful. This fits in with the CHMP guideline which requests as primary “an overall 75% response rate related to the total duration of the study (in weeks)” specifying the total duration of the study rather than just treatment weeks.

Sample size
The sample size calculation was based upon the normal approximation to the binomial distribution. Using the results from a previous study (851 -16) and taking into account potential laxative use, the overall treatment success for the placebo group was expected to be approximately 40%. An absolute increase of 20% in overall treatment success with PEG 3350 over placebo (40% to 60%) was considered clinically important. Based on a two-sided Chi-squared test, a study size of 300 patients (200 on PEG and 100 on placebo) was expected to have 90% power to detect a treatment difference of 20% at the two-sided significance level of 0.05.

There were 306 patients randomised, which is consistent with the planned 300.

Randomisation
Patients were randomised in a 2:1 ratio to 17g daily PEG 3350 or placebo within each participating site by a computer generated randomisation scheme. The randomisation schedule at each site was constructed using random sized blocks of 3 balanced treatment assignments.

Blinding (masking)
Laxative or placebo was provided in identically labelled single dose packets. In case of emergency the investigator was instructed on how to access treatment assignments on a per patient basis through the interactive voice recording system (IVRS). No breaking of the blind occurred during the study.

Statistical methods
The primary analysis was based on an Intent-to-Treat (ITT) analysis and included all patients randomised and receiving any treatment. The primary efficacy analysis was on the primary efficacy endpoint of overall treatment success (responder) or failure rate determined for each patient. The primary analysis for the between treatment comparison used the Cochran-Mantel Haenszel (CMH) statistic stratified by site with no covariate adjustment. In order to maintain at least 24 ITT patients for each site in the CMH stratified analysis, sites that recruited fewer than 24 ITT patients were pooled to form larger pseudo sites within a pre-determined geographic region as specified prior to unblinding and included in the statistical analysis plan. Secondary efficacy endpoints defined in terms of successful treatment rates were analysed using analysis of variance (ANOVA) with factors for treatment group, pooled site and interaction between treatment group and pooled site. Selected secondary endpoints were also analysed using survival analysis to evaluate time to event [treatment response (success) and duration of response (persistence)]. The time to treatment response was defined as time since first dose until obtaining response criteria. The duration of response was defined as the time of first obtaining the response criteria until the first time of failure to obtain the response criteria. The estimated time to event and the proportion of patients obtaining the event at 4, 8, 12, 16 and 24 weeks were based on the Kaplan- Meier product limit method. No interim analysis was performed.
Conclusion

The statistical methodology is adequately described. The use of CMH is acceptable for the analysis of a proportion. For the continuous secondary endpoints use of ANOVA is appropriate; the applicant reanalysed these endpoints without a term for treatment × site interaction in the model.

Patients were randomised in a 2:1 ratio to 17g daily PEG or placebo. Patients called into an IVRS daily to report their BM experiences and answer questions related to efficacy and safety.

Results

A total of 306 patients were randomised; 2 were excluded immediately post randomisation and did not appear in the ITT population. Of the 304 ITT patients, 170 completed all 6 months of treatment.

The higher proportion of premature discontinuations was on the placebo group; 127/204 (62%) patients randomised to PEG 3350 complete the trial, compared to 43/100 (43%) on placebo. The mean time on treatment was 19.5 weeks for PEG 3350, compared to 15.4 weeks for placebo. This means that the approach to the primary analysis (where only weeks on treatment were considered rather than the full planned treatment duration) is not biased in favour of the PEG 3350 group.

Baseline data

The majority of enrollees were female (258 vs. 46). This gender disparity was stated to be consistent with previous constipation studies and the overall demographics of constipation. The treatment groups were similar with regards to age, weight, racial distribution and constipation history. The average age was 53 years (range 20 to 92 years).

The two treatment groups were well balanced in terms of baseline demographics. Constipation affects women more commonly than men. Recruiting a predominantly (>80%) female population was standard when this trial was conducted. The EMA guidelines state that future trials should aim to recruit at least 30% of their patient population from the male gender in order to be representative. However, the gender distribution in the above trial is acceptable.

Primary endpoint

The primary responder analysis for the ITT population showed that 52% of PEG 3350 patients were successfully treated in the study versus 11% of placebo patients (p<0.001). Similar efficacy results were obtained on analysis of the 75 elderly patients enrolled (PEG 3350 59% vs. placebo 13%). No differences in efficacy were noted on the basis of race (53% response on PEG vs. 8% with placebo in non-Caucasians), although the numbers involved were small (n=44 non Caucasians). A lower proportion of males than females responded (45% vs. 53%) but the number of males allocated PEG 3350 was small (n=29 out of 46 males in the study). The placebo response in males was very low (1/17, 6%) and efficacy remained superior to placebo in this subpopulation (p=0.007).

The sensitivity analysis of the number of responders with at least 75% of treatment weeks successful and the last 4 weeks of treatment all successful [26 vs. 2% (17.4, 30.6%, p<0.001)] supported the primary analysis.

Secondary endpoints

The full ITT population (204 PEG 3350 vs. 100 placebo patients) was provided.

For the secondary endpoints, the full ITT analyses confirmed the clinical benefit observed with the full analysis set (FAS 202 PEG 3350 vs. 100 placebo) or observed data analysis (291 patients without missing data replacement) as presented in the clinical study report for 851-CR1.
Efficacy of the main secondary endpoints excluding the term for treatment × site interaction confirmed the clinical benefit observed with a full analysis of variance model. The treatment differences seen are generally large and it seems likely statistical significance would still be seen in the re-analysis.

According to the primary definition, 61.4% of the treatment weeks of PEG 3350 patients were successful versus 21.8% of placebo treatment weeks. By the secondary “super efficacy” measure, 47.3% of PEG 3350 treated patients experienced their treatment weeks as successful versus 14.4% of placebo patients (p<0.001).

PEG 3350 was superior to placebo for each ROME symptoms with the most dramatic differences occurring in straining (symptom 2) and hard stool (symptom 3).

Most PEG 3350 patients achieved a regular BM frequency of one BM per day (mean = 7.8 BM/wk). PEG 3350 treated patients on average used fewer tablets of the rescue medication per week (2.8 vs. 3.9) but this difference did not reach statistical significance. 50% of PEG 3350 patients used a total of ≤8 bisacodyl tablets over the 6 month treatment period and about 21% did not use any bisacodyl.

Additional analysis
An additional analysis, not included as part of the statistical analysis plan, was patients who are responders by month. A successful treatment was defined as a month (4 week period) with ≥2 successful weeks. A successful week was ≥3 satisfactory BMs with a maximum of 1 additional ROME criterion without the aid of rescue medication. For the baseline 2 week period, patients must have had at least 1 successful week to satisfy this endpoint. PEG 3350 treatment resulted in a rapid increase in the number of successfully treated patients within the first month of therapy (about 47%); maximum response occurred by the second month and remained fairly level thereafter. Statistically significant improvements over placebo were seen at each treatment visit.

No significant changes in dose to indicate tachyphylaxis or increase in sensitivity were observed over the course of the study.

Conclusion
Patients treated with PEG 3350 achieved a statistically significant benefit over placebo for the primary endpoint. The primary measure of efficacy was achieved in 52% of PEG 3350 treated patients compared to 11% of placebo. The PEG 3350 response was slightly less than that used in the sample size calculation (predicted 60%) but the placebo response was much lower (predicted 40%), therefore the benefit was considered to be both statistically and clinically significant. Based on the results of Study 851-6, a 20% difference was considered as clinically relevant.

The response was consistent across the subgroups examined, specifically age and race. The response was slightly lower in males than females (45% vs. 53%) but the number of males recruited was low and the response remained significantly superior to placebo (45% vs. 6%).

The response was consistent across the secondary efficacy endpoints according to the ROME criteria and individual ROME symptoms. This was confirmed when the term for treatment × site interaction was excluded from the analysis of variance model.

The use of the permitted rescue medication was not significantly different between the groups, although it was numerically lower with PEG 3350 than placebo (mean 2.8 vs. 3.9 tablets per week). A sensitivity analysis in which every day after premature treatment discontinuation was considered to have had rescue medication use improved the result due to the higher discontinuation rate in the placebo group.
Analyses of time to first spontaneous BM or CSBM and the number of BM/week during the run in phase compared to the average number of BM/week during the study for each patient confirmed the efficacy of MiraLax versus Placebo in the 851-CR1 study with a high level of significance.

Ancillary analyses
Monthly compliance for each patient was calculated based on the number of packets of study medication returned at each study visit divided by the number of treatment days between visits (expressed as a percent). Monthly compliance values were averaged to produce a single study compliance value for each patient. Overall, the mean compliance between treatment groups was similar (p=0.3). PEG 3350 patients were 88.9% (SD=17.9%) compliant and placebo patients were 86.3% (SD=18.4%) compliant. Single patient compliance generally exceeded 90% for both treatments throughout the entire study period.

Compliance, based on the number of sachets returned to the treatment centre, was good. It had to be assumed that this surrogate measure correlated with actual compliance with daily laxative treatment.

Clinical studies in special populations
Effects in the Elderly
No specific studies were conducted in the elderly but the benefit could be assessed on subgroup analysis. Studies 851-CR1 and 851-CR3 enrolled a proportion of elderly patients, aged ≥ 65 years [75 (51 on PEG 3350) and 116 patients respectively].

As discussed above, in study 851-CR1, the 51 elderly patients receiving PEG 3350 demonstrated a statistically significant improvement in the primary efficacy endpoint compared to the 24 patients on placebo (58.8% vs. 12.5% responders). The response was similar to the non-elderly population (50% vs. 11%) and the whole trial population (52% vs. 11%).

In study 851-CR3, an open label study that will be considered in further detail under supportive studies, the proportion of responders according to the global efficacy responder analysis remained relatively constant over time. Efficacy, as measured by this patient reported outcome, appeared numerically better in the elderly population compared to those under the age of 65; 63.2% of enrolled elderly patients were responders at visit 6 compared to 49.5% of the whole enrolled population.

Efficacy in the elderly (age >65 years) appeared at least similar or potentially slightly better compared to the younger patient population. Although the numbers are small, it is requested that this population is further subdivided according to age (>65 ≤75 years; >75 ≤85 years; >85 years) for the 2 studies.

Supportive Studies
Study 851-ZCC
This randomised study compared 1 month of PEG 3350 17 g daily to 1 month of Zelnorm 6mg b.i.d. (tegasarod maleate, Novartis Pharmaceutical Corporation, New Jersey) treatment in patients with a history of constipation. The definition of constipation and the primary and secondary efficacy variables were similar to trial 851-CR1. To be declared a treatment success, a patient had to have at least 50% of their treatment weeks scored as successes.

The ITT population consisted of 237 patients; 203 patients (88.3% of PEG3350 and 82.9% of Zelnorm) completed all 4 weeks of the study. The responder analysis in the ITT population showed a statistically significant 19.2% difference in treatment response between PEG 3350 and Zelnorm in all patients (50.0% vs. 30.8%; p=0.003).

Study 851-ZCC was open –label and therefore prone to bias, short (1 month) and there was no baseline period for assessment of stool frequency (normally 2 weeks). The recruited population was restricted mainly to young females. Zelnorm is not considered to be a valid comparator in the EU. However, despite the methodological limitations, Study 851-ZCC can be considered supportive of the efficacy of PEG 3350.
Study 851-CR3
This was an open-label, multi-centre study to evaluate the safety of extended use (1 year) of PEG 3350 in constipated patients, including a subgroup of elderly patients. It is prone to bias in the assessment of efficacy but provides supportive evidence.

Methods
Inclusion criteria were similar to study 851-CR1. Patients filled out a symptom questionnaire to ascertain their view of product efficacy at each clinic visit, approximately once every 2 months (months 2, 4, 6, 9 and 12). The primary efficacy variable was based on a global efficacy assessment (GEA) question in the questionnaire:

“Consider how you felt since your last visit in regard to your constipation, in particular your overall well-being, number of bowel movements, consistency and completeness of your bowel movements, and symptoms of straining. Compared to the way you usually felt before entering the study, how would you rate your relief of symptoms since your last visit (completely relieved, considerably relieved, somewhat relieved, unchanged or worse)?”

There is no validated patient reported outcome measures (PRO) in constipation suitable for use as a primary endpoint. The concepts of ROME 1 (frequency, consistency, completeness and straining) were incorporated in the questionnaire and this is considered acceptable for a supportive study. A follow-up question requested information on specific ROME constipation criteria for the secondary efficacy variable.

Results
The primary analysis was based on the ITT population. GEA responders were defined as patients that reported ‘completely’ or ‘considerably’ relieved to the GEA question. 311 patients were evaluated in the ITT population; 184 patients (59.2%) completed all 12 months of treatment. The efficacy data was presented according to the number of patients reporting for that clinic visit (‘all by visit’) and the number of ITT patients initially enrolled (‘all by enrolled’).

With respect to the GEA question (dependent on the month of observation), 50-64% of enrolled patients were rated as successfully treated over the course of the study. Most treatment failures occurred early, prior to Visit 2 but there was a gradual decline in the proportion of enrolled patients classified as responders over the course of the study.

Results of the secondary endpoints were in line with the primary efficacy outcome but the number of patients assessed at each visit (‘all by visit’) was higher in the secondary than in the primary outcome analysis. For the secondary outcome measure of modified ROME criteria success, the response was similar to the primary result of study 851-CR1 (54% responders at visit 6 vs. 52% for the primary outcome measure).

Rescue medication (bisacodyl 10mg) was permitted. At least 60% of subjects had at least 1 bisacodyl tablet with a mean of 36.1 tablets over the course of the year.

Effects in the Elderly
Similar efficacy results were obtained on analysis of the 75 elderly patients in Study 851-CRI; the 51 elderly patients receiving PEG 3350 demonstrated a statistically significant improvement in the primary efficacy endpoint compared to the 24 patients on placebo (58.8% vs. 12.5% responders).

In the open label study 851-CR3, the proportion of responders according to the global efficacy responder analysis appeared numerically higher in the elderly population; 63.2% of enrolled elderly patients were responders at visit 6 compared to 49.5% of the whole enrolled population.
There were few patients over 85 years of age. Still a similar magnitude of treatment effect is observed for subgroup analyses of efficacy in the elderly (≥ 65 - <75 years, ≥ 75-< 85 years and > 85 years) for the primary end point for trials 851-CR1 and 851-CR3.

IV.5 Clinical safety
Safety evaluation of PEG 3350 in adults was based on the 2 randomised trials (851-CR1 and 851-ZCC) and the open-label extended use study (851-CR3), giving a total of 635 patients.

Adverse events from the 3 randomised controlled trials conducted over 2 weeks in support of the original NDA in the USA were also included in the assessment (studies 851-3, 851-5 and 851-6). Most adverse events were related to the gastrointestinal (GI) tract. Complications due to volume depletion have been reported. No action was needed.

PEG 3350 is a well-recognised drug substance. The extent of exposure is considered adequate for the evaluation of safety in adults.

Adverse events

Study 851-CR1
Events listed include investigator initiated adverse events (AEs), serious adverse events (SAEs) and individual assessments from the daily IVRS calls.

Most treatment emergent adverse events (TEAEs) were reported in the GI system organ class (SOC) and these demonstrated a statistically significant difference from placebo. Some “diarrhoea” events represent individual patient IVRS calls reporting 3 or more stools on a single day rather than the protocol definition of 3 consecutive days of ≥3 loose, watery stools. GI disorders appear to be driven by abdominal distension, diarrhoea, loose stools, flatulence and nausea. These effects are consistent with laxative therapy. About half of the reports were considered definitely or probably related to treatment for both PEG 3350 and placebo. Most events were mild or moderate in severity. The two severe cases of diarrhoea resolved either spontaneously or on PEG 3350 discontinuation.

Significant diarrhoea was classified as ≥2 consecutive days of ≥3 loose bowel movements per day while on PEG 3350 therapy as reported on the daily IVRS. Significant diarrhoea occurred in 20 patients. Adverse events in this group (n=20) were compared to those that did not experience significant diarrhoea (n=184). Proportionally more patients in the diarrhoea group experienced GI disorders [7 (35.0%) vs. 52 (28.3%)], infections and infestations [7 (35.0%) vs. 41 (22.3%)], injury, poisoning and procedural [2 (10.0%) vs. 7 (3.8%)] and metabolism and nutrition disorders [1 (5.0) vs. 5 (2.7%)]. None of the comparisons were statistically significant.

Three cardiac adverse events were reported for PEG 3350 treated patients. One was considered an SAE and none were considered related to PEG 3350. These were:
• 70 year old female (121-08) with an episode of tachycardia about 4 weeks after starting PEG 3350. This patient had no significant medical history or concomitant medications and continued PEG 3350 for the rest of the study (about 5 months) without additional events.

• 64 year old female (132-3) diagnosed with mitral valve prolapse (SAE) 2 months after starting the study and continued treatment with PEG 3350 for the rest of the study (about 4 months). This patient also reported 3 separate days of diarrhoea starting 1 month after the prolapse diagnosis.

• 32 year old female (149-23) experienced an episode of supraventricular tachycardia (SVT) 3 months after starting the study. This patient had a previous history of SVT and continued PEG 3350 treatment for a further 3 months without additional events. The patient also reported a single day of diarrhoea 1 month prior to the SVT event.

Although 2 of the 3 patients experienced brief episodes of diarrhoea during treatment, these were not temporally related to the cardiac events. No significant out of range electrolyte levels were reported in association with any cardiac or diarrhoea episodes.

Infections and infestations were also reported with a slightly higher frequency in the PEG 3350 than placebo group (23.5 vs. 19.0%). No concern regarding abnormal investigations or metabolism/nutritional disorders is generated from review of the above data.

Withdrawal due to AE

19 of 204 PEG 3350 patients and 6 of 100 placebo patients withdrew from the study due to an adverse event. Most of these were GI events (abdominal distension, flatulence, loose stools and nausea) consistent with laxative use. The only statistically significant difference was detected in the neoplasm category, where 3 placebo patients were diagnosed with breast, colon and gastric cancer compared to 1 PEG 3350 patient diagnosed with prostate cancer. No relationship was apparent between these events and the study medications.

High Risk Patients

29 patients in the PEG 3350 treatment group were classified as higher risk based on a medical history of cardiac or renal problems or diabetes. This group experienced a relatively higher proportion of GI adverse events, injury, poisoning and procedural events and abnormal investigations. However, reported infections were lower and the number of cardiac disorders was too low to comment. Compared to the remaining PEG 3350 patients there was no statistically significant difference for adverse events for any body system, although the number of high risk patients was low.

Most of the reported TEAE affected the GI system, consistent with laxative use. Most were mild-moderate in severity and resolved on dose reduction. Most cases of treatment withdrawal due to an AE involved the GI system. ‘Significant diarrhoea’ affected 20 PEG treated patients and these individuals experienced proportionally more GI disorders [7 (35.0%) vs. 52 (28.3%)], infections and infestations [7 (35.0%) vs. 41 (22.3%)], injury, poisoning and procedural [2 (10.0%) vs. 7 (3.8%)] and metabolism and nutrition disorders [1 (5.0%) vs. 5 (2.7%)] but the actual numbers were small and none of the comparisons were statistically significant. No trend regarding cardiac adverse events was seen in the PEG group, including in patients deemed high risk due to their medical history.

Adverse events
Study 851-CR3
The primary TEAEs in the overall population were GI complaints (111/311; 35.7%) with infections and infestations being the second most commonly reported TEAE (81/311; 26.0%). There were no significant differences in the frequency of adverse events between males and females, although there were proportionally more musculoskeletal disorders (20.6 vs. 11.3%) and nervous system disorders (15.9 vs. 8.1%) in males and psychiatric disorders in females (1.6 vs. 6.9%).

Four cardiac adverse events were reported; none were considered to be an SAE or to be related to PEG 3350. All patients continued with PEG 3350 treatment until the end of study without further events:
- 75 year old female with an exacerbation of atrial fibrillation after 3 months
- 64 year old female on levothyroxine and venlafaxine with an episode of arrhythmia after 3 months
- 50 year old female on meclizine and venlafaxine experienced anxiety and tachycardia after 9 months
- 51 year old female on concomitant medication with a medical history of palpitations experienced palpitations after 11 months

Two of the patients experienced brief episodes of diarrhoea but no cardiac events were temporally related to a diarrhoea episode. There were no out of range electrolyte levels reported in association with any of the cardiac or diarrhoea episodes.

No increase in the number of patients with adverse effects for any body system was evident when the first 6 months of PEG 3350 therapy was compared to the final 6 months of treatment for the 184 patients that completed all 12 months of the study. The number of patients with any AE as well as the MedDRA systems GI disorders and infections and infestations generally declined in the second six months of treatment. With regards to infections/infestations the first 6 months included the winter 2003/2004 which reportedly accounted for the inflated number of episodes of upper respiratory infection, nasopharyngitis and sinusitis.

Withdrawals due to AE
23 of 311 PEG 3350 patients withdrew from the study due to an adverse event. Most of these (87.5%) were GI events, consistent with laxative use, most frequently diarrhoea (5 patients), abdominal distension, abdominal pain and flatulence (2 patients each).

Significant diarrhoea
26 patients reported by their daily IVRS 2 or more consecutive days of ≥ 3 loose bowel movements while on PEG 3350 therapy. The frequency of AEs in this population was compared to the rest of the treatment group.

In general, there were no substantive differences in adverse event frequency between PEG 3350 patients that experienced “significant diarrhoea” and those that did not. A statistically significant difference was noted for blood disorders, based on 2 reports of anaemia in the diarrhoea group, not considered related to treatment. A statistically significant difference was detected for injuries based on 4 reports, including fractures and sprains, considered unrelated to study treatment. Proportionally more patients in the diarrhoea group had abnormal investigations and metabolism and nutritional disorders.

70 patients were classified as high risk based on a medical history of cardiac or renal problems or diabetes. In these high risk patients there were statistically significantly more infections and infestations (35.7% vs. 23.2%, p=0.044), metabolism and nutrition disorders (7.1% vs. 1.2%, p=0.016) and musculoskeletal adverse events (21.4% vs. 10.8%, p=0.027). These differences were not attributed to any particular AE terms within the categories and were considered to represent underlying illness in these patients.
TEAEs were mainly in the GI SOC followed by infections and infestations; a proportion of these were upper respiratory tract infections occurring over the winter months. No increase in TEAEs was observed over the course of the study in those that completed by comparison of the first and second 6 months of treatment. For some TEAEs the incidence fell over the treatment period in study completers. Withdrawals due to an adverse event were low and mainly due to GI AEs. Proportionally more of the 26 patients that had significant diarrhoea reported abnormal investigations and metabolism and nutritional disorders.

**Study 851-ZCC**
In this study the majority of AEs were GI related, particularly nausea and diarrhoea. Most of these were considered related to treatment and either mild or moderate in severity. The nervous system disorders in the Zelnorm group (headache, dizziness) were consistent with the product labelling.

**Serious adverse events and deaths**
There were no on-study deaths.

There were 12 SAEs in study 851-CR1 and 26 in study 851-CR3. One female who presented with chest pain, shortness of breath and nausea was treated for dehydration and low potassium. Although deemed unrelated by the investigator, it is possible that the dehydration and low potassium were linked to use of PEG 3350. One death was reported in study 851-CR3 over 30 days post study, following a post study fall, fracture and hospitalisation in an elderly male patient. It is possible that the original fall in this 86 year old male was related to study treatment.

**Laboratory findings**
Abnormal electrolyte values have been reported in conjunction with use of Macrogol 3350. The mean laboratory values in study 851-CR1 showed no clinically relevant differences between PEG 3350 patients and placebo. Patients in the placebo arm could take bisacodyl rescue medication, a laxative that is also known to cause electrolyte imbalance.

Electrolyte disorders (hypokalaemia and hyponatraemia) are listed in section 4.8 of the SmPC with a frequency of uncommon.

**Study 851-ZCC**
No clinical laboratory investigations were conducted as part of the protocol.

**Safety in special populations**

**Elderly patients**

**Study 851-CR1**
No statistically significant differences in TEAEs, including GI effects, were detected in elderly patients in study 851-CR1. Again the biggest difference from placebo was seen in GI disorders, infection and infestations and also skin and subcutaneous disorders.

With regards to the most common GI adverse effects, these were not seen more frequently in the elderly compared to younger PEG 3350 treated patients.

With regards to laboratory values in the elderly there was a statistically significant difference in chloride levels between PEG 3350 treated patients and placebo. This was due to a uniformly higher mean in the PEG group at baseline and each subsequent visit and was not clinically relevant.
Study 851-CR3
Again the primary treatment emergent adverse events in the elderly were GI complaints. There was no clinically meaningful difference in frequency between the study population as a whole and the elderly group.

With respect to the most common adverse reactions of diarrhoea, flatulence, loose stool and nausea, most were rated as mild or moderate. By inspection, no difference in severity was observed on the basis of age. One elderly male patient experienced severe diarrhoea during the study but he was not taking PEG 3350 at the time of the event.

As for the general study population, there was no significant increase in the number of adverse events between the first and second six months of treatment for the 81 patients over the age of 65 that completed the study protocol.

No clinically relevant difference in the type or frequency of adverse events was noted in the elderly population (aged over 65). The elderly age group was further sub divided into >65-≤75 years, >75 - ≤85 years and > 85 years for both trials and a summary of adverse events were provided. There are more patients (15) aged >85 years and there is no cluster of adverse events in any individual SOC. The warning in section 4.4 of the SmPC mentions that the elderly may be more prone to water-electrolyte balance.

Safety related to drug-drug interactions and other interactions
Narrow Therapeutic Index Drugs
Study 851 – CR1: 19 patients in the PEG 3350 treatment group were taking narrow therapeutic index (NTI) drugs (warfarin, Depakote, dilantin, lanoxin, lithium, synthroid, tegretol and theophylline). Comparison of AE reports for this small number of patients against PEG 3350 patients not taking these medications showed no statistically significant differences in the frequency of adverse events.

Study 851-CR3: There were 25 patients in the PEG 3350 treatment group taking narrow therapeutic index drugs, although a small number, comparison of AE reports against the rest of the PEG 3350 population revealed no obvious difference in the frequency of adverse events. There were more investigations and surgical procedures for NTI than non-NTI patients. No particular investigation or surgery occurred more frequently and all events were considered unrelated or possibly related to treatment. These results were considered likely to represent pre-existing disease in the NTI group.

No specific pattern of adverse events was identified in the small subgroup of patients taking NTI drugs but it is difficult to draw any firm conclusions on drug-drug interactions from this limited data.

Post marketing experience
PEG 3350 (MiraLAX) is currently marketed in the USA with an indication in adults and children aged 17 years and older. The estimated cumulative patient exposure is 5 257 646 patient treatment years.

Overall conclusion on clinical safety
In the clinical trials PEG 3350 therapy was principally associated with GI adverse events, particularly diarrhoea, loose stools, flatulence and nausea. Most events were considered mild/ moderate in severity. These are consistent with the mode of action of a laxative. There was no particular risk of syncope or cardiac adverse events identified in association with PEG 3350 use. There were 2 SAEs associated with dehydration. Patients with diarrhoea, as well as experiencing proportionally more GI disorders [7 (35.0%) vs. 52 (28.3%)], also reported more infections and infestations [7 (35.0%) vs. 41 (22.3%)], injury, poisoning and procedural [2 (10.0%) vs. 7 (3.8%)] and metabolism and nutrition disorders [1 (5.0) vs. 5 (2.7%)] but the numbers involved were small.
There were no substantial increases in adverse events when the last 6 months of treatment was compared to the first 6 months. No age, gender or race related effects were seen. No substantive, drug related differences were noted for patients taking narrow therapeutic index drugs or for high risk patients, although the data was limited.

Abnormal electrolyte values have been reported in conjunction with use of Macrogol 3350. The mean laboratory values in study 851-CR1 showed no clinically relevant differences between PEG 3350 patients and placebo. Patients in the placebo arm could take bisacodyl rescue medication, a laxative that is also known to cause electrolyte imbalance.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
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 TRANSISOFT 8.5 g powder for oral solution in sachet.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:
<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
</table>
| Electrolyte disorders (hyponatraemia, hypokalaemia) | **Proposed text in SmPC:**  
- **Section 4.4**  
  Warnings  
  In case of diarrhoea, caution should be exercised in patients who are prone to a disturbance of water electrolyte balance (e.g. the elderly, patients with impaired hepatic or renal function or patients taking diuretics) and electrolyte control should be considered.  
  If patients develop any symptoms indicating shifts of fluid/electrolytes (e.g. oedema, shortness of breath, increasing fatigue, dehydration, cardiac failure) MACROGOL 3350 MAYOLY SPINDLER should be stopped immediately, electrolytes measured and any abnormality treated appropriately.  
- **Section 4.8**  
  - **Adult population:**  
    Electrolytes disorders (hypokalaemia, hyponatraemia), reported with an uncommon frequency  
  - **Elderly population:**  
    Electrolytes disorders (hypokalaemia, hyponatraemia), reported with an uncommon frequency.  
- **Section 4.9**  
  Overdose leads to diarrhoea which disappears when treatment is temporarily interrupted or the dosage is reduced. Excessive fluid loss by diarrhoea or vomiting may require correction of electrolyte disturbances.  
  **Proposed text in PIL:**  
  2. **What you need to know before you take MACROGOL 3350 Mayoly Spindler**  
  **Warnings and precautions**  
  As this medicine can sometimes cause diarrhoea, check with a doctor or pharmacist before taking this medicine if you:  
  - have impaired liver or kidney function,  
  - are taking diuretics (water tablets) or are elderly as you may be at risk of low sodium (salt) or potassium levels in the blood. | None proposed |
<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
</table>
| 3. How to take MACROGOL 3350 Mayoly Spindler                                  | If you take more MACROGOL 3350 Mayoly Spindler than you should  
- It may cause diarrhoea, which usually disappears when treatment is stopped or the dose reduced.  
- If you suffer from severe diarrhoea or vomiting you should contact a doctor as soon as possible as you may require treatment to prevent loss of salts due to fluid loss. | None proposed                        |
| 4. Possible side effects                                                      | Side effects in adults:  
**Uncommon frequency**: low levels of sodium and potassium in blood especially in elderly patients (over 65 years of age) | None proposed                        |
| Important identified risk                                                     | None proposed                                                                                                                                                                                                                     |                                      |
| Hypersensitivity reactions (including allergic reactions, rash, pruritus, urticaria, swelling/oedema, up to anaphylactic shock) | **Proposed text in SmPC:**  
Section 4.3 Contraindication in case of hypersensitivity to macrogel (polyethylene glycol).  
- **Section 4.4** Special warnings and precautions for use  
Cases of hypersensitivity reactions (rash, urticaria, oedema, anaphylactic shock) have been reported with drugs containing macrogel (polyethylene glycol).  
- **Section 4.8** Adult population  
Hypersensitivity reactions (pruritus, rash, face oedema, Quincke oedema, urticaria, anaphylactic shock) reported with an uncommon frequency | None proposed                        |

**Proposed text in PIL:**

2. What you need to know before you take MACROGOL 3350 Mayoly Spindler  
- Do not take MACROGOL 3350 Mayoly Spindler  
If you are allergic (hypersensitive) to the active substance (macrogel=PEG=polyethylene glycol).  
- **Warnings and precautions**  
An allergic reaction may occur. The warnings signs of an allergic reaction and the actions to be taken are stated in section 4. Please read carefully this section.
<table>
<thead>
<tr>
<th>Safety concern</th>
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</tr>
</thead>
</table>
| 4. Possible side effects                                | **Allergic reactions**  
   - The warning signs of an allergic reaction are: difficulty in breathing, or swelling of the face, lips, tongue or throat, skin rash, itching and reddening of the skin.  
   - If you experience one of these side effects, **you should stop the treatment and consult a doctor immediately.**  

**Side effects in adults:**  
**Uncommon frequency:** oedema peripheral, local swelling, rash, urticaria, allergic reactions  

| Important potential risk                                | **Proposed text in SmPC:**  
   - **Section 4.2**  
     An organic disorder should have been ruled out before initiation of treatment. MACROGOL 3350 MAYOLY SPINDLER 8.5 g powder for oral solution in sachet should remain a temporary adjuvant treatment to appropriate lifestyle and dietary management of constipation. A course of treatment for chronic constipation with MACROGOL 3350 MAYOLY SPINDLER 8.5 g does not normally exceed 2 weeks, although this can be repeated if required. As for all laxatives, prolonged use is not usually recommended. If symptoms persist despite associated dietary measures, an underlying cause should be considered.  

**Proposed text in PIL:**  
   - **3. How to take MACROGOL 3350 Mayoly Spindler**  
     How long it usually takes to work  
     This medicine usually takes 24 to 48 hours to work. However talk to a doctor if symptoms do not improve after 5 days of using MACROGOL 3350 Mayoly Spindler.  

| Important potential risk                                | **Proposed text in SmPC:**  
   - **Section 4.5**  
     No interaction studies have been performed and data is limited. It is theoretically possible that intestinal absorption of other medicinal products could be reduced transiently during use with MACROGOL 3350 MAYOLY SPINDLER 8.5 g. There have been isolated reports of decreased efficacy with some concomitantly administered medicinal products (e.g. anti-coagulants or anti-epileptics).  

| Important potential risk                                | None proposed |

| Important potential risk                                | None proposed |

| Important potential risk                                | None proposed |

| Important potential risk                                | None proposed |

| Important potential risk                                | None proposed |

| Important potential risk                                | None proposed |

| Important potential risk                                | None proposed |

| Important potential risk                                | None proposed |

| Important potential risk                                | None proposed |

| Important potential risk                                | None proposed |

| Important potential risk                                | None proposed |

| Important potential risk                                | None proposed |

| Important potential risk                                | None proposed |
Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

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

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 patient information leaflet (PIL) was English.

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.

VI Overall conclusion, benefit/risk assessment and recommendation
The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with macrogol 3350 is considered to have demonstrated the therapeutic value of the compounds. The benefit-risk 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 is presented below:
Annex 1
Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/non approval</th>
<th>Assessment report attached Y/N (version)</th>
</tr>
</thead>
<tbody>
<tr>
<td>To update SmPC sections 4.6, 5.3 and PIL following comments from the new CMS during a repeat use procedure</td>
<td>UK/H/6021/001/II/004</td>
<td>SmPC sections 4.6, 5.3 and the PIL</td>
<td>09 August 2018</td>
<td>14 November 2018</td>
<td>Approval</td>
<td>Y – see Annex 2</td>
</tr>
</tbody>
</table>
ANNEX 2

Our Reference: PL 19549/0006 - 0009
Product: TRANSISOFT 8.5 g powder for oral solution in sachet
Marketing Authorisation Holder: LABORATOIRES MAYOLY SPINDLER
Active Ingredient(s): MACROGOL 3350
Type of Procedure: Mutual Recognition
Submission Type: Variation
Submission Category: Type II
Submission Complexity: Standard
EU Procedure Number: UK/H/6021/001/II/004

REASON
To update SmPC sections 4.6, 5.3 and PIL following comments from the new CMS during a repeat use procedure.

BACKGROUND
The purpose of this variation is to amend the product information resulting from comments of the new CMS during the repeat use procedure UK/H/6021/001/E/001 for TRANSISOFT 8.5 g powder for oral solution in sachet.

RECOMMENDATION
Based on the review of the updated product information (SmPC, PIL and labelling), the RMS considers that the variation application UK/H/6021//001/II/004 is approvable.

EVALUATION
The updated SmPC sections are satisfactory. The updated PIL is satisfactory. The updated SmPC fragments and PIL have been incorporated into the Marketing Authorisation.

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

Decision – Approved on 14/11/2018