NER1006 (PLENVU/ PLEINVUE)

ATC Code: A06AD65

RISK MANAGEMENT PLAN (RMP)

Version 6.0

EU Risk Management Plan for PLENVU/ PLEINVUE (macrogol 3350, sodium ascorbate, sodium sulfate anhydrous, ascorbic acid, sodium chloride and potassium chloride)

RMP version to be assessed as part of this application:

RMP Version number: 6.0

Data lock point for this RMP: 31-Dec 2021

Date of final sign off: 28-Nov-2022

Rationale for submitting an updated RMP: To be submitted as part of a renewal application.

Summary of significant changes in this RMP:

Updated to EMA Revision 2 RMP template

Other RMP versions under evaluation: N/A

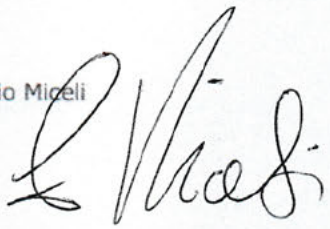
Details of the currently approved RMP:

Version number: 5.0

Approved with procedure: DCP n°SE/H/1801/001

Date of approval (opinion date): 31-May-2017

EU QPPV name: Fabio Miceli

EU QPPV signature: 

Associate Director, Senior Safety Physician name: [redacted]

Associate Director, Senior Safety Physician signature: [redacted]

Table of Contents

Part I: Product Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Macrogol 3350, sodium ascorbate, sodium sulfate anhydrous, ascorbic acid, sodium chloride and potassium chloride
Pharmacotherapeutic group(s) (ATC Code)	Osmotically acting laxative (A06A D65)
Marketing Authorisation Holder	**In all countries except UK, IT and PT:** Norgine B.V. Antonio Vivaldistraat 150, 1083 HP Amsterdam, The Netherlands **In the UK:** Norgine Limited Norgine House, Widewater Place, Moorhall Road, Harefield UB9 6NS United Kingdom **In IT:** Norgine Italia SRL **In PT:** Norgine Portugal Farmacéutica Unipessoal Lda.
Medicinal products to which this RMP refers	One (1)
Invented name(s) in the European Economic Area (EEA)	PLENVU/ PLEINVUE powder for oral solution PLENVU and PLEINVUE are registered trademarks of Norgine group of companies
Marketing authorisation procedure	Decentralised
Brief description of the product	Chemical class NER1006 is a macrogol (PEG) 3350 based bowel-cleansing agent intended for bowel cleansing prior to any procedure requiring a clean bowel. Its clinical efficacy derives from the osmotic action of macrogol 3350, sodium sulfate, ascorbic acid and sodium ascorbate acting together.
	Summary of mode of action NER1006 is an osmotically acting laxative. The oral administration of macrogol-based electrolyte solutions increases the stool volume, which triggers colon motility via neuromuscular pathways. It causes moderate diarrhoea and results in rapid emptying of the colon. The electrolytes included in the formulation and the supplementary clear fluid intake prevent clinically significant variations of sodium, potassium or water, and thus reduce the risk of dehydration and electrolytes imbalance.

	Important information about its composition N/A
Hyperlink to the Product Information	
Indication(s) in the EEA	Current (if applicable): For bowel cleansing prior to any procedure requiring a clean bowel.
	Proposed (if applicable): N/A
Dosage in the EEA	Current (if applicable): For adults and the elderly, a course of treatment consists of two separate non-identical 500 mL (approx. 16 US fl. oz.) doses of PLENVU. At least 500 mL (approx. 16 US fl. oz.) of additional clear fluid (e.g. water, clear soup, fruit juice without pulp, soft drinks, tea and/or coffee without milk) must be taken with each dose. PLENVU is not recommended for use in children below 18 years of age as PLENVU has not been studied in the paediatric population.
	Proposed (if applicable): N/A
Pharmaceutical form(s) and strengths	Current (if applicable): The ingredients of PLENVU are contained in three separate sachets/pouches. The first dose is supplied in one sachet/pouch and the second dose is supplied in two sachets/pouches, A and B. <u>Dose 1: – 1 sachet/pouch, contains the following:</u> Macrogol/Polyethylene Glycol (PEG) 3350 100.0 g Sodium sulfate anhydrous 9.0 g Sodium chloride 2.0 g Potassium chloride 1.0 g <u>Dose 2: – 2 sachets/pouches (A and B)</u> Dose 2 sachet/pouch A contains the following active substances: Macrogol/PEG 3350 40.0 g Sodium chloride 3.2 g Potassium chloride 1.2 g Dose 2 sachet/pouch B contains the following active substances:

	Ascorbic acid 7.5 g Sodium ascorbate 48.1 g
	Proposed (if applicable):
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Bowel cleansing prior to any procedure requiring a clean bowel

Incidence: No epidemiological data are available for bowel preparation. As a surrogate measure epidemiological data for colonoscopy procedure can be used since colonoscopy is the current standard method for evaluating the colon. In 2003, recommendations for screening programs were issued by the Council of the European Union (EU), the manner in which colorectal cancer (CRC) screening is carried out varies significantly from country to country within the EU. In recent years, a screening colonoscopy has been introduced, as either the only method (Poland) or the method of choice (Germany, Czech Republic, United Kingdom [UK][1].

Prevalence: It is estimated that about 15 million colonoscopies are performed every year in the EU, giving an incidence of about 5% of the overall population.

Demographics of the population in the authorised indication and risk factors for the disease: Although all segments of population could need bowel preparation for a colon procedure, the majority is expected to be > 50 years of age. Recent surveys have shown that the proportion of individuals aged 50 years or older who have undergone colonoscopy within the last 10 years is growing and currently ranges from 6%–25% in various European countries to 62% in the United States (US)[2,3].

Age sex distribution:

18-49 years: 20%

50-90 years: 80%

Bowel preparation before procedures requiring a clean bowel is generally considered safe especially with PEG based preparations. Preparation-induced mucosal inflammation has been reported associated with bowel preparation in conditions of suspicious inflammatory bowel disease (IBD) and has been reported 10 times more frequently with oral sodium phosphate and sodium picosulphate plus magnesium citrate inflammation than with PEG[4].

Comorbidities such as diarrhoea, vomiting, dysphagia, hyperglycaemia, and diuretic use can also reduce the threshold for symptomatic hypovolemia, which should be evaluated before the administration of bowel preparation agents. Isotonic electrolyte-mixed fluid is advisable for intravenous fluid replacement[5]. In addition, renal function should be evaluated in patients with any of the known predisposing conditions of kidney disease before bowel preparation and taken into consideration during selection of the most appropriate preparation[6].

The main existing treatment options: N/A

Natural history of the indicated condition in the untreated population, including mortality and morbidity: Bowel preparation before procedures requiring a clean bowel is generally considered safe especially with PEG based preparations. However, since bowel preparation is usually required in patients between 50-90 years age group, comorbidities such as diarrhoea, vomiting, dysphagia, hyperglycaemia, and diuretic use can also reduce the threshold for symptomatic hypovolemia, which should be evaluated before the administration of bowel preparation agents. Isotonic electrolyte mixed fluid is advisable for intravenous fluid replacement[5]. Fluid intake should continue until 2 hours before the colonoscopy, and isotonic electrolyte oral rehydration solutions may be of more benefit than plain water[7].

Part II: Module SII - Non-clinical part of the safety specification

Non-clinical studies have not been performed specifically with NER1006. The safety of NER1006 is based on literature and available non-clinical studies conducted by Norgine with other macrogol/PEG containing products, namely MOVICOL® and MOVIPREP®. Norgine markets macrogol/PEG-based electrolyte-balanced product, MOVICOL® for the treatment of constipation and faecal impaction. This was first launched in Europe in 1996. MOVIPREP® has been available in the EU and the US since 2006 and thus has a well-established clinical use. A comparison of the NER1006, MOVIPREP® and MOVICOL® formulations are presented below:

Table1: Composition and Dosages Comparison (NER1006, MOVIPREP®, MOVICOL®)

	NER1006		MOVIPREP®		MOVICOL®		
	Total Oral Administration		Total Oral Administration		Oral Dose	Oral Dose[2]	Oral Dose[3]
	g/person	mg/kg[1]	g/person	mg/kg[1]	(g/pouch)	(mg/kg/day)	(mg/kg / day)
Macrogol/PEG 3350	140.00	2000	200	2850	13.125	563	1501
Sodium sulfate anhydrous	9.00	129	15	214	-	-	-
Sodium ascorbate	48.11	687	11.8	169	-	-	-
Ascorbic acid	7.54	108	9.4	134	-	-	-
Sodium chloride	5.20	74	5.38	77	0.3507	15	40
Potassium chloride	2.20	31	2.03	29	0.0466	2	5
Sodium bicarbonate	-	-	-	-	0.1785	8	21

1 bodyweight adjustment for a 70 kg person.
2 following administration of 3 sachets/day for constipation to a 70 kg person
3 following administration of 8 sachets/day for faecal impaction to a 70 kg person

Fourteen-day Good Laboratory Practice (GLP) oral dose rat and dog toxicity studies with MOVIPREP® were performed by Norgine. In addition, Norgine has conducted a GLP safety pharmacology study and a range of modern GLP toxicology studies for MOVICOL® as detailed below:

- single oral dose rat diuresis and saluresis study
- 7-day and 3-month oral dose rat toxicity studies
- range-finding and 3-month oral dose dog toxicity studies
- bacterial reverse mutation assay (Ames) test, in vitro mouse lymphoma assay and in vivo mouse micronucleus test
- rat fertility, rat and rabbit embryo-foetal and rat pre- and post-natal studies

Extensive non-clinical literature also exists for the components of NER1006 and relevant data will be presented for each ingredient, with particular reference to the main ingredients macrogol/PEG 3350, sodium ascorbate/ascorbic acid and sodium sulfate. It should be noted that some of these

data are not up to the standard of today's modern study designs and their conduct is not necessarily consistent with current international guidelines. However, the data are still considered to be sufficiently robust to assess the safety of NER1006.

Key safety findings from non-clinical studies and relevance to human usage:

Key Safety findings (from non-clinical studies)	**Relevance to human usage**
<u>Single dose toxicity:</u> Due to the established toxicity profile of the components of macrogol/PEG-3350, no stand-alone single dose toxicity studies were performed.	N/A
<u>Repeat dose toxicity:</u> <u>Macrogol/PEG 3350</u> Repeat dose toxicity studies in rats and dogs of 2 weeks duration showed that huge oral doses (in the high g/kg range) of the associated macrogol/PEG-based electrolyte MOVIPREP® were well tolerated, with no-observed-adverse-effect-levels (NOAEL) of 10000 and 20000 mg/kg, respectively, established. Study findings (which resolved after an off-dose period) at these doses were typical of an expected exaggerated pharmacodynamic (PD) response for an osmotically active material, causing continuous soft faeces (rats) or diarrhoea and emesis (dogs), and in rats, reduced food intake, increased water consumption, minor changes in various clinical pathology and urinalysis parameters, and increased kidney weight. Repeat dose toxicity studies with the related macrogol/PEG-based electrolyte drug for constipation MOVICOL®, in rats and dogs for up to 3 months duration, showed that huge oral doses (in the high g/kg range) were well tolerated, with a NOAEL of 10000 mg/kg established for both species. Findings at higher doses (up to 60000/50000 mg/kg/day) were typical of an expected exaggerated pharmacodynamic response for an osmotically active material, causing continuous soft faeces/diarrhoea (rats) or diarrhoea and emesis (dogs), and included reduced bodyweight and/or food consumption, alterations in various clinical pathology and urinalysis parameters, and in rats, increased water consumption and various organ weight changes, and caecal enlargement. No histopathological findings attributed to MOVICOL® were seen. Study findings showed recovery after non-dose periods. Overall, none of these findings are unexpected given the gastrointestinal disturbances and stress associated with a laxative given over a prolonged period. A further consideration is that the considerable	No specific safety risks were identified with macrogol/PEG 3350 at the therapeutic doses intended for human use.

Key Safety findings (from non-clinical studies)	Relevance to human usage
amount of non-absorbable material (particularly macrogol/PEG 3350) in the gut would be expected to limit the ingestion of much of the animal's diet, even if it had much of an appetite, with a consequential interference with the absorption of nutrients. <u>Other constituents:</u> Sodium sulfate has low toxicity, with an oral LD50 value in the rat of >10000 mg/kg. Although limited, repeat dose toxicity data supports this low toxicity, with only occasional high dose diarrhoea and subsequent dehydration observed. Ascorbic acid and sodium ascorbate have low toxicity, with an oral LD50 value in mice and rats of 3370-8021 and >5000 11900 mg/kg, respectively. Although not to today's standards, repeat dose toxicity studies in rodents supports this lack of general toxicity, with levels in the g/kg levels well tolerated. Citric acid has low oral toxicity, with LD50 value in mice and rats ranging from 5400-5790 mg/kg and 3000-12000 mg/kg, respectively. The NOAEL for 2-year chronic toxicity study in rats was 1200 mg/kg/day. The artificial sweetener sucralose is generally regarded as a non-toxic material, on account that orally administered sucralose is poorly absorbed from the gastrointestinal tract. It has approved use in the US as a table top sweetener and as an additive in a variety of food products, with an acceptable daily intake (ADI) of 0-15 mg/kg. It has low oral toxicity, with LD50 value in mice and rats of >16000 mg/kg and >10000 mg/kg, respectively. Repeated oral gavage administration of sucralose was well tolerated and without toxicity in rats given 3000 mg/kg/day for 26 weeks. The dietary administration of sucralose to dogs at 0.3, 1 and 3% for 52 weeks was well tolerated and without toxicity; achieved doses ranged from 89 to 889 g/kg/day. In contrast, the sub-chronic and chronic dietary administration of sucralose to rats at 0.3, 1 and 3%, resulted in reduced food consumption, reduced body weight gain and alterations in relative organ weights. However, these effects were shown to be related to the unpalatability of the sucralose-containing diets and not as a consequence of a direct toxic effect, as no similar findings were seen in the 26-week oral gavage study in rats. None of the other formulation constituents of NER1006 (sodium chloride, potassium chloride, aspartame, or	No specific safety risks were identified with other constituents of NER1006 at the therapeutic doses intended for human use.

Key Safety findings (from non-clinical studies)	Relevance to human usage
flavours) are expected to show any toxicity from their proposed use.	
<u>Reproductive and developmental toxicity, genotoxocity and carcinogenicity</u> <u>Macrogol/PEG 3350</u> Macrogol/PEG 200 to 1540 have been tested to various extents for potential to interfere with reproduction or to cause harm to the developing foetus. No effects on either parameter have been observed in this class of compounds larger than macrogol/PEG 200, despite the recognised teratogenic effects of ethylene glycol[8]. With regard to ethylene glycol, it has been determined that glycolic acid, one of the metabolites of ethylene glycol, is the proximate teratogen[9]. Developmental effects appear to be diminished for diethylene glycol relative to ethylene glycol. Subcutaneous administration of 2.25 g/kg/day of triethylene glycol to mice, rats and rabbits during selected periods of gestation produced no teratogenic effects. Likewise, no harmful effects on the foetuses were noted when pregnant rats were given as much as 4.5 g/kg/day orally. Macrogol/PEG 200 administered orally to mice at levels of 0.5 to 0.7 mL/mouse resulted in reduced foetal body weight and dose-related increases in malformations of the skeleton. However, in rats given 1.5 to 5 mL/rat, no effects were seen even at maternally toxic doses. Therefore, differential species sensitivity is apparent in response to macrogol/PEG 200. The degree of purity of the macrogol/PEG 200 was not stated. When macrogol/PEG 400 was given orally to rats and rabbits, no effects on body weight, food consumption or reproductive parameters were observed, and fetuses developed normally. Macrogol/PEG 1540 given to rats at 4% in the diet resulted in no effects on fertility or reproductive parameters, e.g. litter size, live births, pups born dead, number of pups weaned, and weights of pups at weaning, when exposure was continued over three generations. Several oral developmental and reproduction toxicity studies, (including a multigeneration study), have been performed in mice and rats by the cosmetics industry using various macrogol/PEG derivatives. Typical results are noted for macrogol/PEG-30, -33, -35, -36, -40 castor oil	No specific safety risks were identified with macrogol/PEG 3350 at the therapeutic doses intended for human use.

Key Safety findings (from non-clinical studies)	Relevance to human usage
and macrogol/PEG-30, -40 hydrogenated castor oil. There was no evidence that these were developmental or reproductive toxicants. Various studies on Macrogol/PEG 200-6000 confirmed no genotoxic potential and a two-year dietary study of PEG 4000 demonstrated no evidence of carcinogenicity. <u>Other constituents:</u> Limited data has shown that sodium sulfate is not genotoxic or reprotoxic, and although data are lacking, it is unlikely to be carcinogenic given its normal presence in the body. Although some positive in vitro genotoxicity findings were seen with ascorbic acid and sodium ascorbate, it is thought that these are related to formation of hydrogen peroxide and reactive oxygen species, (and consequent DNA damage), by the oxidation of high concentrations of ascorbic acid and would not be expected to be expressed in vivo under normal conditions. Indeed, ascorbic acid showed no in vivo genotoxicity and was not carcinogenic. Furthermore, it was not reprotoxic. Citric acid showed no in vitro or in vivo genotoxicity and was not carcinogenic in a limited carcinogenicity study in 20 male rats. Citric acid was not reprotoxic in mice, rats, hamsters and rabbits. Sucralose showed no in vitro or in vivo genotoxicity and was not carcinogenic in mice and rats. Sucralose was not reprotoxic in rats and rabbits. None of the other formulation constituents of NER1006 (sodium chloride, potassium chloride, aspartame, or flavours) are expected to show any genotoxicity, reproductive toxicity or carcinogenicity from their proposed use.	No specific safety risks were identified with other constituents of NER1006 at the therapeutic doses intended for human use.
<u>Drug-drug interactions:</u> No interactions of macrogol/PEG 3350 with other drugs are apparent, but various molecular weights of macrogol/PEG are used in pharmaceutical formulations to increase the aqueous solubility of drugs, so there may be some potential for macrogol/PEG in this product to affect the absorption of oral drugs taken concurrently. However, such an occurrence is clinically unlikely, so this possibility is self-limiting. Large doses of ascorbic acid (1g vitamin C) daily for several days have been reported to increase the plasma	No specific drug-drug interactions are anticipated with NER1006.

Key Safety findings (from non-clinical studies)	Relevance to human usage
concentration of the contraceptive hormone ethinylestradiol in women[10,11], but it is not known whether these changes would result from a single dose. The dissociation products of sodium sulfate enter into the body's pools and are incorporated into many physiological reactions involving sulfation. No specific drug interactions are anticipated.	

Part II: Module SIII – Clinical trial exposure

NER1006 is a macrogol (PEG) 3350 based bowel-cleansing agent intended for bowel cleansing prior to any procedure requiring a clean bowel. Its clinical efficacy derives from the osmotic action of macrogol 3350, sodium sulfate, ascorbic acid and sodium ascorbate acting together. NER1006 (PLENVU) has been developed as an improved macrogol 3350-electrolyte balanced lavage solution. It provides improved bowel cleansing efficacy, improved taste and a drinking volume of only 1 L of the reconstituted NER1006 bowel preparation.

The clinical development programme for NER1006 consisted of one Phase I study (NER1006-01/2011 [OUT]), one Phase II study (NER1006-01/2012 [OPT]), three Phase III studies (NER1006-01/2014 [NOCT], NER1006-02/2014 [MORA] and NER1006-03/2014 [DAYB]) and pharmacokinetic study NER1006-03/2016 (PKPU).

The early development followed a two-stage process conducted via the OUT and OPT studies. The preferred evening and morning formulation combination was identified using the OUT study. Here, the preferred combination was identified primarily through assessment of stool weight, together with demonstration of the actives in expelled stool. To improve patient acceptability and tolerability of the prototype NER1006 for Phase II, optimisation of the taste and flavour of the preferred evening and morning doses from Phase I was performed. A different flavour was assigned to each of the two doses. Different regimens of the taste- and flavour-optimised doses were then assessed in the OPT study to identify the most suitable treatment regimen for further investigation in larger studies (Phase III). Pharmacodynamic and pharmacokinetic assessments were included in both the OUT and the OPT studies. For blood plasma and faeces, samples were taken for PEG, ascorbate (including oxalate), sulfate and electrolytes (sodium, potassium and chloride). Tests were also performed for ascorbate, sulfate and electrolytes in urine. The NER1006 regimen for Phase III was selected primarily through assessment of stool weight, cleansing efficacy, and confirmation of actives in expelled stool. Cleansing efficiency was assessed using the Harefield Cleansing Score in the early stages, and both Harefield Cleansing Scale and the Boston Bowel Preparation Scale in the Phase III efficacy and safety studies (NOCT, MORA and DAYB).

NER1006-03/2016 (PKPU) was a pharmacokinetic study of PLENVU in healthy subjects. This was a single centre, open-label, non-randomised, study in healthy adult subjects to investigate the PK of PLENVU as a powder for oral solution formulation (PLENVU Dose 1 and PLENVU Dose 2).

All studies have been completed, no studies are ongoing and no further studies in adult population are currently planned. A Paediatric Investigation Plan (PIP) is in place following a positive decision from the EMA.

NER1006 is an osmotically acting laxative. The oral administration of macrogol-based electrolyte solutions increases the stool volume, which triggers colon motility via neuromuscular pathways. It causes moderate diarrhoea and results in rapid emptying of the colon. The electrolytes present in the formulation and the supplementary clear liquid intake are included to prevent clinically significant variations of sodium, potassium or water, and thus reduce the risk of dehydration. The ingredients of NER1006 are contained in three separate sachets. A course of treatment consists of two separate non-identical 500 mL doses of NER1006. At least 500 mL of additional clear fluid (e.g. water, clear soup, fruit juice without pulp, soft drinks, tea and/or coffee without milk) must be taken with each dose. This course of treatment can be taken according to any of the three schedules specified below:

- Two-day split dosing schedule with the first dose taken in the evening before the clinical procedure (approximately 18:00H) and the second dose taken in the early morning of the day of the clinical procedure (approximately 06:00H).
- Morning only dosing schedule with both doses taken in the morning of the day of the clinical procedure (the first dose taken at approximately 05:00H). The two doses should be separated by a minimum 1-hour interval.
- Day before dosing schedule with both doses taken in the evening before the clinical procedure (the first dose taken at approximately 18:00H). The two doses should be separated by a minimum 1-hour interval.

It is mandated that one litre of clear fluid, which may include, water, clear soup, fruit juice without pulp, soft drinks, tea and/or coffee without milk, is also taken during the course of treatment.

NER1006 is not recommended for use in children below 18 years of age as NER1006. A paediatric investigation plan (PIP) for PLENVU was approved by the EMA on 07-Oct-2016, and the most recent modification was accepted by the EMA on 01-Dec-2020. With regards to the indication of bowel cleansing to prior procedures, the waiver applies to:

- the paediatric population from birth to less than 1 year of age;
- powder for oral solution, oral use, gastric use;
- on the grounds that the specific medicinal product does not represent a significant therapeutic
- benefit over existing treatments

The below table describes the measures in the PIP:

Area	**Number of Measures**	**Description**
Quality-related studies	2	**Study 1** Development of a measuring/dispenser device with suitable graduation for all paediatric age groups. **Study 2** Evaluation of physical compatibility of NER1006 with feeding tubes.
Non-clinical studies	0	N/A
Clinical studies	3	**Study 3** Randomised, colonoscopist-blind, controlled, parallel group study, with a dose determination run-in phase, to evaluate efficacy, safety, pharmacokinetics, tolerability, acceptability and palatability of NER1006 in children from 12 to less than 18 years of age undergoing colonoscopy, using a standardised active comparator. **Study 4** Randomised, colonoscopist-blind, controlled, parallel group study, with a dose determination run-in phase, to evaluate efficacy, safety, pharmacokinetics, tolerability, acceptability and palatability of NER1006 in children from 2 to less than 12 years of age undergoing colonoscopy, using a standardised active comparator. **Study 5** Randomised, colonoscopist-blind, controlled, parallel group study, with a dose determination run-in phase, to evaluate efficacy, safety, pharmacokinetics and tolerability of NER1006 in children from 1 to less than 2 years of age undergoing colonoscopy, using a standardised active comparator.
Extrapolation, modelling and simulation studies	0	N/A
Other studies	0	N/A
Other measures	0	N/A

Randomised, blinded trial population only

Dosage for all randomised blinded studies:

There are no randomised subject-blinded studies. All studies were open-label with respect to subject, and blinded only with respect to the colonoscopist; the dosage for these studies is detailed below. The metrics reported in Tables 1-5 below are for the taste/flavour-optimised NER1006 regimens used in the Phase II and Phase III clinical trials.

Doses used in randomised clinical trials:

NER1006 is not intended for continuous use, i.e. it was administered in randomised clinical trials as a single split-dosing treatment taken over one to two days according to one of the following dosing schedules:

- The first dose in the evening before the procedure and the second dose in the morning of the day of the procedure, or
- Both doses in the morning of the day of the procedure, or
- Both doses in the evening before the procedure

Irrespective of dosing schedule the total dose is administered within a single 24-hour period. Data presented in the tables below include subjects who took any amount of NER1006.

Table 1: Duration of exposure (by indication)

Indication: For bowel cleansing prior to any procedure requiring a clean bowel		
Duration of exposure (at least)	**Persons**	**Person time**
24 hours	1047	1047 days
Total person time		**1047 days**
Healthy Volunteers		
Duration of exposure (at least)	**Persons**	**Person time**
24 hours	19	19 days
Total person time		**19 days**

Table 2: By age group[1] (by indication)

Indication: For bowel cleansing prior to any procedure requiring a clean bowel		
Age group	**Persons**	**Person time**
< 45	191	191 days
45 ≤ age ≤ 65	639	639 days
65 ≤ age	217	217 days
Total	**1208**	**1208 days**

Table 3: By gender (by indication)		
Indication: For bowel cleansing prior to any procedure requiring a clean bowel		
Gender	**Persons**	**Person time**
Male	463	463 days
Female	584	584 days
Total	**1047**	**1047 days**

Table 4: Ethnic origin of study population – clinical trials		
Indication: For bowel cleansing prior to any procedure requiring a clean bowel		
Ethnicity	**Persons**	**Person time**
Not Hispanic/Latino	825	825 days
Hispanic/Latino	203	203 days
Unknown	19	19 days
Total	1047	1047 days
Race	**Persons**	**Person time**
White	990	990 days
Black	43	43 days
Asian	11	11 days
Other	3	3 days
Total	1047	1047 days

Part II: Module SIV – Populations not studied in clinical trials

SIV. 1 Exclusion criteria in pivotal clinical studies within the development programme

Patients recruited to the clinical programme were representative of the population for which NER1006 use is intended. In general, most of the criteria in the NER1006 clinical development programme, such as the exclusion of patients with concomitant diseases, are consistent with those commonly used in drug development clinical trials and are required by Ethics Committees. The following populations were not studied in the clinical trials:

Paediatric populations

Reason for exclusion: No study was conducted in children under the age of 18 years. NER1006 is not intended to be used in this patient population.

Is it considered to be included as missing information?: No

Rationale: PLENVU is not indicated for use in children below 18 years of age, as stated in the EU common SmPC. No further characterisation or risk minimisation through additional risk management activities are considered necessary.

Patients who are pregnant or lactating, or intending to become pregnant during the study

Reason for exclusion: These patients were excluded. Colonoscopy may be conducted in pregnant patients. NER1006 is not intended to be used in this patient population.

Is it considered to be included as missing information?: No

Rationale: Use of PLENVU should be avoided, as stated in the SmPC. The SmPC states that it is unknown whether PLENVU is excreted in human milk, however a risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to abstain from PLENVU therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. No further characterisation or risk minimisation through additional risk management activities are considered necessary.

Patients with severe renal, cardiac or hepatic impairment:

Reason for exclusion: Patients with severe renal insufficiency, Grade III and IV cardiac insufficiency and Grade B and C liver disease according to the Child Pugh classification were excluded from the clinical trials, as in these situations, the procedure itself can be considered dangerous. However, if a colonoscopy is absolutely necessary, NER1006 may be used under strict medical monitoring.

Is it considered to be included as missing information?: No

Rationale: There are warnings in the SmPC to state PLENVU should be used with caution in patients with renal impairment whose creatinine clearance is less than 30 mL/minute/1.73 m^2 or patients with grade III or IV cardiac failure.

No special dosage adjustment of PLENVU is deemed necessary in patients with mild to moderate renal or hepatic impairment.

Patients with impaired consciousness that might predispose them to pulmonary aspiration:

Reason for exclusion: These patients were excluded from the clinical trials. Patients fed with gastric tubes and patients in poor condition unable to drink, should be given special attention due to the risk of aspiration - especially in case of administration via a nasogastric tube.

Is it considered to be included as missing information?: No.

Rationale: There are warnings in the SmPC to state PLENVU should be used with caution in patients with impaired gag reflex, with the possibility of regurgitation or aspiration, or with diminished levels of consciousness. Such patients should be closely observed during administration especially if given via a nasogastric route.

G6PD deficient patients:

Reason for exclusion: This genetic deficiency is a rare event, generally not known by the patient; the theoretical risk related to high doses of ascorbic acid and based on literature survey only, is a possibility of blood haemolysis. If the condition is known, use of NER1006 is not recommended. In case of use, close monitoring of red cell count, haptoglobin, and bilirubin is recommended. It is of interest to notice that after 15 years of use of macrogol/PEG 3350 containing products in different markets, and more than 19 million patients exposed, no case of acute haemolysis has been reported so far.

Is it considered to be included as missing information?: No

Rationale: Use in patients with glucose-6-phosphate dehydrogenase deficiency is contraindicated as per the SmPC.

Patients with ongoing severe acute Inflammatory Bowel Disease (IBD):

Reason for exclusion: These patients were excluded from the clinical trials since bowel preparation in such patients may cause or aggravate mucosal damage. NER1006 is not recommended for this patient population.

Is it considered to be included as missing information?: No

Rationale: There are warnings in the SmPC to state PLENVU should be used with caution in patients with severe acute inflammatory bowel disease. PLENVU is contraindicated for use in patients with gastrointestinal obstruction or perforation, ileus, disorders of gastric emptying, e.g. gastroparesis, gastric retention, etc., and toxic megacolon.

Patients with active intestinal bleeding episodes or with a clinically significant low haemoglobin level <9 g/dL for women and <11 g/dL for men at screening:

Reason for exclusion: These patients were excluded from the clinical trials.

Is it considered to be included as missing information?: No

Rationale: There are warnings in the SmPC to state PLENVU should be used with caution in patients with severe acute inflammatory bowel disease. PLENVU is contraindicated for use in patients with known or suspected gastrointestinal obstruction or perforation.

History of uncontrolled hypertension with systolic blood pressure >170 mmHg and diastolic blood pressure >100 mmHg:

Reason for exclusion: These patients were excluded from the clinical trials.

Is it considered to be included as missing information?: No

Rationale: The SmPC for PLENVU states that transient increase in blood pressure is a listed event with a frequency of uncommon (≥1/1,000 to <1/100).

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency.

Children

No study was conducted in children. NER1006 is not recommended for use in children below 18 years of age.

A paediatric investigation plan (PIP) for PLENVU was approved by the EMA on 07-Oct-2016, and the most recent modification was accepted by the EMA on 01-Dec-2020. With regards to the indication of bowel cleansing to prior procedures, the waiver applies to:

- the paediatric population from birth to less than 1 year of age;
- powder for oral solution, oral use, gastric use;
- on the grounds that the specific medicinal product does not represent a significant therapeutic
- benefit over existing treatments

The below table describes the measures in the PIP:

Area	Number of Measures	Description
Quality-related studies	2	**Study 1** Development of a measuring/dispenser device with suitable graduation for all paediatric age groups. **Study 2** Evaluation of physical compatibility of NER1006 with feeding tubes.
Non-clinical studies	0	N/A
Clinical studies	3	**Study 3** Randomised, colonoscopist-blind, controlled, parallel group study, with a dose determination run-in phase, to evaluate efficacy, safety, pharmacokinetics, tolerability, acceptability and palatability of NER1006 in children from 12 to less than 18 years of age undergoing colonoscopy, using a standardised active comparator. **Study 4** Randomised, colonoscopist-blind, controlled, parallel group study, with a dose determination run-in phase, to evaluate efficacy, safety, pharmacokinetics, tolerability, acceptability and palatability of NER1006 in children from 2 to less than 12 years of age undergoing colonoscopy, using a standardised active comparator. **Study 5** Randomised, colonoscopist-blind, controlled, parallel group study, with a dose determination run-in phase, to evaluate efficacy, safety, pharmacokinetics and tolerability of NER1006 in children from 1 to less than 2 years

		of age undergoing colonoscopy, using a standardised active comparator.
Extrapolation, modelling and simulation studies	0	N/A
Other studies	0	N/A
Other measures	0	N/A

Elderly

Not applicable; elderly patients were not excluded from the clinical development programme. The clinical trial population included patients between 18 and 85 years of age.

Pregnant or breast-feeding women The EU SmPC states there are no or limited amount of data (less than 300 pregnancy outcomes) from the use of PLENVU active ingredients in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Clinically, no effects during pregnancy are anticipated, since systemic exposure to macrogol 3350 is negligible. As a precautionary measure, it is preferable to avoid the use of PLENVU during pregnancy.

Patients with hepatic impairment

Patients with hepatic impairment (Grade B and C liver disease according to the Child Pugh classification) were not studied in the clinical trials programme. However, the product is regarded as a biologically inert polymer which is barely absorbed and is not believed to be metabolised. Therefore, hepatic impairment is not considered to be a concern.

Patients with renal impairment

In the Phase 3 studies, two studies (NOCT and DAYB) excluded patients with moderate to severe renal insufficiency (i.e. with GFR <60 mL/min/1.73m^2). However, in the MORA study patients with only severe renal insufficiency (i.e. with GFR <30 mL/min/1.73m^2) were excluded.

Overall 31 patients with moderate renal insufficiency and 660 patients with mild renal insufficiency were treated with NER1006 in the phase 3 studies. No relevant safety differences were identified for all the subgroups.

Table 1: Patients with renal insufficiency

Study	Renal insufficiency	NER1006 Subjects (subjects with TEAEs)	Comparator (Trisulfate/MOVIPREP/SP+MS)
NOCT		**N=262**	**N=265**
	Mild	164 (48)	160 (27)
	Moderate	2 (1)	1 (1)
MORA		**N=531**	**N=263**
	Mild	360 (57)	172 (19)
	Moderate	26 (8)	11(0)
DAYB		**N=235**	**N=241**
	Mild	136 (21)	148 (14)
	Moderate	3 (1)	4 (1)
Overall		**N=1028**	**N=769**

	Mild	660 (126)	480 (60)
	Moderate	31 (10)	16 (2)

NER1006 contains macrogol 3350, a biologically inert polymer which is barely absorbed. It does not exert its activity through pharmacological means, but via an osmotic effect in the gut where absorption is negligible.

A course of treatment consists of two separate non-identical 500 ml doses of NER1006. At least 500 ml of additional clear fluid, which may include water, clear soup, fruit juice without pulp, soft drinks, tea and/or coffee without milk must be taken with each dose. This course of treatment can be taken according to any of the three schedules specified below:

- Two-day split dosing schedule with the first dose of NER1006 taken in the evening before the clinical procedure (approximately 18.00H) and the second dose in the early morning of the day of the clinical procedure (approximately 06.00H), or
- Morning only dosing schedule with both doses taken in the morning of the day of the clinical procedure (the first dose taken at approximately 05.00H); the two doses should be separated by a minimum 1-hour interval, or
- Day before dosing schedule with both doses taken in the evening before the clinical procedure (the first dose taken at approximately 18.00H); the two doses should be separated by a minimum 1-hour interval.

Since in total, one litre of fluid is taken with each NER1006 dose (500 ml prepared dose plus 500 ml additional clear fluid), there is a theoretical risk of fluid overload in the patients with severe renal insufficiency. Two-day split dosing in these patients may be more appropriate.

A previous post-marketing safety review of the Applicant's other bowel preparations containing macrogol/PEG 3350 was undertaken using data from launch of each product to the data lock of 15 May 2016. This included a review of renal impairment/renal failure. The data reviewed suggested that renal events occur only infrequently with these products in the context of over 20 million patients exposed. However, potential risk remains and hence the precautionary labelling advice for treatment with caution in severe renal impairment patients whose creatinine clearance is less than 30 mL/minute.

Patients with other relevant co-morbidities

Patients with cardiovascular disease

A total of 56 patients were included in this subgroup analysis, of which 30 were treated with NER1006 and 26 with comparators. No significant difference in the rate of AEs was seen in the two subgroups and when compared with overall incidence of TEAEs.

Table 2: Presence of cardiovascular diseases

Study	Cardiac disease	NER1006 Subjects (subjects with TEAEs)	Comparator (Trisulfate/MOVIPREP/SP+MS)
NOCT		**N=262**	**N=265**
	Present	10 (3)	11 (2)
MORA		**N=531**	**N=263**
	Present	10 (3)	5 (3)
DAYB		**N=235**	**N=241**
	Present	10 (5)	10 (1)
Overall		**N=1028**	**N=769**
	Present	30 (11)	26 (6)

A previous cumulative review of post-marketing reports of cardiac events across the Applicant's other macrogol/PEG 3350 containing bowel preparations (May 2016) did not identify a causal link between macrogol and cardiac events. Based on a cumulative review of post- marketing reports in patients with a history of cardiac disorder (including but not limited to cardiac failure, previous myocardial infarction, hypertension, arrhythmias,) being treated with macrogol containing bowel preparations, though there have been infrequent reports, there is no clear evidence that these patients are experiencing cardiac decompensation or worsening of cardiac events, in the context of approximately 20 million patients exposed. However, a theoretical risk remains and hence the precautionary labelling advice for treatment with caution in grade III or IV cardiac failure and those at risk of arrhythmia, for example those on treatment for cardiovascular disease or who have thyroid disease.

Patients with inflammatory bowel disease (IBD)

Few patients with IBD have been exposed in clinical trials. A total of 39 patients were considered in this subgroup analysis, 20 treated with NER1006 and 19 treated with comparators. No significant difference in the rate of AEs was seen in the two subgroups and when compared with overall incidence of TEAEs.

Table 3: Inflammatory bowel disease

Study	Inflammatory bowel disease	NER1006 Subjects (subjects with TEAEs)	Comparator (Trisulfate/MOVIPREP/SP+MS)
NOCT		**N=262**	**N=265**
	Present	3 (0)	5 (1)
MORA		**N=531**	**N=263**
	Present	9 (1)	4 (1)
DAYB		**N=235**	**N=241**
	Present	8 (1)	10 (1)
Overall		**N=1028**	**N=769**
	Present	20 (2)	19 (3)

Since NER1006 is an osmotic laxative, inflamed intestinal mucosa in severe IBD (Crohn's disease, Ulcerative Colitis) may affect the clinical effectiveness and may also be at risk of rupture/perforation

at least theoretically, hence the precautionary labelling advice for treatment with caution in severe acute IBD and contraindication for toxic megacolon.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Type of special population	Exposure
Use in paediatric population	N/A - not included in the clinical development program.
Use in pregnancy and lactation	
Patients with hepatic impairment	
Population with relevant different ethnic origin	Not applicable; patients of different racial and/or ethnic origin have not been formally studied in the NER1006 clinical development programme. As macrogol 3350 is a biologically inert polymer, which is barely absorbed and does not exert its activity through pharmacological means, differences in racial and/or ethnic origin are unlikely to have an impact on patient safety.
Subpopulations carrying relevant genetic polymorphisms	Not applicable; genetic polymorphisms have not been formally studied in the NER1006 clinical trial population. As macrogol 3350 is considered to be a biologically inert polymer, which is barely absorbed and does not exert its activity through pharmacological means, sub-population differences based on polymorphisms are unlikely to have an impact on patient safety.
Patients with a disease severity different from the inclusion criteria in the clinical trial population	Not applicable – the indication is not a disease. NER1006 is indicated for bowel cleansing prior to any procedure requiring a clean bowel.
Patients with renal impairment	In the Phase 3 studies, two studies (NOCT and DAYB) excluded patients with moderate to severe renal insufficiency (i.e. with GFR <60 mL/min/1.73m2). However, in the MORA study patients with only severe renal insufficiency (i.e. with GFR <30 mL/min/1.73m2) were excluded. Overall 31 patients with moderate renal insufficiency and 660 patients with mild renal insufficiency were treated with NER1006 in the phase 3 studies. No relevant safety differences were identified for all the subgroups.
Patients with intermittent or continuous presence of cardiovascular diseases	A total of 56 patients were included in this subgroup analysis, of which 30 were treated with NER1006 and 26 with comparators. No significant difference in the rate of AEs was seen in the two subgroups and when compared with overall incidence of TEAEs.

Patients with inflammatory bowel disease (IBD)	Few patients with IBD have been exposed in clinical trials. A total of 39 patients were considered in this subgroup analysis, 20 treated with NER1006 and 19 treated with comparators. No significant difference in the rate of AEs was seen in the two subgroups and when compared with overall incidence of TEAEs.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

An estimate of patient exposure is calculated based on worldwide sales volume in grams of active substance sold during the reporting interval. PLENVU is indicated for bowel cleansing prior to any procedure requiring a clean bowel, and therefore it is assumed that one pack sold would equate to one patient exposed.

SV.1.2 Exposure

Cumulatively from Nov-2017 to Dec-2021, there were a total of 7,216,179 units of PLENVU sold and therefore exposure was calculated to be 7,216,179 patients.

Post authorization exposure data are not available by age or gender. There is only one dose and one indication for PLENVU. A breakdown of data by age, gender, indication, route of administration and dose is not currently available.

Part II: Module SVI – Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

PLENVU contains no active ingredients that would have abuse potential, and will be prescribed as a single treatment for bowel cleansing, hence there is no potential for misuse for illegal purposes.

Part II: Module SVII – Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

The safety concerns listed below were present in the initial approved RMP version 5 dated 31-Jul-2017: **Summary of safety concerns**	
Important identified risks	Dehydration
	Electrolyte disturbance
	Transient increase in blood pressure
	Transient increase in liver enzymes
	Allergic reactions (including anaphylaxis)
Important potential risks	Arrhythmias (including atrial fibrillation)
	Perforation/aggravation of the condition in patients with toxic megacolon as a result of severe IBD
	Aspiration in patients with diminished levels of consciousness/severely debilitated patients especially if prepared with a nasogastric tube
	Cardiac failure/decompensation
	Acute renal failure/decompensation
	Potential to alter absorption and decrease efficacy of other medicinal products
Missing information	Use in patients with glucose-6-phosphate dehydrogenase deficiency
	Use in paediatric population
	Use in pregnancy/lactation

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable as the initial RMP was approved in RMP EMA template Rev 1.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable as the initial RMP was approved in RMP EMA template Rev 1.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable as no safety concerns have been added or reclassified.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk: Dehydration

Potential mechanisms: NER1006 is an osmotic laxative used for bowel cleansing prior to any procedure requiring a clean bowel. Diarrhoea is an expected outcome of this treatment. In total, both doses of NER1006 when prepared contain 1 litre of fluid. At least 1 litre of additional clear fluid is mandated to provide fluid haemostasis in the body. Patients with lesser sensation of thirst and not abiding by the fluid intake instructions are at a higher risk of losing more water in stools than the intake and hence can develop dehydration. Fluid replacement (orally or intravenous) may be required in these patients.

Evidence source(s) and strength of evidence: In one American study, dehydration was diagnosed in 6.7% of hospitalised patients age 65 and over, and 1.4% had dehydration as the principal diagnosis[12]. Prospective studies in long-term care facilities (LTCs) showed that residents were dehydrated in 50% of the febrile episodes and that 27% of the LTC resident population referred to hospitals was admitted due to dehydration[13,14]. Dehydration also proved to be very common in community-dwelling older adults[15].

Characterisation of the risk: The incidence of dehydration during the clinical development programme was low. Dehydration was reported in 16 of 1028 patients (1.6%) in the NER1006 treatment group. Two of these cases were considered not related to the study treatment by the investigator and the remaining 14 cases (1.4%) were considered related. Hyperosmolar state was reported in 3 cases (0.3%) and blood osmolarity increased was reported in 2 cases (0.2%), all considered related.

All of the 16 cases of dehydration were reported as non-serious. Outcome was reported as resolved in all cases. Severity was reported to be mild to moderate in all 16 cases of dehydration.

Risk factors and risk groups: Older people are vulnerable to dehydration due to physiological changes in the ageing process, but this can be complicated by many disease states, and mental and physical frailty that can further increase risk of dehydration. Age-related changes include a reduced sensation of thirst, and this may be more pronounced in those with Alzheimer's disease or in those that have suffered a stroke. This indicates that thirst in older people may not be relied on as an indicator of dehydration. Reduced renal function is also a risk factor. The kidneys play a vital role in fluid regulation but their function deteriorates with age, and the hormonal response to dehydration (which is key to fluid balance) may be impaired. Dehydration is more common in those with cognitive impairment and changes in functional ability. Swallowing difficulties, dementia and poorly controlled diabetes are more common in older people and are all associated with poor hydration. The likelihood of dehydration may also be exacerbated by medications including diuretics and laxatives. Importantly incontinence predisposes to dehydration as people may limit their fluid intake. Inadequate fluid intake is a major contributor to preventable dehydration. Poor oral intake of fluids can be related to the inability to feed independently and having poor availability and access to fluids. This can be exacerbated in the residential care setting by inadequate staff training and lack of awareness of the importance of hydration[16].

Preventability: Dehydration-related complications may be avoided through proper patient screening, for example, renal function and comorbid conditions should be considered when choosing an appropriate bowel preparation. In addition, patient education regarding the importance of

maintaining adequate hydration before, during and after bowel preparation may promote compliance with fluid volume recommendations and reduce the risk of dehydration-related adverse events[17].

Impact on the risk-benefit balance of the product: Most cases of dehydration and electrolyte imbalance have been reported in elderly patients. This patient population is fragile and recognised for poor food and drink intake. Caution and clear instructions should be provided to the patients. The vast majority of electrolyte abnormalities are clinically undetectable. However, in the elderly population (usually multiple comorbidities) caution should be exercised before using bowel cleansing products. Syncope, fall, shock, arrhythmias or acute kidney injury may occur in rare cases. Proper patient screening and rigorous attention by patients and healthcare providers to hydration during bowel preparation may provide a safer, more effective screening for colonoscopy.

Public health impact: Unknown.

Important Identified Risk: Electrolyte disturbance

Potential mechanisms: The transient increase in sodium almost certainly reflects the sodium load of the preparation itself. Although well within the renal handling capacity of a patient with normal baseline electrolyte balance, this volume of intake will usually result in transient mild hypernatraemia, as observed in the clinical trials. As a secondary homoeostatic effect reflecting raised plasma osmolality, there may well be concomitant tissue dehydration, especially if the patient has failed to consume the recommended volume of fluids. When reductions in plasma sodium are seen, this may simply reflect dilutional effects consequent on high volumes of associated fluid intake.

Total potassium load in macrogol/PEG-based bowel preparation is relatively low and therefore the observed infrequency of hyperkalaemia is unsurprising. One may theorise that patients with impaired renal function would be more likely to display hyperkalaemia, but there are no data from clinical trials to confirm or refute this. Hypokalaemia may reflect an ADH-induced dilutional effect[18], although its longer duration compared to sodium disturbance suggests that other mechanisms are operating. It has been suggested that the therapeutically induced diarrhoea may be culpable, resulting in net loss of potassium from the body.

Evidence source(s) and strength of evidence: The incidence of electrolyte disturbance during the clinical development programme was lower than dehydration. In total, electrolyte disturbance was reported in 8 of 1028 patients (0.8%) in the NER1006 treatment group. All cases were considered related to the treatment. There were 4 cases (0.4%) of hypernatremia, and 1 case (0.1%) each of hyperkalaemia, hypophosphatemia and hypokalaemia. There were no case reports of hyponatremia or hyperkalaemia.

Target population defined using age data from French colonoscopy audit[19]:

<50 yrs: 30.5%

51-70 yrs: 46.5%

71-80 yrs: 18.9%

>80 yrs: 4.1%

Prevalence of one or more electrolyte abnormalities defined using NHANES III data (- Sodium: 133-145 mmol/L, Potassium: 3.2-4.7 mmol/L, Bicarbonate: 19-30 mmol/L, Osmolality: 264-290 mOsmol/Kg)[20]. Detailed table printed below. Applying these rates to the age profile of the colonoscopy population defined above yields expected prevalence rates of:

Any abnormality: 14.2%

Low Na: 2.1%

High Na: 0.2%

Low K: 1.1%

High K: 4.9%

Low Osmolality: 1.1%

High Osmolality: 3.4%

Low bicarbonate: 3.4%

High bicarbonate: 1.3%

Incidence derived from Hospital Episode Statistics for 2005/6[21]. Detailed table printed below. Applying these rates to the age profile of the colonoscopy population yields an expected overall annual incidence rate of 59.3/100,000 (0.06%).

Characterisation of the risk: Hypokalaemia decreases the contractility of smooth, skeletal, and cardiac muscles, so patients may have signs and symptoms of leg and general body cramps, weakness, constipation, abdominal distention, anorexia, nausea, paralytic ileus, confusion and lethargy. At very low levels, cardiac arrhythmias such as ventricular tachycardia may occur[71]. Complications of severe and rapidly developing hyponatremia include seizures, coma, brainstem herniations, respiratory arrest, permanent brain damage, and death[22]. However, the risk of hyponatraemia is minimal with NER1006 owing to higher sodium content.

Patients developing hypernatremia outside of the hospital are generally elderly people who are mentally and physically impaired, often with an acute infection. Patients who develop hypernatremia during the course of hospitalisation have an age distribution similar to that of the general hospital population. In both patient groups, hypernatremia is caused by impaired thirst and/or restricted access to water, often exacerbated by pathologic conditions with increased fluid loss. The development of hyperosmolality from the water loss can lead to neuronal cell shrinkage and resultant brain injury. Loss of volume can lead to circulatory problems (e.g. tachycardia, hypotension). Rapid free-water replacement can cause cerebral oedema[20].

Risk factors and risk groups: In 9 randomised controlled trials bowel preparation using up to 4L macrogol/PEG 3350 has been shown to be associated with small mean changes in electrolytes[23-31]. In these studies sodium changes ranged from a mean fall of 1.0 mmol/l to a rise of 1.4 mmol/l. Potassium fell by a mean of 0.1-0.3 mmol/l. The presented data are insufficient to determine whether there is a dose-response relationship.

One study[24] presented individual patient data for potassium changes: 25 patients showed a decrease of between 0.06 mmol/L and 0.62 mmol/L; 13 patients showed an increase of between 0.13 mmol/L and 0.65 mmol/L; in 6 patients the potassium was unchanged. One patient, who had a starting potassium at the lower limit of normal had a post-treatment potassium level outside the normal range. One patient, who had a starting potassium below the lower limit of normal, had a final potassium level within the normal range. No specific patient criteria were identified that indicated predisposition to electrolyte disturbance, although good clinical practice would dictate that abnormal baseline electrolytes should be corrected prior to treatment. One study[26] was carried out in children, using the adult dose scaled to calculated body area. The type and magnitude of electrolyte changes was comparable to that seen in adults.

Three studies[23,28,31] assessed the timescale of electrolyte changes. In two cases, sodium levels returned rapidly to normal, with no net change being detected immediately post colonoscopy[23] or 48-72 hours later. Potassium changes were longer lasting, with residual change being noted both post procedure[23] and 48-72 hours later. In the third study[31] , electrolytes were measured at baseline, immediately after colonoscopy and one hour later. The authors observed small reductions in both sodium and potassium occurring between the second two time points, suggesting that the procedure itself had an influence on electrolyte balance.

Preventability: The normal electrolyte effects themselves are probably inherent to the treatment and cannot therefore be avoided. They are generally modest in nature, though, and provided baseline electrolyte levels are within the normal range, it is unlikely that clinically apparent effects will be observed. As part of normal clinical practice, electrolyte levels should be checked, in patients at risk, and if necessary corrected before bowel preparation is carried out.

Regarding water intoxication following procedurally-induced inappropriate ADH, this is extremely rare. General patient support to reduce stress and an instruction to report low urine output following consumption of the bowel preparation would be reasonable.

Impact on the risk-benefit balance of the product: Most cases of dehydration and electrolyte imbalance have been reported in elderly patients. This patient population is fragile and recognised for poor food and drink intake. Caution and clear instructions should be provided to the patients. The vast majority of electrolyte abnormalities are clinically undetectable. However, in the elderly population (usually multiple comorbidities) caution should be exercised before using bowel cleansing products. Syncope, fall, shock, arrhythmias or acute kidney injury may occur in rare cases.

Public health impact: Unknown.

Important Identified Risk: Transient increase in blood pressure

Potential mechanisms: Blood pressure increase is a normal physiological response to exercise, stress, as part of diurnal variation, or may be secondary to diet (e.g. excessive salt or caffeine intake). However, it can also be an artefact following incorrect measurement (incorrect cuff size, wrongly calibrated equipment or inaccurate readings).

Transient increases in BP occurs with all bowel preps. Patients take bowel preparation in advance of a planned colonoscopy and this may be a stressful situation for some patients. In addition, bowel preparations may induce gagging and/or vomiting and these may induce blood pressure increases. Anxiety about the procedure itself can contribute to increased blood pressure. Decreased gastrointestinal transit time, or vomiting shortly after taking medication, resulting in reduced absorption of blood pressure therapies can also be contributing factors.

Evidence source(s) and strength of evidence: Globally, the overall prevalence of raised blood pressure in adults aged 25 and over was around 40% in 2008. The proportion of the world's population with high blood pressure, or uncontrolled hypertension, fell modestly between 1980 and 2008. However, because of population growth and ageing, the number of people with uncontrolled hypertension rose from 600 million in 1980 to nearly 1 billion in 2008[32].

Characterisation of the risk: The incidence of an increase in blood pressure during the clinical development programme was low. In total, increase in blood pressure was reported in 2 of 1028 patients (0.2%) in the NER1006 treatment group. One case was considered not related to the treatment by the investigator, while one case (0.1%) was considered related to the treatment. Both cases were reported as non-serious and the outcome was reported to be resolved.

Both cases were reported as mild to moderate in severity. Owing to the diarrhoea being the expected outcome of NER1006 and the electrolyte content (especially sodium chloride) in the formulation, a transient increase in blood pressure, especially in known hypertensive patients may be expected.

Risk factors and risk groups: Known cases of hypertension (especially uncontrolled/poorly controlled).

Patients with renal impairment.

Patients with excessive vomiting/gag reflex.

Preventability: Caution in patients with significant renal impairment, adherence to recommended volumes of fluid intake and proper control of blood pressure in hypertensive patients can prevent the incidence of this risk.

Impact on the risk-benefit balance of the product: Patients with a history of hypertension are more at risk of a transient increase in blood pressure. In most cases blood pressure would normalise within a few hours of colonoscopy. In some patients intervention with low dose anti-hypertensive agents or anti-anxiety agents may help.

Public health impact: Unknown

Important Identified Risk: Transient increase in liver enzymes

Potential mechanisms: NER1006 is an osmotically acting laxative and absorption in the body is minimal; direct hepatic injury is therefore highly unlikely. The exact mechanism is unknown for this increased liver enzymes and may have some roots in the background disease. It is important to note that patients with Grade A liver disease according to the Child Pugh classification were allowed in the studies as well as diabetic patients.

Evidence source(s) and strength of evidence: Prevalence of abnormal LFTs depends on the definition and population but is likely to be between 10 and 20% in the general population. Abnormal LFTs are associated with a range of health outcomes but are not necessarily strongly diagnostic of severe liver pathology[33]. It is common for general practitioners (GPs) to refer patients suspected of impaired liver function for laboratory tests (alkaline phosphatase, lactate dehydrogenase, bilirubin, prothrombin, aspartate aminotransferase). In a prospective multipractice study over a six-month period, including 30 GPs, 55 patients were recorded as having, for the first time, a high level of alkaline phosphatase (AP) as an isolated finding, 14 with an increase of aspartate aminotransferase (ASAT), eight with an increase of both AP and ASAT, three with an increase of ASAT, AP, and bilirubin, two with an isolated increase of lactate dehydrogenase (LDH), one with an increase of ASAT, AP, and bilirubin, combined with a low prothrombin (PP), and, finally, one patient with a low prothrombin in isolation. In most cases the tests were requested because of unspecific symptoms. The most common causes of abnormal test results were neoplasms, alcoholic liver disease, and heart failure. Thirty patients were referred to hospital for further investigations. During the same study period, 50 patients with known abnormal liver function tests were recorded, and the most common causes of these abnormalities were neoplasms, rheumatoid arthritis, and alcoholic liver disease[34].

Characterisation of the risk: The incidence of increase in liver enzymes during the clinical development programme was low. In total, increase in liver enzymes was reported in 2 of 1028 patients (0.2%) in the NER1006 treatment group. Both cases (0.2%) were considered related to the treatment and reported an increase in AST, ALT and GGT.

Both cases were reported as non-serious and reported as mild in severity. The outcome in both cases was reported to be resolved without sequelae.

Risk factors and risk groups: In the study mentioned above, the most common causes of abnormal test results were neoplasms, alcoholic liver disease, and heart failure[33]. Undiagnosed diabetes is also associated with liver injury, compared to diagnosed diabetes with treatment. The effect of diabetes treatment on liver injury in individuals with diabetes remains uncertain[35].

Preventability: Caution in patients with liver disease, adherence to recommended volumes of fluid intake and monitoring the liver enzymes before colonoscopy can prevent the incidence of any associated risk.

Impact on the risk-benefit balance of the product: A transient increase in liver enzymes with a single use treatment (NER1006) is unlikely to have a severe impact on individual health. Patients with Grade B or C liver disease according to the Child Pugh classification were not allowed in the studies and hence use in such patients should only be considered with caution.

Public health impact: Unknown.

Important Identified Risk: Allergic reactions (including anaphylaxis)

Potential mechanisms: Both urticarial rash and angioedema are likely to be caused by classic IgE/histamine mediated mechanisms, in direct response to the macrogol/PEG macromolecule. Non-urticarial skin rashes are not reported in the literature, so it seems unlikely that any other direct effects are involved.

Evidence source(s) and strength of evidence: The incidence of allergic reactions during the clinical development programme was very low. Drug hypersensitivity was reported in 1 case (0.1%), pruritus was reported in 2 cases (0.2%), erythema in 1 case (0.1%) and skin discoloration in 1 case (0.1%). All five cases were considered related to the treatment by the investigators. However, this risk is included as an identified risk based on the post-marketing experience of the Applicant with other macrogol/PEG 3350 containing products.

Characterisation of the risk: Allergic reactions to macrogol/PEG 3350 are an idiosyncratic reaction to product exposure and can be life threatening.

Risk factors and risk groups: It is not possible to identify risk groups in advance, other than prior experience of an allergic reaction to macrogol/PEG 3350.

The effect is not subject to a dose-response effect, as even low levels of exposure can trigger full-scale clinical reactions in a susceptible individual.

Preventability: The only practical strategy to prevent allergic reactions is to specifically seek a history of prior allergy, before administering treatment. In the four reported severe cases in the published literature[36-39], however, there was no evidence of prior reaction to exposure.

Impact on the risk-benefit balance of the product: Severe allergic reactions especially anaphylactic reactions could be quite debilitating or even life-threatening especially when coupled with shock. Immediate medical assistance is required in such cases since this could be a real medical emergency.

Public health impact: Unknown.

Important Potential Risk: Arrythmias (including atrial fibrillation)

Potential mechanisms: A comprehensive literature review looking at drug induced atrial fibrillation[40] did not identify any specific problems relating to macrogol/PEG 3350 (or any other form of bowel preparation).

Two possible mechanisms could be operating. Stress and surgery have both been implicated as triggers for transient arrhythmias[40], so it is possible that the colonoscopy procedure itself could be implicated, especially in the elderly and those with pre-existing cardiac impairment[41.42].

Alternatively, changes to serum electrolytes could underlie the problem. Although the mean effect of macrogol/PEG 3350 on electrolytes is small, a reduction in potassium of up to 0.6 mmol/L has been seen in individual patients[43]. If baseline potassium was near or below the lower limit of normal, it is conceivable that this could trigger an arrhythmia in a susceptible patient.

Evidence source(s) and strength of evidence: Atrial fibrillation is a common condition amongst older adults. A retrospective review of a UK primary care database[44] identified prevalence rates of <1% in patients aged 40-55, rising to around 8% in those aged 80+. A prospective cohort study from Rotterdam[45] actively sought patients by carrying out ECGs and identified somewhat higher rates: <1% in those aged 55-59, rising to 17.8% in the over 85s. Given that primary care records depend on a diagnosis having been made and recorded the Rotterdam study probably gives a truer estimate of underlying prevalence. Additionally, the UK researchers excluded patients with paroxysmal AF.

Age-specific prevalence data for atrial fibrillation from Rotterdam study[45]:

55-59 yrs; 0.7%

60-64 yrs; 1.7%

65-69 yrs; 4.0%

70-74 yrs; 6.0%

75-79 yrs; 9.0%

80-84 yrs; 13.5%

85+ yrs; 17.8%

Age distribution of the colonoscopy population is[19]:

<50 yrs: 30.5%

51-70 yrs: 46.5%

71-80 yrs: 18.9%

>80 yrs: 4.1%

Based on these demographics, and assuming a rate of 0.1% in the under 50s[44] we can estimate an overall prevalence in the target population of approximately 3% (3018/100,000). Reliable incidence data cannot be derived from the UK study[44], due to the exclusion of paroxysmal AF, which is likely to be relevant to drug-induced arrhythmias. Annual incidence rates from Rotterdam[45] were:

55-59 yrs; 1.1/1000 person years

60-64 yrs; 3.3/1000 person years

65-69 yrs; 5.5/1000 person years

70-74 yrs; 11.5/1000 person years

75-79 yrs; 14.7/1000 person years

80-84 yrs; 20.7/1000 person years

85+ yrs; 18.2/1000 person years

Based on the demographics above, and assuming an incidence rate of 0.2/1000 person years in the under 50s, we can estimate an overall incidence in the target population of approximately 5.2/1000 (518/100,000).

Characterisation of the risk: Atrial fibrillation was reported in 2 cases (0.2%) in the NER1006 treatment group. Both were considered not related to the treatment by the investigators. In addition there were 2 cases (0.2%) reporting palpitation and sinus tachycardia (same patients). However, this risk is included as a potential risk based on the post-marketing experience of the Applicant with other macrogol/PEG 3350 containing products. Both cases of Atrial fibrillation reported were considered non-serious by the investigators and the outcome was resolved.

Atrial fibrillation is rarely a cause of death in itself, although it may contribute to death through cerebral embolism or as a component of broader ischaemic or rheumatic heart disease.

Risk factors and risk groups: It would be reasonable to suppose that older patients, those with established ischemic heart disease, a prior history of atrial fibrillation, or patients with pre-treatment electrolyte abnormalities would be more likely to experience arrhythmias. Some known risk factors that can increase the chance of developing arrhythmias include: coronary artery disease, hypertension, diabetes mellitus, smoking, high cholesterol, obesity, high-fat diet, excessive use of alcohol (more than 2 drinks per day), drug abuse, anxiety/stress, family history of heart disease, advancing age, sleep apnoea, certain OTC and prescription medications, dietary supplements, and herbal remedies[46].

Preventability: Carrying out baseline electrolyte estimation is reasonable prior to administration of any bowel preparation, particularly in the elderly or patients taking concomitant medication which may affect electrolyte levels. Identifying and correcting any abnormal or borderline potassium deficiency would be a reasonable precaution to reduce the risk of arrhythmia or atrial fibrillation.

Impact on the risk-benefit balance of the product: Atrial fibrillation is a common heart rhythm disturbance. Atrial fibrillation can affect adults of any age, but it becomes more common with increasing age. It affects about 7 in 100 people aged over 65, and is more common in men than women. Atrial fibrillation is more likely to occur in people with other conditions, such as hypertension, atherosclerosis, or a heart valve problem. Atrial fibrillation isn't usually life-threatening, but it can be uncomfortable and often requires treatment.

Public health impact: Unknown.

Important Potential Risk: Perforation/aggravation of the condition in patients with toxic megacolon as a result of severe IBD

Potential mechanisms: In toxic megacolon the bowel wall is extremely friable. Ingestion of large volumes of fluid as part of bowel preparation may cause distension and therefore increase the likelihood of perforation. There does not appear to be a specific toxic effect of polyethylene glycol as, once decompressed, the daily use of macrogol/PEG appears to reduce the risk of recurrence of toxic megacolon[47-50].

Evidence source(s) and strength of evidence: In the US, it is currently estimated that about 1 –1.3 million people suffer from IBD[51]. Ulcerative colitis is slightly more common in males, while Crohn's disease is more frequent in women. IBD occurs more in people of Caucasian and Ashkenazic Jewish origin than in other racial and ethnic subgroups. However, previously noted racial and ethnic differences seem to be narrowing[52].

Incidence rates[52]: Crohn's disease: 3.1 to 14.6 cases per 100,000 person-years; Ulcerative colitis: 2.2 to 14.3 cases per 100,000 person-years

Prevalence: Crohn's Disease: 26 to 199 cases per 100,000 persons; Ulcerative colitis: 37 to 246 cases per 100,000 persons[52].

Crohn's Disease: 201 per 100,000 adults; Ulcerative Colitis: 238 per 100,000 adults[51].

Characterisation of the risk: Intestinal perforation is always severe and can be life threatening. In most cases of intestinal perforation the patients develop peritonitis and needs immediate surgery.

Risk factors and risk groups: Generally, toxic megacolon, perforation and mortality are all more common in patients with ulcerative colitis than Crohn's disease. There are insufficient numbers of cases following the use of polyethylene glycol to ascertain whether the pattern of incidence is different in this circumstance.

Preventability: Prevention hinges on the clinical diagnosis of toxic megacolon prior to the use of bowel preparation.

Impact on the risk-benefit balance of the product: Intestinal perforation is a serious and potentially life threatening event, however numbers of reported cases are small and so the risk-benefit balance remains positive.

Public health impact: Unknown.

Important Potential Risk: Aspiration in patients with diminished levels of consciousness/severely debilitated patients especially if prepared with a nasogastric tube

Potential mechanisms: Incorrect placement of nasogastric catheters, large infusions and bolus delivery can all lead to accidental delivery of the feed into the lungs. There is evidence that oropharyngeal dysphagia plays a critical role in aspiration pneumonia and ventilator-associated pneumonia (VAP) in mechanically ventilated patients[53-54]. Brain injury, severe stroke and unconsciousness, due to sedatives and hypnotics, disturb the swallowing reflex. This results in the development of aspiration pneumonia in humans and animals[55].

Evidence source(s) and strength of evidence: In a randomised trial of 86 ventilated patients microbiologically confirmed aspiration pneumonia occurred in 23% of patients in a supine position and 5% of patients in a semi-recumbent position[56].

Characterisation of the risk: Aspiration pneumonia can be a debilitating disease. Fatality with this condition in elderly is quite high. However, once diagnosed, the condition is treatable with antibiotics.

Risk factors and risk groups: Patients with diminished levels of consciousness/severely debilitated patients.

Preventability: After correction of the risk factors (ensuring correct emplacement of the nasogastric tube, slow infusion and avoidance of boluses, and the use of a semi-recumbent position), the addition of ACE inhibitors may also enhance the cough reflex[57].

Impact on the risk-benefit balance of the product: In the absence of any reported cases of aspiration pneumonia in association with the use of NER1006 the potential risk is low, therefore the risk-benefit balance remains positive.

Public health impact: Unknown.

Important Potential Risk: Cardiac failure / decompensation

Potential mechanisms: Heart failure following use of macrogol/PEG bowel preparation probably reflects the consequences of fluid overload in the vascular compartment with consequent increase in cardiac preload. Normally, the mode of action of macrogol/PEG ensures that very little of the fluid volume ingested is absorbed from the bowel, therefore making this occurrence unlikely. However as outlined in the section on electrolyte disturbances, in some circumstances the stress of the colonoscopy procedure may cause inappropriate ADH secretion, with consequent sodium loss and fluid retention. When extreme, this can cause frank water intoxication[58]. However, it has been postulated that the same mechanism may underlie more minor alterations in fluid and electrolyte balance[31]. For most patients this will not have any clinical consequences but, in a patient with heart failure, it may be sufficient to trigger peripheral and/or pulmonary oedema.

Evidence source(s) and strength of evidence: Heart failure is a common problem encountered in the age group undergoing colonoscopy. Overall prevalence of clinically significant heart failure ranges from 0.5-1.0% in the under 65s up to 9-10% in the over 80s[59-62].

The most detailed demographic breakdown of the European target population derives from a French national colonoscopy audit[19]:

<50 yrs: 30.5%

51-70 yrs: 46.5%

71-80 yrs: 18.9%

>80 yrs: 4.1%

Age-specific prevalence data are available for similar age groups from two large population studies[59-60]:

Reference 1	Reference 2
50-59 yrs 0.8%	45-54 yrs 0.7%
60-69 yrs 2.3%	55-64 yrs 1.4%
70-79 yrs 4.9%	65-74 yrs 2.0%
80-89 yrs 9.1%	> 75 yrs 8.9%

Based on mean values for these data, we can estimate an overall prevalence in the target population of approximately 1.7% (1,700/100,000).

Annual incidence rates of new cases in the Framingham study were typically 2-3/1000 in patients aged under 65 and 8-10/1000 in those over 65[60]. Other population studies have identified rates higher than this – 6-9/1000 in under 64s[63] and 26-33/1000 in over 65s[64]. The diagnostic criteria, however, were less stringent in the latter studies and probably included patients with less clinically significant disease.

Age-specific annual incidence data from Framingham study (rates/1000)[60].

	Male	Female
45-54 yrs	2	1
55-64 yrs	4	3
65-74 yrs	8	5
75-84 yrs	14	13
85-94 yrs	54	85

Based on these data, we can estimate an overall annual incidence in the target population of approximately 6.8/1000 (680/100,000).

Characterisation of the risk: Cardiac failure is a debilitating condition especially in the elderly population.

No cases were reported in clinical trials of NER1006.

Risk factors and risk groups: Heart failure is unlikely to occur as a de novo effect of macrogol/PEG bowel preparation, rather it is an exacerbation of pre-existing disease. Susceptible patients will therefore include patients with prior diagnosis of heart failure, myocardial infarction, atrial fibrillation and age 75+ or very anxious patients (may predispose to inappropriate ADH secretion).

Preventability: A prior history of heart failure, myocardial infarction or atrial fibrillation should be sought. In the absence of this, the use of diuretics, ACE inhibitors or angiotensin receptor blockers, or signs of left ventricular hypertrophy on ECG may all alert the clinician to risk. Treatment is not contraindicated in these patients but careful attention should be paid to baseline electrolytes and fluid balance during the course administration of the bowel preparation and following the procedure.

Impact on the risk-benefit balance of the product: Cardiac failure is a debilitating condition, and in most cases cannot be cured. Treatment therefore aims to find a combination of measures, including lifestyle changes, medicines, devices or surgery that will improve heart function or help the body get rid of excess water.

Public health impact: Unknown.

Important Potential Risk: Acute renal failure / decompensation

Potential mechanisms: Severe dehydration (if this occurs) and rehydration not managed in time, may result in kidney injury, however an exact mechanism is currently not known with PEG.

Evidence source(s) and strength of evidence: The incidence of acute renal failure has been assessed in a number of UK populations[65-67]. Annual overall incidence estimates were 505 cases/million population[65], 545 cases/million[66] and 620 cases/million[67]. Annual requirement for renal replacement therapy (RRT) in population studies ranges from 358/million to 445/million[65,68], although long term renal replacement was only required for 110/million[69].

Age-specific incidence data for acute renal failure are available from one study[65]:

20-49 yrs : 47/million

50-69 yrs : 120/million

70-79 yrs : 335/million

80+ yrs : 597/million

Age distribution of the colonoscopy population is[19]:

<50 yrs: 30.5%

51-70 yrs: 46.5%

71-80 yrs: 18.9%

>80 yrs: 4.1%

Based on these demographics, we can estimate an overall annual incidence in the target population of approximately 158/million (15.8/100,000).

Characterisation of the risk: Acute kidney injury can be an acute insult to the kidney due to dehydration and electrolyte imbalance or acute aggravation of chronic renal insufficiency. In any case, it is a debilitating condition and can involve disability, need for urgent dialysis or even lifelong dialysis in severely affected patients.

Risk factors and risk groups: None known. There are insufficient cases to identify any causative or associated factors[70].

Preventability: Given the lack of a mechanism and no known predisposing factors, there are no macrogol/PEG-specific measures that can be recommended.

Impact on the risk-benefit balance of the product: There is an expected annual incidence of acute renal failure of 158/million in the colonoscopy population, given the low incidence of reporting the risk-benefit balance remains positive.

Public health impact: Unknown.

Important Potential Risk: Potential to alter absorption and decrease efficacy of other medicinal products

Potential mechanisms: PLENVU induces a laxative effect and medicinal products taken orally (e.g. oral contraceptive pill) within one hour of starting colonic lavage with PLENVU may be flushed from the gastrointestinal tract unabsorbed.

Evidence source(s) and strength of evidence: No drug interactions were identified during the clinical development programme, but as seen with other drugs in the same class, concomitant oral drug can be flushed by the bowel preparation and therefore may not be absorbed.

No expected effect/interaction with food was identified, except effects on the quality of bowel cleansing.

Characterisation of the risk: Alteration of absorption and decreased efficacy can result in potentially serious events, depending on the concurrent medicine received. However, PLENVU is indicated to be taken as a one-off course for bowel cleansing prior to any procedure requiring a clean bowel and so the risk is minimised.

Risk factors and risk groups: Patients receiving concurrent treatment with other medications.

Preventability: Patients should be advised to not take any concurrent medications within one hour of starting colonic lavage with PLENVU.

Impact on the risk-benefit balance of the product: PLENVU is indicated to be taken as a one-off course for bowel cleansing prior to any procedure requiring a clean bowel and so the risk is minimised.

Public health impact: Unknown.

SVII.3.2. Presentation of the missing information

Missing Information: Use in patients with glucose-6-phosphate dehydrogenase deficiency

Evidence source: Patients with glucose-6-phosphate dehydrogenase deficiency may be at risk of acute haemolysis due to the presence of ascorbate (sodium ascorbate and ascorbic acid).

Population in need of further characterisation: Patient with glucose-6-phosphate dehydrogenase deficiency receiving PLENVU for bowel cleansing.

Anticipated risk/consequence of the missing information: There is a warning in the RSI regarding the risk of administering PLENVU to patients with glucose-6-phosphate dehydrogenase deficiency due to the presence of ascorbate.

Missing Information: Use in paediatric population

Evidence source: There are no data on the use of PLENVU in paediatric patients <18 years.

Population in need of further characterisation: Paediatric patients <18 years receiving PLENVU for bowel cleansing.

Anticipated risk/consequence of the missing information: The RSI states that PLENVU is not recommended for use in children below 18 years of age as it has not been studied in the paediatric population.

Missing Information: Use in pregnancy/lactation

Evidence source: There are no data on the use of PLENVU during pregnancy or lactation.

Population in need of further characterisation: Pregnant patients and patients currently breastfeeding receiving PLENVU for bowel cleansing.

Anticipated risk/consequence of the missing information: The RSI states that PLENVU should only be used during pregnancy or lactation if considered essential by the physician.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Dehydration • Electrolytes disturbance • Transient increase in blood pressure • Transient increase in liver enzymes • Allergic reactions (including anaphylaxis)

Summary of safety concerns	
Important potential risks	• Arrhythmias (including atrial fibrillation) • Perforation/aggravation of the condition in patients with toxic megacolon as a result of severe IBD • Aspiration in patients with diminished levels of consciousness/severely debilitated patients especially if prepared with a nasogastric tube • Cardiac failure/decompensation • Acute renal failure/decompensation • Potential to alter absorption and decrease efficacy of other medicinal products
Missing information	• Use in patients with glucose-6-phosphate dehydrogenase deficiency • Use in paediatric population • Use in pregnancy/lactation

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

Norgine is not using any further specific adverse reaction follow up questionnaires for PLENVU.

Other forms of routine pharmacovigilance activities:

No other forms of routine pharmacovigilance activities are considered necessary.

III.2 Additional pharmacovigilance activities

Additional pharmacovigilance activities are not considered necessary and routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the product and detect any safety concerns.

III.3 Summary Table of additional Pharmacovigilance activities

There are no additional pharmacovigilance activities.

Part IV: Plans for post-authorisation efficacy studies

N/A - there are no plans for Post Authorisation Efficacy studies.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Dehydration	**Routine risk communication:** *SmPC/RSI Sections 4.4 and 4.8.* *PIL sections 2 and 4.* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *SmPC/RSI Section 4.4 states that PLENVU should be used in caution in patients with dehydration. Any suspected dehydration should be corrected for before use of PLENVU. The fluid content of PLENVU when reconstituted with water does not replace regular fluid intake and adequate fluid intake must be maintained.* *PIL Section 2 states to talk to your doctor, pharmacist or nurse before taking PLENVU if any of the below are applicable to you. If you:* • *have a high or low blood salt level (e.g. sodium, potassium)* • *have any other medical conditions (e.g. seizures)* *Section 2 additionally states to drink clear fluids before, during, and after you take PLENVU to help prevent fluid loss (dehydration). It is important for you to drink the additional prescribed amounts of clear fluids.* **Other routine risk minimisation measures beyond the Product Information:** *Medicinal product subject to medical prescription*
Electrolyte disturbance	**Routine risk communication:** *SmPC/RSI Sections 4.4 and 4.8.* *PIL sections 2 and 4.* **Routine risk minimisation activities recommending specific clinical measures to address the risk:**

	SmPC/RSI Section 4.4 states that in patients at risk of electrolyte imbalance the physician should consider performing a baseline and post-treatment electrolyte test as appropriate. Any suspected dehydration should be corrected for before use of PLENVU. *If patients develop any symptoms indicating arrhythmia or shifts of fluid/electrolytes during or after treatment (e.g. oedema, shortness of breath, increasing fatigue, cardiac failure), plasma electrolytes should be measured, ECG monitored and any abnormality treated appropriately.* *PIL section 2 states to talk to your doctor, pharmacist or nurse before taking PLENVU if any of the below are applicable to you. If you:* • *have a high or low blood salt level (e.g. sodium, potassium)* • *have any other medical conditions (e.g. seizures)* **Other routine risk minimisation measures beyond the Product Information:** *Medicinal product subject to medical prescription*
Transient increase in blood pressure	**Routine risk communication:** *SmPC/RSI Section 4.8.* *PIL Section 4.* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *No specific clinical measures recommended.* **Other routine risk minimisation measures beyond the Product Information:** *Medicinal product subject to medical prescription*
Transient increase in liver enzymes	**Routine risk communication:** *SmPC/RSI Section 4.8.* *PIL Section 4.* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *No specific clinical measures recommended.* **Other routine risk minimisation measures beyond the Product Information:** *Medicinal product subject to medical prescription*

Allergic reactions (including anaphylaxis)	**Routine risk communication:** *SmPC/RSI Sections 4.3, 4.4 and 4.8.* *PIL Sections 2 and 4.* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *SmPC/RSI Section 4.3 contraindicates use of PLENVU in patients with known or suspected hypersensitivity to the active substances or to any of the excipients.* *SmPC/RSI Section 4.4 warns as with other macrogol/PEG containing products, allergic reactions including rash, urticaria, pruritus, angioedema and anaphylaxis are a possibility.* *PIL Section 2 states do not take PLENVU if you are allergic (hypersensitive) to the active substances or any of the other ingredients of PLENVU.* *PIL Section 4 states to stop taking PLENVU and tell your doctor immediately if you experience symptoms of a severe allergic reaction including: extreme fatigue, palpitations, rash or itching, shortness of breath and swelling of your face, ankles or other part of your body.* **Other routine risk minimisation measures beyond the Product Information:** *Medicinal product subject to medical prescription*
Arrhythmias (including atrial fibrillation)	**Routine risk communication:** *SmPC/RSI Sections 4.4 and 4.8.* *PIL Sections 2 and 4.* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *SmPC/RSI Section 4.4 warns PLENVU should be used in caution with patients at risk of arrhythmia, for example those with or on treatment for cardiovascular disease, thyroid disease or electrolyte imbalance. In patients with arrhythmia the physician should consider performing a baseline and post-treatment ECG as appropriate.* *There have been rare reports of serious arrhythmias including atrial fibrillation associated with the use of ionic osmotic laxatives for bowel preparation. These occur predominantly in patients with underlying cardiac risk factors and electrolyte disturbance.* *If patients develop any symptoms indicating arrhythmia or shifts of fluid/electrolytes during or after treatment (e.g. oedema, shortness of breath, increasing fatigue, cardiac failure), plasma*

	electrolytes should be measured, ECG monitored and any abnormality treated appropriately. *PIL Section 2 states to your doctor, pharmacist or nurse before taking PLENVU if any of the below are applicable to you. If you:* • *have heart problems and/or heart rhythm problems* • *have kidney problems and/or dehydration* • *have a high or low blood salt level (e.g. sodium, potassium)* • *have any other medical conditions (e.g. seizures)* **Other routine risk minimisation measures beyond the Product Information:** *Medicinal product subject to medical prescription*
Perforation / aggravation of the condition in patients with toxic megacolon as a result of severe IBD	**Routine risk communication:** *SmPC/RSI sections 4.3 and 4.4.* *PIL Section 2.* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *SmPC/RSI Section 4.3 contraindicates use of PLENVU in patients with known or suspected toxic megacolon, gastrointestinal obstruction or perforation, ileus, disorders of gastric emptying, e.g. gastroparesis, gastric retention, etc.* *SmPC/RSI Section 4.4 warns PLENVU should be used in caution with patients with severe acute inflammatory bowel disease. If patients experience severe bloating, abdominal distension, or abdominal pain, administration should be slowed or temporarily discontinued until the symptoms subside.* *PIL Section 2 states do not take PLENVU:* • *if you have a blockage in your bowel (bowel obstruction)* • *if you have an opening in the wall of your stomach or bowel (bowel perforation)* • *if you have paralysis of the gut (ileus)* • *if you experience problems with food and fluid emptying from your stomach (e.g. gastric paresis, gastric retention)* • *if you have a very dilated bowel (toxic megacolon)* *Talk to your doctor, pharmacist or nurse before taking PLENVU if any of the below are applicable to you. If you:*

	• *have stomach or bowel problems, including bowel inflammation* **Other routine risk minimisation measures beyond the Product Information:** *Medicinal product subject to medical prescription*
Aspiration in patients with diminished levels of consciousness/ severely debilitated patients especially if prepared with a nasogastric tube	**Routine risk communication:** *SmPC/RSI Section 4.4.* *PIL Section 2.* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *SmPC/RSI Section 4.4 warns caution should be used with the administration of PLENVU to frail or debilitated patients. PLENVU should also be used with caution in patients with impaired gag reflex, with the possibility of regurgitation or aspiration, or with diminished levels of consciousness. Such patients should be closely observed during administration especially if given via a nasogastric route.* *In debilitated fragile patients and patients with poor health the physician should consider performing a baseline and post-treatment electrolyte, renal function test and ECG as appropriate.* *PIL Section 2 states that PLENVU should not be given to patients with impaired consciousness without medical supervision.* **Other routine risk minimisation measures beyond the Product Information:** *Medicinal product subject to medical prescription*
Cardiac failure/decompensation	**Routine risk communication:** *SmPC/RSI Section 4.4.* *PIL Section 2.* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *SmPC/RSI Section 4.4 warns PLENVU should be used in caution in patients with grade III or IV cardiac failure. In patients with poor health and with arrhythmia the physician should consider performing a baseline and post-treatment ECG as appropriate.* *PIL Section 2 states to talk to your doctor, pharmacist or nurse before taking PLENVU if any of the below are applicable to you. If you:* • *have heart problems and/or heart rhythm problems*

	Other routine risk minimisation measures beyond the Product Information: *Medicinal product subject to medical prescription*
Acute renal failure / decompensation	**Routine risk communication:** *SmPC/RSI Section 4.4.* *PIL Section 2.* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *SmPC/RSI Section 4.4 warns PLENVU should be used in caution in patients with renal impairment whose creatinine clearance is less than 30 mL/minute/1.73 m2. In patients with clinically significant renal impairment the physician should consider performing a baseline and post-treatment renal function test as appropriate.* *PIL Section 2 states to talk to your doctor, pharmacist or nurse before taking PLENVU if any of the below are applicable to you. If you:* • *have kidney problems and/or dehydration* • *have a high or low blood salt level (e.g. sodium, potassium)* *PLENVU contains a source of phenylalanine which may be harmful for people with phenylketonuria.* **Other routine risk minimisation measures beyond the Product Information:** *Medicinal product subject to medical prescription*
Potential to alter absorption and decrease efficacy of other medicinal products	**Routine risk communication:** *SmPC/RSI Section 4.5.* *PIL Section 2.* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *RSI Section 4.5 warns medicinal products taken orally (e.g. oral contraceptive pill) one hour before, during and one hour after PLENVU administration may be flushed from the gastrointestinal tract unabsorbed.* *SmPC Section 4.5 warns medicinal products taken orally (e.g. oral contraceptive pill) within one hour of starting colonic lavage with PLENVU may be flushed from the gastrointestinal tract unabsorbed. The therapeutic effect of drugs with a narrow therapeutic index or short half-life may be particularly affected.*

	PIL Section 2 states to talk to your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines (including oral contraceptives). Medicines taken by mouth may not be absorbed properly when taken within 1 hour before the start of PLENVU. **Other routine risk minimisation measures beyond the Product Information:** *Medicinal product subject to medical prescription*
Use in patients with glucose-6-phosphate dehydrogenase deficiency	**Routine risk communication:** *SmPC Section 4.3* *RSI Section 4.4.* *PIL Section 2.* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *SmPC Section 4.3 contraindicates use in patients with known or suspected glucose-6-phosphate dehydrogenase deficiency (due to presence of ascorbate).* *RSI Section 4.4 warns patients with glucose-6-phosphate dehydrogenase deficiency may be at risk of acute haemolysis due to the presence of ascorbate (sodium ascorbate and ascorbic acid).* *PIL Section 2 states do no take PLENVU if your body is unable to produce enough glucose-6-phosphate dehydrogenase.* **Other routine risk minimisation measures beyond the Product Information:** *Medicinal product subject to medical prescription*
Use in paediatric population	**Routine risk communication:** *SmPC/RSI Section 4.2.* *PIL Section 2.* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *SmPC Section 4.2 states the safety and efficacy in children below 18 years of age has not yet been established. PLENVU is therefore not recommended for use in this population.* *RSI Section 4.2 states PLENVU is not recommended for use in children below 18 years of age as it has not been studied in the paediatric population.*

	PIL Section 2 states PLENVU is not recommended for use in children under 18 years of age. **Other routine risk minimisation measures beyond the Product Information:** *Medicinal product subject to medical prescription*
Use in pregnancy / lactation	**Routine risk communication:** *SmPC/RSI Section 4.6.* *PIL Section 2.* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *SmPC Section 4.6 states there are no or limited amount of data (less than 300 pregnancy outcomes) from the use of PLENVU active ingredients in pregnant women. Animal studies have shown indirect harmful effects with respect to reproductive toxicity. Clinically, no effects during pregnancy are anticipated, since systemic exposure to macrogol 3350 is negligible. As a precautionary measure, it is preferable to avoid the use of PLENVU during pregnancy.* *RSI Section 4.6 states there are no data on the use of PLENVU during pregnancy or lactation. The preparation should only be used during pregnancy or lactation if considered essential by the physician. There are no data on the effects of PLENVU on fertility.* *PIL Section 2 states there are no data on the use of PLENVU during pregnancy or breast-feeding and is therefore not recommended. It should only be used if considered essential by the doctor.* **Other routine risk minimisation measures beyond the Product Information:** *Medicinal product subject to medical prescription*

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risk: Dehydration	**Routine risk minimisation measures:** SmPC/RSI Section 4.4 states that PLENVU should be used in caution in patients with dehydration. Any suspected dehydration should be corrected for before use of PLENVU. The fluid content of PLENVU when reconstituted with water does not replace regular fluid intake and adequate fluid intake must be maintained. PIL Section 2 states to talk to your doctor, pharmacist or nurse before taking PLENVU if any of the below are applicable to you. If you: • have a high or low blood salt level (e.g. sodium, potassium) • have any other medical conditions (e.g. seizures) Section 2 additionally states to drink clear fluids before, during, and after you take PLENVU to help prevent fluid loss (dehydration). It is important for you to drink the additional prescribed amounts of clear fluids. PIL section 4 lists dehydration as a common side effect (may affect up to 1 in 10 people). Prescription only medicine. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Important Identified Risk: Electrolyte disturbance	**Routine risk minimisation measures:** SmPC/RSI Section 4.4 states that in patients at risk of electrolyte imbalance the physician should consider performing a baseline and post-treatment electrolyte test as appropriate. Any suspected dehydration should be corrected for before use of PLENVU.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	If patients develop any symptoms indicating arrhythmia or shifts of fluid/electrolytes during or after treatment (e.g. oedema, shortness of breath, increasing fatigue, cardiac failure), plasma electrolytes should be measured, ECG monitored and any abnormality treated appropriately. PIL section 2 states to talk to your doctor, pharmacist or nurse before taking PLENVU if any of the below are applicable to you. If you: • have a high or low blood salt level (e.g. sodium, potassium) • have any other medical conditions (e.g. seizures) Prescription only medicine. **Additional risk minimisation measures:** None	
Important Identified Risk: Transient increase in blood pressure	**Routine risk minimisation measures:** No specific clinical measures recommended. Prescription only medicine. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Important Identified Risk: Transient increase in liver enzymes	**Routine risk minimisation measures:** No specific clinical measures recommended. Prescription only medicine. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risk: Allergic reactions (including anaphylaxis)	**Routine risk minimisation measures:** SmPC/RSI Section 4.3 contraindicates use of PLENVU in patients with known or suspected hypersensitivity to the active substances or to any of the excipients. SmPC/RSI Section 4.4 warns as with other macrogol/PEG containing products, allergic reactions including rash, urticaria, pruritus, angioedema and anaphylaxis are a possibility. PIL Section 2 states do not take PLENVU if you are allergic (hypersensitive) to the active substances or any of the other ingredients of PLENVU. PIL Section 4 states to stop taking PLENVU and tell your doctor immediately if you experience symptoms of a severe allergic reaction including: extreme fatigue, palpitations, rash or itching, shortness of breath and swelling of your face, ankles or other part of your body. Prescription only medicine. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Important Potential Risk: Arrhythmias (including atrial fibrillation)	**Routine risk minimisation measures:** SmPC/RSI Section 4.4 warns PLENVU should be used in caution with patients with those at risk of arrhythmia, for example those with or on treatment for cardiovascular disease, thyroid disease or electrolyte imbalance. In patients with arrhythmia the physician should consider performing a baseline and post-treatment ECG as appropriate. There have been rare reports of serious arrhythmias including atrial fibrillation associated with the use of ionic osmotic laxatives for bowel preparation. These occur predominantly in patients with	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	underlying cardiac risk factors and electrolyte disturbance. If patients develop any symptoms indicating arrhythmia or shifts of fluid/electrolytes during or after treatment (e.g. oedema, shortness of breath, increasing fatigue, cardiac failure), plasma electrolytes should be measured, ECG monitored and any abnormality treated appropriately. PIL Section 2 states to your doctor, pharmacist or nurse before taking PLENVU if any of the below are applicable to you. If you: • have heart problems and/or heart rhythm problems • have kidney problems and/or dehydration • have a high or low blood salt level (e.g. sodium, potassium) • have any other medical conditions (e.g. seizures) Prescription only medicine. **Additional risk minimisation measures:** None	
Important Potential Risk: Perforation / aggravation of the condition in patients with toxic megacolon as a result of severe IBD	**Routine risk minimisation measures:** SmPC/RSI Section 4.3 contraindicates use of PLENVU in patients with known or suspected toxic megacolon, *gastrointestinal obstruction or perforation, ileus, disorders of gastric emptying, e.g. gastroparesis, gastric retention, etc.* SmPC/RSI Section 4.4 warns PLENVU should be used in caution with patients with severe acute inflammatory bowel disease. If patients experience severe bloating, abdominal distension, or	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	abdominal pain, administration should be slowed or temporarily discontinued until the symptoms subside. PIL Section 2 states do not take PLENVU: • if you have a blockage in your bowel (bowel obstruction) • if you have an opening in the wall of your stomach or bowel (bowel perforation) • if you have paralysis of the gut (ileus) • if you experience problems with food and fluid emptying from your stomach (e.g. gastric paresis, gastric retention) • if you have a very dilated bowel (toxic megacolon) Talk to your doctor, pharmacist or nurse before taking PLENVU if any of the below are applicable to you. If you: • have stomach or bowel problems, including bowel inflammation Prescription only medicine. **Additional risk minimisation measures:** None	
Important Potential Risk: Aspiration in patients with diminished levels of consciousness/ severely debilitated patients especially if prepared with a nasogastric tube	**Routine risk minimisation measures:** SmPC/RSI Section 4.4 warns caution should be used with the administration of PLENVU to frail or debilitated patients. PLENVU should also be used with caution in patients with impaired gag reflex, with the possibility of regurgitation or aspiration, or with diminished levels of consciousness. Such patients should be closely observed during administration especially if given via a nasogastric route. In debilitated fragile patients and patients with poor health the physician	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	should consider performing a baseline and post-treatment electrolyte, renal function test and ECG as appropriate. PIL Section 2 states that PLENVU should not be given to patients with impaired consciousness without medical supervision. Prescription only medicine. **Additional risk minimisation measures:** None	
Important Potential Risk: Cardiac failure / decompensation	**Routine risk minimisation measures:** SmPC/RSI Section 4.4 warns PLENVU should be used in caution in patients with grade III or IV cardiac failure. In patients with poor health and with arrhythmia the physician should consider performing a baseline and post-treatment ECG as appropriate. PIL Section 2 states to talk to your doctor, pharmacist or nurse before taking PLENVU if any of the below are applicable to you. If you: • have heart problems and/or heart rhythm problems Prescription only medicine. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Important Potential Risk: Acute renal failure / decompensation	**Routine risk minimisation measures:** SmPC/RSI Section 4.4 warns PLENVU should be used in caution in patients with renal impairment whose creatinine clearance is less than 30 mL/minute/1.73 m2. In patients with clinically significant renal impairment the physician should consider performing a baseline and post-treatment renal function test as appropriate.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	PIL Section 2 states to talk to your doctor, pharmacist or nurse before taking PLENVU if any of the below are applicable to you. If you: • have kidney problems and/or dehydration • have a high or low blood salt level (e.g. sodium, potassium) PLENVU contains a source of phenylalanine which may be harmful for people with phenylketonuria. Prescription only medicine. **Additional risk minimisation measures:** None	
Important Potential Risk: Potential to alter absorption and decrease efficacy of other medicinal products	**Routine risk minimisation measures:** RSI Section 4.5 warns medicinal products taken orally (e.g. oral contraceptive pill) one hour before, during and one hour after PLENVU administration may be flushed from the gastrointestinal tract unabsorbed. SmPC Section 4.5 warns medicinal products taken orally (e.g. oral contraceptive pill) within one hour of starting colonic lavage with PLENVU may be flushed from the gastrointestinal tract unabsorbed. The therapeutic effect of drugs with a narrow therapeutic index or short half-life may be particularly affected. PIL Section 2 states to talk to your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines (including oral contraceptives). Medicines taken by mouth may not be absorbed properly when taken within 1 hour before the start of PLENVU. Prescription only medicine.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None	
Missing information: Use in patients with glucose-6-phosphate dehydrogenase deficiency	**Routine risk minimisation measures:** SmPC Section 4.3 contraindicates use in patients with known or suspected glucose-6-phosphate dehydrogenase deficiency (due to presence of ascorbate). RSI Section 4.4 warns patients with glucose-6-phosphate dehydrogenase deficiency may be at risk of acute haemolysis due to the presence of ascorbate (sodium ascorbate and ascorbic acid). PIL Section 2 states do no take PLENVU if your body is unable to produce enough glucose-6-phosphate dehydrogenase. Prescription only medicine. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Missing information: Use in paediatric population	**Routine risk minimisation measures:** SmPC Section 4.2 states the safety and efficacy in children below 18 years of age has not yet been established. PLENVU is therefore not recommended for use in this population. RSI Section 4.2 states PLENVU is not recommended for use in children below 18 years of age as it has not been studied in the paediatric population. PIL Section 2 states PLENVU is not recommended for use in children under 18 years of age. Prescription only medicine. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information: Use in pregnancy / lactation	**Routine risk minimisation measures:** SmPC Section 4.6 states there are no or limited amount of data (less than 300 pregnancy outcomes) from the use of PLENVU active ingredients in pregnant women. Animal studies have shown indirect harmful effects with respect to reproductive toxicity. Clinically, no effects during pregnancy are anticipated, since systemic exposure to macrogol 3350 is negligible. As a precautionary measure, it is preferable to avoid the use of PLENVU during pregnancy. RSI Section 4.6 states there are no data on the use of PLENVU during pregnancy or lactation. The preparation should only be used during pregnancy or lactation if considered essential by the physician. There are no data on the effects of PLENVU on fertility. PIL Section 2 states there are no data on the use of PLENVU during pregnancy or breast-feeding and is therefore not recommended. It should only be used if considered essential by the doctor. Prescription only medicine. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Part VI: Summary of the risk minimisation plan

Summary of risk management plan for PLENVU (NER1006)

This is a summary of the risk management plan (RMP) for PLENVU. The RMP details important risks of PLENVU, how these risks can be minimised, and how more information will be obtained about PLENVU's risks and uncertainties (missing information).

PLENVU's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how PLENVU should be used.

I. The medicine and what it is used for

PLENVU is authorised in adults over the age of 18 years for bowel cleansing prior to any clinical procedures requiring a clean bowel. It contains macrogol 3350, sodium ascorbate, sodium sulfate anhydrous, ascorbic acid, sodium chloride and potassium chloride as the active substances and it is given orally.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of PLENVU, together with measures to minimise such risks and the proposed studies for learning more about PLENVU's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation measures*.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of PLENVU are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of PLENVU. Potential risks are concerns for which an association with the

use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• Dehydration • Electrolyte disturbance • Transient increase in blood pressure • Transient increase in liver enzymes • Allergic reactions (including anaphylaxis)
Important potential risks	• Arrhythmias (including atrial fibrillation) • Perforation/aggravation of the condition in patients with toxic megacolon as a result of severe IBD • Aspiration in patients with diminished levels of consciousness/severely debilitated patients especially if prepared with a nasogastric tube • Cardiac failure/decompensation • Acute renal failure/decompensation • Potential to alter absorption and decrease efficacy of other medicinal products
Missing information	• Use in patients with glucose-6-phosphate dehydrogenase deficiency • Use in paediatric population • Use in pregnancy/lactation

II.B Summary of important risks

Important identified risk: Dehydration	
Evidence for linking the risk to the medicine	In one American study, dehydration was diagnosed in 6.7% of hospitalised patients age 65 and over, and 1.4% had dehydration as the principal diagnosis[12]. Prospective studies in long-term care facilities (LTCs) showed that residents were dehydrated in 50% of the febrile episodes and that 27% of the LTC resident population referred to hospitals was admitted due to dehydration[13,14]. Dehydration also proved to be very common in community-dwelling older adults[15].
Risk factors and risk groups	Older people are vulnerable to dehydration due to physiological changes in the ageing process, but this can be complicated by many disease states, and mental and physical frailty that can further increase risk of dehydration. Age-related changes include a reduced sensation of thirst, and this may be more pronounced in those with Alzheimer's disease or in those that have

	suffered a stroke. This indicates that thirst in older people may not be relied on as an indicator of dehydration. Reduced renal function is also a risk factor. The kidneys play a vital role in fluid regulation but their function deteriorates with age, and the hormonal response to dehydration (which is key to fluid balance) may be impaired. Dehydration is more common in those with cognitive impairment and changes in functional ability. Swallowing difficulties, dementia and poorly controlled diabetes are more common in older people and are all associated with poor hydration. The likelihood of dehydration may also be exacerbated by medications including diuretics and laxatives. Importantly incontinence predisposes to dehydration as people may limit their fluid intake. Inadequate fluid intake is a major contributor to preventable dehydration. Poor oral intake of fluids can be related to the inability to feed independently and having poor availability and access to fluids. This can be exacerbated in the residential care setting by inadequate staff training and lack of awareness of the importance of hydration[16].
Risk minimisation measures	**Routine risk minimisation measures:** SmPC/RSI Section 4.4 states that PLENVU should be used in caution in patients with dehydration. Any suspected dehydration should be corrected for before use of PLENVU. The fluid content of PLENVU when reconstituted with water does not replace regular fluid intake and adequate fluid intake must be maintained. PIL Section 2 states to talk to your doctor, pharmacist or nurse before taking PLENVU if any of the below are applicable to you. If you: • have a high or low blood salt level (e.g. sodium, potassium) • have any other medical conditions (e.g. seizures) Section 2 additionally states to drink clear fluids before, during, and after you take PLENVU to help prevent fluid loss (dehydration). It is important for you to drink the additional prescribed amounts of clear fluids. Prescription only medicine. **Additional risk minimisation measures:** None

Important identified risk: Electrolyte disturbance	
Evidence for linking the risk to the medicine	The incidence of electrolyte disturbance during the clinical development programme was lower than dehydration. In total, electrolyte disturbance was reported in 8 of 1028 patients (0.8%) in the NER1006 treatment group. All cases were considered related to the treatment. There were 4 cases (0.4%) of hypernatremia, and 1 case (0.1%) each of hyperkalaemia, hypophosphatemia and hypokalaemia. There were no case reports of hyponatremia or hyperkalaemia. Target population defined using age data from French colonoscopy audit[19]: <50 yrs: 30.5% 51-70 yrs: 46.5% 71-80 yrs: 18.9% >80 yrs: 4.1% Prevalence of one or more electrolyte abnormalities defined using NHANES III data (- Sodium: 133-145 mmol/L, Potassium: 3.2-4.7 mmol/L, Bicarbonate: 19-30 mmol/L, Osmolality: 264-290 mOsmol/Kg)[20]. Detailed table printed below. Applying these rates to the age profile of the colonoscopy population defined above yields expected prevalence rates of: Any abnormality: 14.2% Low Na: 2.1% High Na: 0.2% Low K: 1.1% High K: 4.9% Low Osmolality: 1.1% High Osmolality: 3.4% Low bicarbonate: 3.4% High bicarbonate: 1.3% Incidence derived from Hospital Episode Statistics for 2005/6[21]. Detailed table printed below. Applying these rates to the age profile of the colonoscopy population yields an expected overall annual incidence rate of 59.3/100,000 (0.06%).
Risk factors and risk groups	In 9 randomised controlled trials bowel preparation using up to 4L macrogol/PEG 3350 has been shown to be

	associated with small mean changes in electrolytes[23-31]. In these studies sodium changes ranged from a mean fall of 1.0 mmol/l to a rise of 1.4 mmol/l. Potassium fell by a mean of 0.1-0.3 mmol/l. The presented data are insufficient to determine whether there is a dose-response relationship. One study[24] presented individual patient data for potassium changes: 25 patients showed a decrease of between 0.06 mmol/L and 0.62 mmol/L; 13 patients showed an increase of between 0.13 mmol/L and 0.65 mmol/L; in 6 patients the potassium was unchanged. One patient, who had a starting potassium at the lower limit of normal had a post-treatment potassium level outside the normal range. One patient, who had a starting potassium below the lower limit of normal, had a final potassium level within the normal range. No specific patient criteria were identified that indicated predisposition to electrolyte disturbance, although good clinical practice would dictate that abnormal baseline electrolytes should be corrected prior to treatment. One study[26] was carried out in children, using the adult dose scaled to calculated body area. The type and magnitude of electrolyte changes was comparable to that seen in adults. Three studies[23,28,31] assessed the timescale of electrolyte changes. In two cases, sodium levels returned rapidly to normal, with no net change being detected immediately post colonoscopy[23] or 48-72 hours later. Potassium changes were longer lasting, with residual change being noted both post procedure[23] and 48-72 hours later. In the third study[31], electrolytes were measured at baseline, immediately after colonoscopy and one hour later. The authors observed small reductions in both sodium and potassium occurring between the second two time points, suggesting that the procedure itself had an influence on electrolyte balance.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC/RSI Section 4.4 states that in patients at risk of electrolyte imbalance the physician should consider performing a baseline and post-treatment electrolyte test as appropriate. Any suspected dehydration should be corrected for before use of PLENVU. If patients develop any symptoms indicating arrhythmia or shifts of fluid/electrolytes during or after treatment (e.g. oedema, shortness of breath, increasing fatigue, cardiac

	failure), plasma electrolytes should be measured, ECG monitored and any abnormality treated appropriately. PIL section 2 states to talk to your doctor, pharmacist or nurse before taking PLENVU if any of the below are applicable to you. If you: • have a high or low blood salt level (e.g. sodium, potassium) • have any other medical conditions (e.g. seizures) Prescription only medicine. **Additional risk minimisation measures:** None

Important identified risk: Transient increase in blood pressure	
Evidence for linking the risk to the medicine	Globally, the overall prevalence of raised blood pressure in adults aged 25 and over was around 40% in 2008. The proportion of the world's population with high blood pressure, or uncontrolled hypertension, fell modestly between 1980 and 2008. However, because of population growth and ageing, the number of people with uncontrolled hypertension rose from 600 million in 1980 to nearly 1 billion in 2008[32].
Risk factors and risk groups	Known cases of hypertension (especially uncontrolled/poorly controlled). Patients with renal impairment. Patients with excessive vomiting/gag reflex.
Risk minimisation measures	**Routine risk minimisation measures:** No specific clinical measures recommended. Prescription only medicine. **Additional risk minimisation measures:** None

Important identified risk: Transient increase in liver enzymes	
Evidence for linking the risk to the medicine	Prevalence of abnormal LFTs depends on the definition and population but is likely to be between 10 and 20% in the general population. Abnormal LFTs are associated with a range of health outcomes but are not necessarily strongly diagnostic of severe liver pathology[33]. It is common for general practitioners (GPs) to refer patients suspected of

	impaired liver function for laboratory tests (alkaline phosphatase, lactate dehydrogenase, bilirubin, prothrombin, aspartate aminotransferase). In a prospective multipractice study over a six-month period, including 30 GPs, 55 patients were recorded as having, for the first time, a high level of alkaline phosphatase (AP) as an isolated finding, 14 with an increase of aspartate aminotransferase (ASAT), eight with an increase of both AP and ASAT, three with an increase of ASAT, AP, and bilirubin, two with an isolated increase of lactate dehydrogenase (LDH), one with an increase of ASAT, AP, and bilirubin, combined with a low prothrombin (PP), and, finally, one patient with a low prothrombin in isolation. In most cases the tests were requested because of unspecific symptoms. The most common causes of abnormal test results were neoplasms, alcoholic liver disease, and heart failure. Thirty patients were referred to hospital for further investigations. During the same study period, 50 patients with known abnormal liver function tests were recorded, and the most common causes of these abnormalities were neoplasms, rheumatoid arthritis, and alcoholic liver disease[34].
Risk factors and risk groups	In the study mentioned above, the most common causes of abnormal test results were neoplasms, alcoholic liver disease, and heart failure[33]. Undiagnosed diabetes is also associated with liver injury, compared to diagnosed diabetes with treatment. The effect of diabetes treatment on liver injury in individuals with diabetes remains uncertain[35].
Risk minimisation measures	**Routine risk minimisation measures:** No specific clinical measures recommended. Prescription only medicine. **Additional risk minimisation measures:** None

Important identified risk: Allergic reactions (including anaphylaxis)	
Evidence for linking the risk to the medicine	The incidence of allergic reactions during the clinical development programme was very low. Drug hypersensitivity was reported in 1 case (0.1%), pruritus was reported in 2 cases (0.2%), erythema in 1 case (0.1%) and skin discoloration in 1 case (0.1%). All five cases were considered related to the treatment by the investigators. However, this risk is included as an identified risk based on

	the post-marketing experience of the Applicant with other macrogol/PEG 3350 containing products.
Risk factors and risk groups	It is not possible to identify risk groups in advance, other than prior experience of an allergic reaction to macrogol/PEG 3350. The effect is not subject to a dose-response effect, as even low levels of exposure can trigger full-scale clinical reactions in a susceptible individual.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC/RSI Section 4.3 contraindicates use of PLENVU in patients with known or suspected hypersensitivity to the active substances or to any of the excipients. SmPC/RSI Section 4.4 warns as with other macrogol/PEG containing products, allergic reactions including rash, urticaria, pruritus, angioedema and anaphylaxis are a possibility. PIL Section 2 states do not take PLENVU if you are allergic (hypersensitive) to the active substances or any of the other ingredients of PLENVU. PIL Section 4 states to stop taking PLENVU and tell your doctor immediately if you experience symptoms of a severe allergic reaction including: extreme fatigue, palpitations, rash or itching, shortness of breath and swelling of your face, ankles or other part of your body. Prescription only medicine. **Additional risk minimisation measures:** None

Important potential risk: Arrhythmias (including atrial fibrillation)	
Evidence for linking the risk to the medicine	Atrial fibrillation is a common condition amongst older adults. A retrospective review of a UK primary care database[44] identified prevalence rates of <1% in patients aged 40-55, rising to around 8% in those aged 80+. A prospective cohort study from Rotterdam[45] actively sought patients by carrying out ECGs and identified somewhat higher rates: <1% in those aged 55-59, rising to 17.8% in the over 85s. Given that primary care records depend on a diagnosis having been made and recorded the Rotterdam study probably gives a truer estimate of underlying prevalence. Additionally, the UK researchers excluded patients with paroxysmal AF.

	Age-specific prevalence data for atrial fibrillation from Rotterdam study[45]: 55-59 yrs; 0.7% 60-64 yrs; 1.7% 65-69 yrs; 4.0% 70-74 yrs; 6.0% 75-79 yrs; 9.0% 80-84 yrs; 13.5% 85+ yrs; 17.8% Age distribution of the colonoscopy population is[19]: <50 yrs: 30.5% 51-70 yrs: 46.5% 71-80 yrs: 18.9% >80 yrs: 4.1% Based on these demographics, and assuming a rate of 0.1% in the under 50s[44] we can estimate an overall prevalence in the target population of approximately 3% (3018/100,000). Reliable incidence data cannot be derived from the UK study[44], due to the exclusion of paroxysmal AF, which is likely to be relevant to drug-induced arrhythmias. Annual incidence rates from Rotterdam[45] were: 55-59 yrs; 1.1/1000 person years 60-64 yrs; 3.3/1000 person years 65-69 yrs; 5.5/1000 person years 70-74 yrs; 11.5/1000 person years 75-79 yrs; 14.7/1000 person years 80-84 yrs; 20.7/1000 person years 85+ yrs; 18.2/1000 person years Based on the demographics above, and assuming an incidence rate of 0.2/1000 person years in the under 50s, we can estimate an overall incidence in the target population of approximately 5.2/1000 (518/100,000).
Risk factors and risk groups	It would be reasonable to suppose that older patients, those with established ischemic heart disease, a prior history of atrial fibrillation, or patients with pre-treatment electrolyte abnormalities would be more likely to

	experience arrhythmias. Some known risk factors that can increase the chance of developing arrhythmias include: coronary artery disease, hypertension, diabetes mellitus, smoking, high cholesterol, obesity, high-fat diet, excessive use of alcohol (more than 2 drinks per day), drug abuse, anxiety/stress, family history of heart disease, advancing age, sleep apnoea, certain OTC and prescription medications, dietary supplements, and herbal remedies[46].
Risk minimisation measures	**Routine risk minimisation measures:** SmPC/RSI Section 4.4 warns PLENVU should be used in caution with patients with those at risk of arrhythmia, for example those with or on treatment for cardiovascular disease, thyroid disease or electrolyte imbalance. In patients with arrhythmia the physician should consider performing a baseline and post-treatment ECG as appropriate. There have been rare reports of serious arrhythmias including atrial fibrillation associated with the use of ionic osmotic laxatives for bowel preparation. These occur predominantly in patients with underlying cardiac risk factors and electrolyte disturbance. If patients develop any symptoms indicating arrhythmia or shifts of fluid/electrolytes during or after treatment (e.g. oedema, shortness of breath, increasing fatigue, cardiac failure), plasma electrolytes should be measured, ECG monitored and any abnormality treated appropriately. PIL Section 2 states to your doctor, pharmacist or nurse before taking PLENVU if any of the below are applicable to you. If you: • have heart problems and/or heart rhythm problems • have kidney problems and/or dehydration • have a high or low blood salt level (e.g. sodium, potassium) • have any other medical conditions (e.g. seizures) Prescription only medicine. **Additional risk minimisation measures:** None

Important potential risk: Perforation / aggravation of the condition in patients with toxic megacolon as a result of severe IBD

Evidence for linking the risk to the medicine	In the US, it is currently estimated that about 1 –1.3 million people suffer from IBD[51]. Ulcerative colitis is slightly more common in males, while Crohn's disease is more frequent in women. IBD occurs more in people of Caucasian and Ashkenazic Jewish origin than in other racial and ethnic subgroups. However, previously noted racial and ethnic differences seem to be narrowing[52]. Incidence rates[52]: Crohn's disease: 3.1 to 14.6 cases per 100,000 person-years; Ulcerative colitis: 2.2 to 14.3 cases per 100,000 person-years Prevalence: Crohn's Disease: 26 to 199 cases per 100,000 persons; Ulcerative colitis: 37 to 246 cases per 100,000 persons[52]. Crohn's Disease: 201 per 100,000 adults; Ulcerative Colitis: 238 per 100,000 adults[51].
Risk factors and risk groups	Generally, toxic megacolon, perforation and mortality are all more common in patients with ulcerative colitis than Crohn's disease. There are insufficient numbers of cases following the use of polyethylene glycol to ascertain whether the pattern of incidence is different in this circumstance.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC/RSI Section 4.3 contraindicates use of PLENVU in patients with known or suspected toxic megacolon, *gastrointestinal obstruction or perforation, ileus, disorders of gastric emptying, e.g. gastroparesis, gastric retention, etc.* SmPC/RSI Section 4.4 warns PLENVU should be used in caution with patients with severe acute inflammatory bowel disease. If patients experience severe bloating, abdominal distension, or abdominal pain, administration should be slowed or temporarily discontinued until the symptoms subside. PIL Section 2 states do not take PLENVU: • if you have a blockage in your bowel (bowel obstruction) • if you have an opening in the wall of your stomach or bowel (bowel perforation) • if you have paralysis of the gut (ileus)

	• if you experience problems with food and fluid emptying from your stomach (e.g. gastric paresis, gastric retention) • if you have a very dilated bowel (toxic megacolon) Talk to your doctor, pharmacist or nurse before taking PLENVU if any of the below are applicable to you. If you: • have stomach or bowel problems, including bowel inflammation Prescription only medicine. **Additional risk minimisation measures:** None

Important potential risk: Aspiration in patients with diminished levels of consciousness/severely debilitated patients especially if prepared with a nasogastric tube	
Evidence for linking the risk to the medicine	In a randomised trial of 86 ventilated patients microbiologically confirmed aspiration pneumonia occurred in 23% of patients in a supine position and 5% of patients in a semi-recumbent position[56].
Risk factors and risk groups	Patients with diminished levels of consciousness/severely debilitated patients.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC/RSI Section 4.4 warns caution should be used with the administration of PLENVU to frail or debilitated patients. PLENVU should also be used with caution in patients with impaired gag reflex, with the possibility of regurgitation or aspiration, or with diminished levels of consciousness. Such patients should be closely observed during administration especially if given via a nasogastric route. In debilitated fragile patients and patients with poor health the physician should consider performing a baseline and post-treatment electrolyte, renal function test and ECG as appropriate. PIL Section 2 states that PLENVU should not be given to patients with impaired consciousness without medical supervision. Prescription only medicine. **Additional risk minimisation measures:**

	None

Important potential risk: Cardiac failure / decompensation	
Evidence for linking the risk to the medicine	Heart failure is a common problem encountered in the age group undergoing colonoscopy. Overall prevalence of clinically significant heart failure ranges from 0.5-1.0% in the under 65s up to 9-10% in the over 80s[59-62]. The most detailed demographic breakdown of the European target population derives from a French national colonoscopy audit[19]: <50 yrs: 30.5% 51-70 yrs: 46.5% 71-80 yrs: 18.9% >80 yrs: 4.1% Age-specific prevalence data are available for similar age groups from two large population studies[59-60]: Reference 1 Reference 2 50-59 yrs 0.8% 45-54 yrs 0.7% 60-69 yrs 2.3% 55-64 yrs 1.4% 70-79 yrs 4.9% 65-74 yrs 2.0% 80-89 yrs 9.1% > 75 yrs 8.9% Based on mean values for these data, we can estimate an overall prevalence in the target population of approximately 1.7% (1,700/100,000). Annual incidence rates of new cases in the Framingham study were typically 2-3/1000 in patients aged under 65 and 8-10/1000 in those over 65[60]. Other population studies have identified rates higher than this – 6-9/1000 in under 64s[63] and 26-33/1000 in over 65s[64]. The diagnostic criteria, however, were less stringent in the latter studies and probably included patients with less clinically significant disease. Age-specific annual incidence data from Framingham study (rates/1000)[60]. Male Female 45-54 yrs 2 1 55-64 yrs 4 3

	65-74 yrs 8 5 75-84 yrs 14 13 85-94 yrs 54 85 Based on these data, we can estimate an overall annual incidence in the target population of approximately 6.8/1000 (680/100,000).
Risk factors and risk groups	Heart failure is unlikely to occur as a de novo effect of macrogol/PEG bowel preparation, rather it is an exacerbation of pre-existing disease. Susceptible patients will therefore include patients with prior diagnosis of heart failure, myocardial infarction, atrial fibrillation and age 75+ or very anxious patients (may predispose to inappropriate ADH secretion).
Risk minimisation measures	**Routine risk minimisation measures:** SmPC/RSI Section 4.4 warns PLENVU should be used in caution in patients with grade III or IV cardiac failure. In patients with poor health and with arrhythmia the physician should consider performing a baseline and post-treatment ECG as appropriate. PIL Section 2 states to talk to your doctor, pharmacist or nurse before taking PLENVU if any of the below are applicable to you. If you: • have heart problems and/or heart rhythm problems Prescription only medicine. **Additional risk minimisation measures:** None

Important potential risk: Acute renal failure / decompensation	
Evidence for linking the risk to the medicine	The incidence of acute renal failure has been assessed in a number of UK populations[65-67]. Annual overall incidence estimates were 505 cases/million population[65], 545 cases/million[66] and 620 cases/million[67]. Annual requirement for renal replacement therapy (RRT) in population studies ranges from 358/million to 445/million[65,68], although long term renal replacement was only required for 110/million[69]. Age-specific incidence data for acute renal failure are available from one study[65]: 20-49 yrs : 47/million 50-69 yrs : 120/million

	70-79 yrs : 335/million 80+ yrs : 597/million Age distribution of the colonoscopy population is[19]: <50 yrs: 30.5% 51-70 yrs: 46.5% 71-80 yrs: 18.9% >80 yrs: 4.1% Based on these demographics, we can estimate an overall annual incidence in the target population of approximately 158/million (15.8/100,000).
Risk factors and risk groups	None known. There are insufficient cases to identify any causative or associated factors[70].
Risk minimisation measures	**Routine risk minimisation measures:** SmPC/RSI Section 4.4 warns PLENVU should be used in caution in patients with renal impairment whose creatinine clearance is less than 30 mL/minute/1.73 m2. In patients with clinically significant renal impairment the physician should consider performing a baseline and post-treatment renal function test as appropriate. PIL Section 2 states to talk to your doctor, pharmacist or nurse before taking PLENVU if any of the below are applicable to you. If you: • have kidney problems and/or dehydration • have a high or low blood salt level (e.g. sodium, potassium) PLENVU contains a source of phenylalanine which may be harmful for people with phenylketonuria. Prescription only medicine. **Additional risk minimisation measures:** None

Important potential risk: Potential to alter absorption and decrease efficacy of other medicinal products	
Evidence for linking the risk to the medicine	No drug interactions were identified during the clinical development programme, but as seen with other drugs in the same class, concomitant oral drug can be flushed by the bowel preparation and therefore may not be absorbed. No expected effect/interaction with food was identified, except effects on the quality of bowel cleansing.

Risk factors and risk groups	Patients receiving concurrent treatment with other medications.
Risk minimisation measures	**Routine risk minimisation measures:** RSI Section 4.5 warns medicinal products taken orally (e.g. oral contraceptive pill) one hour before, during and one hour after PLENVU administration may be flushed from the gastrointestinal tract unabsorbed. SmPC Section 4.5 warns medicinal products taken orally (e.g. oral contraceptive pill) within one hour of starting colonic lavage with PLENVU may be flushed from the gastrointestinal tract unabsorbed. The therapeutic effect of drugs with a narrow therapeutic index or short half-life may be particularly affected. PIL Section 2 states to your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines (including oral contraceptives). Medicines taken by mouth may not be absorbed properly when taken within 1 hour before the start of PLENVU. Prescription only medicine. **Additional risk minimisation measures:** None

Missing information: Use in patients with glucose-6-phosphate dehydrogenase deficiency	
Evidence for linking the risk to the medicine	Patients with glucose-6-phosphate dehydrogenase deficiency may be at risk of acute haemolysis due to the presence of ascorbate (sodium ascorbate and ascorbic acid).
Risk factors and risk groups	Patients with glucose-6-phosphate dehydrogenase deficiency receiving PLENVU for bowel cleansing.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.3 contraindicates use in patients with known or suspected glucose-6-phosphate dehydrogenase deficiency (due to presence of ascorbate). RSI Section 4.4 warns patients with glucose-6-phosphate dehydrogenase deficiency may be at risk of acute

	haemolysis due to the presence of ascorbate (sodium ascorbate and ascorbic acid). PIL Section 2 states do no take PLENVU if your body is unable to produce enough glucose-6-phosphate dehydrogenase. Prescription only medicine. **Additional risk minimisation measures:** None

Missing information: Use in paediatric population	
Evidence for linking the risk to the medicine	There are no data on the use of PLENVU in paediatric patients <18 years.
Risk factors and risk groups	Paediatric patients <18 years receiving PLENVU for bowel cleansing.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 states the safety and efficacy in children below 18 years of age has not yet been established. PLENVU is therefore not recommended for use in this population. RSI Section 4.2 states PLENVU is not recommended for use in children below 18 years of age as it has not been studied in the paediatric population. PIL Section 2 states PLENVU is not recommended for use in children under 18 years of age. Prescription only medicine. **Additional risk minimisation measures:** None

Missing information: Use in pregnancy / lactation	
Evidence for linking the risk to the medicine	There are no data on the use of PLENVU during pregnancy or lactation.

Risk factors and risk groups	Pregnant patients and patients currently breastfeeding receiving PLENVU for bowel cleansing.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.6 states there are no or limited amount of data (less than 300 pregnancy outcomes) from the use of PLENVU active ingredients in pregnant women. Animal studies have shown indirect harmful effects with respect to reproductive toxicity. Clinically, no effects during pregnancy are anticipated, since systemic exposure to macrogol 3350 is negligible. As a precautionary measure, it is preferable to avoid the use of PLENVU during pregnancy. RSI Section 4.6 states there are no data on the use of PLENVU during pregnancy or lactation. The preparation should only be used during pregnancy or lactation if considered essential by the physician. There are no data on the effects of PLENVU on fertility. PIL Section 2 states are no data on the use of PLENVU during pregnancy or breast-feeding and is therefore not recommended. It should only be used if considered essential by the doctor. Prescription only medicine. **Additional risk minimisation measures:** None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of PLENVU.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for PLENVU.

Part VII: Annexes

Annex 1 – EudraVigilance Interface

N/A

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

N/A

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

No studies are proposed or ongoing.

Annex 4 - Specific adverse drug reaction follow-up forms

There are no specific adverse drug reaction follow-up forms in place.

Annex 5 – Protocols for proposed and on-going studies in RMP part IV

N/A. No studies are proposed or ongoing.

Annex 6 – Details of proposed additional risk minimisation activities (if applicable)

No additional risk minimisation measures are planned.

Annex 7 – Other supporting data (including referenced material)

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Annex 8 – Summary of changes to the risk management plan over time

Version	Approval date Procedure	Change
5.0	31 Jul 2017 SE/H/1801/001	N/A Approved at MA application
5.1	N/A	Updated to EMA Revision 2 RMP template. Safety concerns were additionally removed; however, this was rejected by the assessor.
5.2	N/A	Updated to EMA Revision 2 RMP template.
6.0	09 Dec 2022 EU- SE/H/1801/001/R/001	Approved, Signed version of updates made to version 5.2.