EU Risk Management Plan for MOVIPREP® Product Range (Macrogol 3350)

RMP version to be assessed as part of this application:

RMP Version number: 5.0

Data lock point for this RMP: 31-Aug-2021

Date of final sign off: 03-Nov-2021

Rationale for submitting an updated RMP: Revision of safety concerns

Summary of significant changes in this RMP:

All the below safety concerns have been removed:

Important identified risk:

- Dehydration and electrolyte abnormalities
- Anaphylaxis/ significant allergic reactions
- Transient increases in blood pressure
- Convulsions in association with severe hyponatremia

Important potential risk:

- Cardiac failure/decompensation
- Acute renal failure/decompensation
- Perforation of toxic megacolon secondary to severe IBD
- Aspiration (in unconscious patients especially if prepared with a nasogastric tube)
- Atrial fibrillation

Missing information:

- Patients with G6PD deficiency (there are no studies in this patient population due to the ascorbate content of MOVIPREP®
- Use in paediatric population
- Use in pregnant/lactating women

Part II – Populations not studied in clinical trials

Updated safety concerns previously considered as missing information in line with the above safety concerns removed.

Other RMP versions under evaluation: N/A

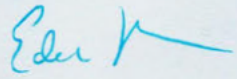
Details of the currently approved RMP:

Version number: 4.3

Approved with procedure: SE/H/1800/02/II/80

Date of approval (opinion date): 04-Apr-2022

EU QPPV name: Edel Behan

EU QPPV signature: 

Associate Director, Senior Safety Physician name: [redacted]

Associate Director, Senior Safety Physician signature: [redacted]

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Macrogol 3350
Pharmacotherapeutic group(s) (ATC Code)	A06AD
Marketing Authorisation Holder	Norgine BV Antonio Vivaldistraat 150, 1083 HP Amsterdam, The Netherlands
Medicinal products to which this RMP refers	Two (2)
Invented name(s) in the European Economic Area (EEA)	1. MOVIPREP®, powder for oral solution 2. MOVIPREP® Orange, powder for oral solution
Marketing authorisation procedure	Mutual recognition
Brief description of the product	Chemical class MOVIPREP® is a polyethylene glycol (PEG)-based bowel-cleansing agent intended for use prior to colonoscopy, intestinal surgery and barium enema X ray examination. Its clinical efficacy derives from the osmotic action of PEG 3350, sodium sulphate, ascorbic acid and sodium ascorbate acting together. MOVIPREP® Orange is a PEG-based bowel-cleansing agent intended for use prior to colonoscopy, intestinal surgery and barium enema X-ray examination. Its clinical efficacy derives from the osmotic action of PEG 3350, sodium sulfate, ascorbic acid and sodium ascorbate acting together.
	Summary of mode of action MOVIPREP® and MOVIPREP® Orange are osmotically acting laxatives. 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.
	Important information about its composition The ingredients of MOVIPREP® and MOVIPREP® Orange are contained in two separate sachets. Sachet A contains the following active substances: Macrogol 3350, sodium sulfate anhydrous, sodium chloride, and potassium chloride. Sachet B contains ascorbic acid and sodium ascorbate.

	MOVIPREP® Orange additional contains orange flavour (containing natural flavouring substances and preparations, maltodextrin, dextrose). 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 dehydration risk.
Hyperlink to the Product Information	
Indication(s) in the EEA	Current (if applicable): For bowel cleansing prior to any clinical procedures requiring a clean bowel, e.g. bowel endoscopy or radiology, or digestive tract surgery.
	Proposed (if applicable): N/A
Dosage in the EEA	Current (if applicable): **MOVIPREP®:** *Adults and elderly*: A course of treatment consists of two litres of MOVIPREP®. It is strongly recommended that one litre of clear liquid, 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. Patients should be advised to allow for appropriate time to travel to the colonoscopy unit. No solid food should be taken from the start of the course of treatment until after the clinical procedure. *Children*: Not recommended for use in children below 18 years of age as MOVIPREP® has not been studied in the paediatric population. **MOVIPREP® Orange:** Adults and Older people: A course of treatment consists of two litres of MOVIPREP® Orange. It is strongly recommended that one litre of clear liquid, 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. Patients should be advised to allow for appropriate time to travel to the colonoscopy unit. No solid food should be taken from the start of the course of treatment until after the clinical procedure

	Paediatric population: Not recommended for use in children below 18 years of age, as Moviprep Orange has not been studied in the paediatric population.
	Proposed (if applicable): N/A
Pharmaceutical form(s) and strengths	Current (if applicable): Powder for oral solution. Strength Sachet A: Macrogol 3350 100g Sodium sulfate anhydrous 7.500g Sodium chloride 2.691g Potasium chloride 1.015g Sachet B: Ascorbic acid 4.700g Sodium ascorbate 5.900g
	Proposed (if applicable):
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

The market authorisation applications for MOVIPREP® have been submitted under Article 10b fixed combination application.

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

Please note: throughout this document, MOVIPREP® is used as the parent name for the product family. i.e. MOVIPREP® and MOVIPREP® Orange.

The MOVIPREP® product range is indicated for:

- Bowel cleansing prior to any clinical procedures requiring a clean bowel, e.g. bowel endoscopy or radiology, or digestive tract surgery.

Incidence: In Europe, about 15 million colonoscopies are performed every year, giving an incidence of about 5% of the overall population. In 2003, recommendations for screening programs for colorectal cancer were issued by the Council of the European Union (EU), and these currently serve as the basis for the preparation of European guidelines for colorectal cancer (CRC) screening. The manner in which CRC screening is carried out varies significantly from country to country within the EU, both in terms of organization and the screening test chosen. A screening program of one sort or another has been implemented in 19 of 27 EU countries[1].

Based on 2010 data, more than 3.3 million outpatient colonoscopies are performed annually in the United States, and colonoscopy for CRC screening and colon polyp surveillance accounts for approximately 50% of colonoscopies[2].

Prevalence:

Demographics of the population in the authorised indication and risk factors for the disease: Although all segments of population could need a colon procedure, the majority is expected to be > 50 years of age.

Age sex distribution:

18-49 20%

50-90 80%

The main existing treatment options: N/A

Natural history of the indicated condition in the untreated population, including mortality and morbidity: Colonoscopy for CRC screening and colon polyp surveillance accounts for approximately 50% of colonoscopies[3]. Mortality rate of colonoscopy is very low (< 0.1%), morbidity of colonoscopy varies between 1 and 5%.

Important co-morbidities: Atrial fibrillation[3], cardiac failure[4], colon cancer[5] and inflammatory bowel disease[6].

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

Limited toxicology data are available for MOVIPREP® but comprises a 14-day repeat dose oral toxicity study in the rat and dog. In addition, literature data on PEGs in general and the other constituents of MOVIPREP® has been used to examine its safety. According to the nonclinical data, there are no safety concerns which have not been resolved by clinical data or are of unknown significance. A summary of the nonclinical findings and their relevance to humans is outlined below.

Single dose toxicity: Due to the established toxicity profile of the components of PEG-3350, no stand-alone single dose toxicity studies were performed.

In the study conducted by Smyth et al., (1950), oral LD50 of Carbowax 4000 was established to be 59 g/kg and the maximum non-lethal dose to be 32 g/kg. No lethality and no obvious toxicity resulted when PEG 4000 was given by the intraperitoneal route up to 20 g/kg to rats and up to 10 g/kg to guinea pigs. Similar responses were obtained in dogs dosed intravenously with PEG 4000. No deaths occurred up to 12 g/kg, the maximum dosage administered. Some parasympathomimetic responses (cardiovascular, respiratory) were noted in dogs at very high dosages, but these progressed slowly over a 6-hour period, and then levelled off. This is likely to be a species specific effect and are not expected in humans at indicated doses.

Other Constituents: Sodium sulphate has low toxicity, with an oral LD50 value in the rat of >10000 mg/kg. 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. An acute rat study and reverse mutation assay confirm the lack of toxicity for lemon spray-dried flavour V3938-1N1 which is used as a flavouring agent in MOVIPREP®.

Repeat dose toxicity:

14-Day repeat dose oral rat toxicity study (LPT Study No. 18290/04): Groups of 10 male and 10 female rats were administered MOVIPREP® orally at doses of 0, 5000, 10000 or 20000 mg/kg for 14 days, followed by a 4-week recovery period (with additional groups of 5 males and 5 females for control and high dose groups). Two animals that received 20000 mg/kg died after showing soft faeces, increased water consumption, reduced food consumption, changes in biochemical and urinary parameters (increased bilirubin, ALT and urea, decreased chloride and potassium levels, and increased urine specific gravity) and increased kidney weights. The only findings at 10000 mg/kg/day were minor clinical pathology changes (increased urea and decreased chloride and potassium levels, and increased urine specific gravity). There were no adverse findings on histopathology, and all surviving animals regained their normal state within the 4-week recovery period. The study NOAEL was considered to be 10000 mg/kg/day, with study changes related to the pharmacodynamic effects of MOVIPREP®.

14-Day repeat dose oral dog toxicity study (LPT Study No. 18291/04): Groups of 3 dogs per sex per group received MOVIPREP® orally at doses of 5000, 10000 or 20000 mg/kg/day for 14 days, followed by a 2-week recovery period (with additional groups of 2 males and 2 females for control and high dose groups). Study findings were limited to diarrhoea and emesis at all dosages, along with salivation and decreased sodium levels noted in the high dosage group. All of the findings completely subsided by the end of the 2-week recovery period. Overall, as the responses were considered to be due to exaggerated pharmacodynamic properties of MOVIPREP®, the study NOAEL was considered to be 20000 mg/kg/day.

Reproductive and developmental toxicity:

PEG 3350: 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 PEG 200, despite the recognized teratogenic effects of ethylene glycol (Shepard, 1998). With regard to ethylene glycol, it has been determined that glycolic acid, one of the metabolites of ethylene glycol, is the proximate teratogen (Carney et al., 1996).

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.

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 PEG 200. The degree of purity of the PEG 200 was not stated.

When 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.

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 PEG derivatives. Typical results are noted for PEG-30, -33, -35, -36, -40 castor oil and PEG-30, -40 hydrogenated castor oil. There was no evidence that these were developmental or reproductive toxicants.

Other constituents: Limited data has showed that sodium sulphate is not reprotoxic. With respect to ascorbic acid, it is not reprotoxic. Ascorbic acid crosses the human placenta with cord blood concentrations 2-4 times that of the mother. It also passes into the milk of nursing mothers and appears to be concentrated there as well. Normal plasma levels are 10 – 20 µg/mL, where levels in milk may be 40 – 70 µg/mL (McEvoy et al., 1993). Nevertheless, there are no reports of problems with nursing human infants (USP DI, 1994).

PEG 3350: Polyethylene glycols from PEG 200 to PEG 6000 have been the subject of in vitro and in vivo genotoxicity assays. PEG 200 and 1000 are not mutagenic in the Salmonella typhimurium reverse mutation assay. In fact, PEG is an acceptable test article diluent in the more rigorous 60 minute pre-incubation protocol for this assay. PEG 200 was also negative when tested in vivo for clastogenic potential. PEG 400 and 1000 produced no mutations in CHO cells and no increase in DNA damage as evidenced by increased sister chromatid exchanges. There was no increase in unscheduled DNA synthesis (UDS) in response to PEG 4000 (Satory and Racz, 1982), and when PEG 6000 was tested in the mouse lymphoma forward mutation assay, it showed no potential for inducing mammalian point mutations (Cosmetic Ingred. Rev. Pnl, 1993).

Other constituents: Limited data has showed that sodium sulphate is not genotoxic. With respect to ascorbic acid, although some positive in vitro genotoxicity findings were seen, 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.

Carcinogenicity:

PEG 3350: In a rodent carcinogenicity bioassay, rats received 0.5, 1.0, 2.0, 4.0 or 8.0% PEG 4000 in the diet for two years. Potential effects on diet consumption, mortality, infections, life span, liver and kidney weight and histopathology of the adrenal, heart, small intestine, kidney, liver, lung, pancreas,

spleen and testis, haematology and neoplasms were evaluated. The only criterion that was affected was body weight gain, which was reduced in male and female animals consuming 8% PEG 4000. The no effect level was therefore set at 4% (Dow/Union Carbide, 5/7/54).

Other constituents: Although data are lacking, ascorbic acid is unlikely to be carcinogenic given its normal presence in the body. No information on the carcinogenic potential of sodium sulphate has been identified.

Due to the intended short-term clinical exposure to these drug products, carcinogenicity studies on the final MOVIPREP® product were not performed.

General safety pharmacology:

Tests in animals examining the safety of PEGs on different organ systems by different routes revealed only a few effects at high, or extremely high, doses. Some premature drop-off of rats in the Roto-rod test at 0.6 g/kg, and some crenation of erythrocytes and pulmonary haemorrhages leading to death in rabbits receiving 10% PEG-75 i.v. were observed. However, when the dose was reduced to 5% i.v. (still a very high dose), no effects were seen in the rabbits. Other dosages, oral or i.p., of PEG-8 or PEG–75, up to 6 g/kg, produced either no nervous system effects in mice (anticonvulsant properties) or an increase in anticonvulsant effects as the molecular weight increased. In an epileptic monkey model i.v. infusion of PEG-8 resulted in a decrease in epileptic seizures. High molecular weight PEG (PEG 4000) has shown some parasympathomimetic activity in dogs, but only at extraordinarily large intravenous dosages between 4 and 12 g/kg, and these were not life-threatening (Dow/Union Carbide 7/26/54). Likewise, no curare-like or sedative effects were observed in rats given from 5 – 20 g/kg intraperitoneally, or in guinea pigs receiving up to 10 g/kg by the same route (Dow/Union Carbide 7/26/54).

Drug interactions:

No interactions of PEG with other drugs are apparent, but various molecular weights of PEG are used in pharmaceutical formulations to increase the aqueous solubility of drugs, so there may be some potential for 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 concentration of the contraceptive hormone ethinylestradiol in women (Morris, J. C., et al., 1981; Briggs, M. H., 1981), but it is not known whether these changes would result from a single dose. The dissociation products of sodium sulphate enter into the body's pools and are incorporated into many physiological reactions involving sulphation. No specific drug interactions are anticipated.

Part II: Module SIII - Clinical trial exposure

MOVIPREP® is a PEG-based bowel-cleansing agent intended for use prior to colonoscopy, intestinal surgery and barium enema X-ray examination. Its clinical efficacy derives from the osmotic action of PEG 3350, sodium sulfate, ascorbic acid and sodium ascorbate acting together. MOVIPREP® was first approved in the EEA on 19 Jan 2006 (UK and Germany) and is indicated for bowel cleansing prior to any clinical procedures requiring a clean bowel e.g. bowel endoscopy or radiology. The safety and efficacy of MOVIPREP® has been evaluated in 5 clinical trials.

MOVIPREP® Orange, additionally contains orange flavour (containing natural flavouring substances and preparations, maltodextrin, dextrose) and was first approved in the UK on 06 Aug 2010 and is approved for the same indication and dosage as MOVIPREP®.

The ingredients of MOVIPREP® are contained in two separate sachets. All active materials are inorganic. MOVIPREP® 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 dehydration risk.

A course of treatment consists of two litres of MOVIPREP®. It is strongly recommended that one litre of clear liquid, 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. A litre of MOVIPREP® consists of one 'Sachet A' and one 'Sachet B' dissolved together in one litre of solution. This reconstituted solution should be drunk over a period of one to two hours. This process should be repeated with a second litre of MOVIPREP® to complete this course.

This course of treatment can be taken: either as divided or as single doses as specified below:

1. Divided doses: one litre of MOVIPREP® in the evening before and one litre of MOVIPREP® in the early morning of the day of the clinical procedure.
2. Single dose: two litres in the evening preceding the clinical procedure or two litres in the morning of the clinical procedure.

For the divided dose and single dose taken in the evening before the procedure there should be at least one hour between the end of intake of fluid (MOVIPREP® or clear liquid) and the start of the colonoscopy. For the single dose in the morning of the procedure, there should be at least two hours between the end of intake of MOVIPREP® and at least one hour between the end of intake of any clear liquid and the start of the colonoscopy. Patients should be advised to allow for appropriate time to travel to the colonoscopy unit. No solid food should be taken from the start of the course of treatment until after the clinical procedure. MOVIPREP® is not recommended for the use in children below 18 years of age, as MOVIPREP® has not been studied in the paediatric population.

Dosage for all randomised blinded studies: total dose: two doses of 1 litre (total = 2 litres). One dose = 100g Macrogol 3350; 7.500g sodium sulphate anhydrous; 4.700g ascorbic acid; 5.900 g sodium ascorbate; 2.691g sodium chloride and 1.015g potassium chloride.

Table SIII.1: Duration of exposure

Cumulative for all indications (person time)		
Duration of exposure	Patients	Person time
24hrs	825	825 days
Total person time	825	825 days

Indication: For bowel cleansing prior to any clinical procedures requiring a clean bowel, e.g. bowel endoscopy or radiology, or digestive tract surgery.		
Duration of exposure	Patients	Person time
Dose level 1: Split dose: 1st dose afternoon/evening prior to colonoscopy; 2nd dose on the morning of colonoscopy.	454	454 days
Dose level 2: 2 doses the evening before the colonoscopy	371	371 days
Total person time for indication	825	825 days

Table SIII.2: Age group* and gender

Age group	Patients	Person time
< 18	0	0
18 ≤ age < 30	8	8 days
30 ≤ age < 45	33	33 days
45 ≤ age < 60	62	62 days
60 ≤ age < 75	80	80 days
75 ≤ age^	37	37 days
Total	220	220 days

Gender	Patients	Person time
Male	422	422 days
Female	403	403 days
Total	825	825 days

* NB: Data from studies NRL994-01/2001 and NRL994-01/2004 only

^ NB: Data added from study NRL994-02/2006

Table SIII.3: Dose

Dose of exposure	Patients	Person time
Dose level 1: Split dose: 1st dose afternoon/evening prior to colonoscopy; 2nd dose on the morning of colonoscopy.	484	484 days
Dose level 2: 2 doses the evening before the colonoscopy	405	405 days
Total	889	889 days

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

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

Patients with severe renal, cardiac or hepatic impairment

Reason for exclusion: These patients were excluded, as in these situations, the procedure itself can be considered at risk. However, if a colonoscopy is absolutely necessary, MOVIPREP® could be used under strict medical monitoring.

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

Rationale: 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. It is recommended that patients with poor health, those with clinically significant renal impairment, arrhythmia and those at risk of electrolyte imbalance, the physician should consider performing a baseline and post-treatment electrolyte, renal function test and ECG as appropriate. If patients develop any symptoms indicating arrhythmia or shifts of fluid/electrolytes (e.g. oedema, shortness of breath, increasing fatigue, cardiac failure), plasma electrolytes should be measured, ECG monitored and any abnormality treated appropriately.

In unconscious patients

Reason for exclusion: Patients fed with gastric tubes and patients in poor condition unable to drink, special attention should be given 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 have been a small number of reports observed concerning risk of aspiration in patients administered MOVIPREP® via nasogastric tube. In this instance, the product is administered in a hospital setting, allowing for immediate treatment if a reaction were to occur.

Paediatric populations:

Reason for exclusion: No study was conducted in children but the product, on the model of PEG lavage solutions, should be safe at the dosage recommended (40 to 50 ml per Kg).

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

Rationale: MOVIPREP® is not indicated for use in the paediatric population, the RSI states: ‘Children: Not recommended for use in children below 18 years of age as MOVIPREP® has not been studied in the paediatric population.’ No further characterization or risk minimization through additional risk management activities are considered necessary.

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 MOVIPREP® is not recommended.

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

Rationale: It is known to healthcare professionals that various drugs can precipitate a haemolytic crisis in G6PD-deficient individuals. The RSI contains a warning of risk in these individuals. No further characterization or risk minimization through additional risk management activities are considered necessary.

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

Special groups were studied in one of the two pivotal studies (NRL994 01/2001): Renal impaired patients, patients with cardiovascular disease (without obvious cardiac insufficiency) and inflammatory bowel disease (IBD). No increase of adverse reactions was observed in these populations and overall MOVIPREP® proved to be as safe as the comparator. Summaries of the adverse event (AE) profiles are given below.

Children

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

Elderly

Not applicable; elderly patients were included in the clinical development programme.

Pregnant or breast feeding women

Pregnant or breast feeding women were not studied in the clinical trials programme. The preparation should only be used during pregnancy or lactation if considered essential by the physician.

Patients with hepatic impairment

Patients with hepatic impairment were not studied in the clinical trials programme. The product is a biologically inert polymer which is barely absorbed and is not metabolised. Therefore hepatic impairment is not considered to be a concern.

Patients with renal impairment

Sixty-eight patients treated with MOVIPREP® had an abnormal renal function, attested by a calculated creatinine clearance < 80 ml/min. No relevant safety differences were identified for all the subgroups categorised on the basis of their calculated creatinine clearance.

Table SIV.2.1: Patients with renal insufficiency (selected by the calculated reduced

Creatinine Clearance (CC)	MOVIPREP®	Comparator (PEG+E)
	N=109	N=99
CC > 80 mL/min NAE*	38	52
CC > 80 mL/min RAE**	35	43
	N=50	N=63
50 < CC ≤ 80 mL/min NAE	27	27
50 < CC ≤ 80 mL/min RAE	26	22

	N=18	N=16
CC ≤ 50 mL/min NAE	8	7
CC ≤ 50 mL/min RAE	7	6

* NAE: Number of patients with AE ** RAE: Number of patients with related AE

MOVIPREP® contains PEG3350 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 litre of MOVIPREP® consists of one 'Sachet A' and one 'Sachet B' dissolved together in one litre of solution. This reconstituted solution should be drunk over a period of one to two hours. This process should be repeated with a second litre of MOVIPREP® to complete this course. This course of treatment can be taken either as divided (one litre of MOVIPREP® in the evening before and one litre of MOVIPREP® in the early morning of the day of the procedure) or single dose (two litres in the evening preceding the clinical procedure or two litres in the morning of the clinical procedure). Whilst there is no net absorption of the water component of MOVIPREP®, an additional litre of water should be ingested with it, and there is known to be transient fluid flux. Therefore, there is the potential for fluid overload in a renal failure population. Divided doses in these cases may be more appropriate.

A post-marketing safety review of the MOVIPREP® product family was undertaken using data from launch of each product to the data lock of 30-Sep-2015. This included a review of renal impairment/ renal failure. The data reviewed suggested that renal events occur infrequently with MOVIPREP® in the context of approximately 20 million patients exposed. However, potential risk remains and hence the precautionary labelling advice for treatment with caution in renal impairment patients whose creatinine clearance is less than 30 mL/minute.

Patients with other relevant co-morbidities

Patients with intermittent or continuous presence of cardiovascular diseases

A total of 75 patients were included in this subgroup analysis, of which 41 were treated with MOVIPREP® and 34 with PEG+E. No significant difference in the rate of AEs was seen in the two subgroups.

Table SIV.2.2: Intermittent or continuous presence of cardiovascular diseases

	MOVIPREP®	**Comparator (PEG+E)**
	N=41	N=34
Patients with AE	14	10
Patients with related AE	13	7

A cumulative review of post-marketing reports of cardiac events across MOVIPREP® products (Sep 2015) did not identify a causal link between MOVIPREP® 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 MOVIPREP®, 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, although there have been infrequent reports of these events. However, the 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 26 patients were considered in this subgroup analysis, 17 treated with MOVIPREP® and nine treated with PEG+E. No differences of AE rates were seen between the two groups.

Table SIV.2.3: Inflammatory bowel disease

	MOVIPREP®	**Comparator (PEG+E)**
	N=17	N=9
Patients with AE	8	9
Patients with related AE	7	9

Since MOVIPREP® is an osmotic laxative, inflamed intestinal mucosa in severe IBD (Crohn's disease, ulcerative colitis) may theoretically affect the clinical effectiveness of MOVIPREP®. There is also an increased risk of rupture/perforation at colonoscopy, particularly in severe disease, hence the precautionary labelling advice for treatment with caution in severe acute IBD and contraindication for toxic megacolon.

Patients with a disease severity different from the inclusion criteria in the clinical trial population

Not applicable. MOVIPREP® is indicated for bowel cleansing prior to any clinical procedures requiring a clean bowel, e.g. bowel endoscopy or radiology, or digestive tract surgery, rather than treating the disease.

Sub-populations carrying known and relevant polymorphisms

Not applicable; genetic polymorphisms have not been formally studied in the MOVIPREP® clinical trial population. As PEG 3350 is 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 of different racial and/or ethnic origin

Not applicable; patients of different racial and/or ethnic origin have not been formally studied in the MOVIPREP® clinical development programme. As PEG3350 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.

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

Table SIV.3.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**
Use in paediatric population	N/A - not included in the clinical development program.

<table>
<tr><td>Use in pregnancy and lactation</td><td rowspan="2"></td></tr>
<tr><td>Patients with hepatic impairment</td></tr>
<tr><td>Patients of different racial and/or ethnic origin</td><td>Not applicable; patients of different racial and/or ethnic origin have not been formally studied in the MOVIPREP® clinical development programme. As PEG3350 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.</td></tr>
<tr><td>Patients with renal impairment</td><td>Sixty-eight patients treated with MOVIPREP® had an abnormal renal function, attested by a calculated creatinine clearance < 80 ml/min. No relevant safety differences were identified for all the subgroups categorised on the basis of their calculated creatinine clearance.
<table>
<tr><th>Creatinine Clearance (CC)</th><th>MOVIPREP®</th><th>Comparator (PEG+E)</th></tr>
<tr><td></td><td>N=109</td><td>N=99</td></tr>
<tr><td>CC > 80 mL/min NAE*</td><td>38</td><td>52</td></tr>
<tr><td>CC > 80 mL/min RAE**</td><td>35</td><td>43</td></tr>
<tr><td></td><td>N=50</td><td>N=63</td></tr>
<tr><td>50 < CC ≤ 80 mL/min NAE</td><td>27</td><td>27</td></tr>
<tr><td>50 < CC ≤ 80 mL/min RAE</td><td>26</td><td>22</td></tr>
<tr><td></td><td>N=18</td><td>N=16</td></tr>
<tr><td>CC ≤ 50 mL/min NAE</td><td>8</td><td>7</td></tr>
<tr><td>CC ≤ 50 mL/min RAE</td><td>7</td><td>6</td></tr>
</table></td></tr>
<tr><td>Patients with intermittent or continuous presence of cardiovascular diseases</td><td>A total of 75 patients were included in this subgroup analysis, of which 41 were treated with MOVIPREP® and 34 with PEG +E. No significant difference in the rate of AEs was seen in the two subgroups.

Intermittent or continuous presence of cardiovascular diseases
<table>
<tr><th></th><th>MOVIPREP®</th><th>Comparator (PEG+E)</th></tr>
<tr><td></td><td>N=41</td><td>N=34</td></tr>
<tr><td>Patients with AE</td><td>14</td><td>10</td></tr>
<tr><td>Patients with related AE</td><td>13</td><td>7</td></tr>
</table></td></tr>
</table>

<table>
<tr>
<td>Patients with inflammatory bowel disease (IBD)</td>
<td>Few patients with IBD have been exposed in clinical trials. A total of 26 patients were considered in this subgroup analysis, 17 treated with MOVIPREP® and 9 treated with PEG+E. No differences of AE rates were seen between the two groups.

Inflammatory bowel disease
<table>
<tr><td></td><td>MOVIPREP®</td><td>Comparator (PEG+E)</td></tr>
<tr><td></td><td>N=17</td><td>N=9</td></tr>
<tr><td>Patients with AE</td><td>8</td><td>9</td></tr>
<tr><td>Patients with related AE</td><td>7</td><td>9</td></tr>
</table>
</td>
</tr>
</table>

Part II: Module SV - Post-authorisation experience

MOVIPREP® was first approved in the EEA on 19-Jan-2006 (UK and is indicated for bowel cleansing prior to any clinical procedures requiring a clean bowel e.g. bowel endoscopy or radiology.

MOVIPREP® Orange additionally contains orange flavour (containing natural flavouring substances and preparations, maltodextrin, dextrose) and was first approved in the UK on 06-Aug-2010 and is approved for the same indication and dosage as MOVIPREP®.

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Sales data has been used to estimate patient exposure.

The first approval (International Birth Date) for MOVIPREP® was granted in the UK on 19-Jan-2006. Sales data is only available from 01-Jan-2008 and the exposure calculation is based on this data.

The calculation of patient exposure is based on the assumption that one MOVIPREP® pack sold corresponds to exposure in one patient, since MOVIPREP® is indicated in adults for bowel cleansing prior to any clinical procedures requiring a clean bowel e.g. bowel endoscopy or radiology and therefore no repeat dose is necessary.

SV.1.2 Exposure

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

Table SV.1.2.1: Exposure table

Indication	Cumulative Doses
Bowel cleansing prior to any clinical procedures requiring a clean bowel, e.g., bowel endoscopy or radiology, or digestive tract surgery	47,950,819
Cumulative Period: through 31 August 2021	

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

Potential for misuse for illegal purposes

MOVIPREP® contains no active ingredients that would have abuse potential and therefore its potential for misuse for illegal purposes is zero.

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 RMP version 0 dated 24-May-2006: **Summary of safety concerns**	
Important identified risks	Dehydration and Electrolytes abnormalities in elderly or co medicated patients with underlying pathological conditions
	Aspiration in unconscious patients especially if prepared with a naso gastric tube
Important potential risks	Perforation/aggravation of the condition in patients with toxic megacolon as a result of severe inflammatory bowel disease
	Anaphylaxis / severe allergic reactions
	Cardiac or renal decompensation in patients with cardiac or renal severe insufficiency
Missing information	Patients with G6PD deficiency

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

Reclassification of safety concerns:

Dehydration and electrolyte abnormalities previously classified as an important identified risk has been removed as '*Dehydration*' and '*Electrolyte disturbances including blood bicarbonate decreased, hyper and hypocalcaemia, hypophosphataemia, hypokalaemia and hyponatremia and changes in the blood chloride levels*' are listed events in section 4.8 of the MOVIPREP® RSI. Section 4.8 additionally states '*Dehydration may occur as a result of diarrhoea and/or vomiting.*' There is extensive wording in 4.4 of the RSI which notes: '*The fluid content of MOVIPREP® when re-constituted with water does not replace regular fluid intake and adequate fluid intake must be maintained. MOVIPREP® should be used with caution in patients with: dehydration. In debilitated fragile patients, patients with poor health, those with clinically significant renal impairment, arrhythmia and those at risk of electrolyte imbalance, the physician should consider performing a baseline and post-treatment electrolyte, renal function test and ECG as appropriate. If patients develop any symptoms indicating arrhythmia or shifts of fluid/electrolytes (e.g. oedema, shortness of breath, increasing fatigue, cardiac failure), plasma electrolytes should be measured, ECG monitored and any abnormality treated appropriately.*' No additional risk minimization measures are put in place for this risk.

It is considered that dehydration and electrolyte abnormalities would be a well-known risk by medical professionals given the pharmacology of macrogol 3350.

Anaphylaxis/ Significant allergic reactions previously classified as an important identified risk has been removed as '*Allergic reaction including anaphylactic reaction, dyspnoea and skin reactions including angioedema, urticaria, pruritus, rash, erythema*' are listed events in section 4.8 of the MOVIPREP® RSI. Section 4.3 of the RSI contraindicates use of MOVIPREP® in patients with known or suspected hypersensitivity to MOVIPREP® and its excipients. The risk of MOVIPREP® triggering anaphylactic reactions is known to healthcare professionals and any appropriate measures which should be taken are part of routine clinical practice. No additional risk minimization measures are put in place for this risk.

Transient increases in blood pressure previously classified as an important identified risk has been removed as '*Cardiac disorders: Transient increase in blood pressure. Arrhythmia, palpitations'* is listed in section 4.8 of the MOVIPREP® RSI. There is extensive wording in section 4.4 of the RSI which notes: '*MOVIPREP® should be used with caution in patients with: grade III or IV cardiac failure, those at risk of arrhythmia, for example those on treatment for cardiovascular disease or who have thyroid disease. 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 (e.g. oedema, shortness of breath, increasing fatigue, cardiac failure), plasma electrolytes should be measured, ECG monitored and any abnormality treated appropriately*.' No additional risk minimization measures are put in place for this risk.

This safety concern can be prevented if adhering to the recommended volumes of intake detailed in the RSI, and is also temporary and reversible.

Convulsions in association with severe hyponatremia previously classified as an important identified risk has been removed as '*Nervous system disorders: Convulsions associated with severe hyponatraemia*' and '*Metabolism and Nutrition Disorders: Electrolyte disturbances including blood bicarbonate decreased, hyper and hypocalcaemia, hypophosphataemia, hypokalaemia and hyponatremia and changes in the blood chloride levels*' are listed in section 4.8 of the MOVIPREP® RSI. There is extensive wording in section 4.4 of the RSI which notes: '*In debilitated fragile patients, patients with poor health, those with clinically significant renal impairment, arrhythmia and those at risk of electrolyte imbalance, the physician should consider performing a baseline and post-treatment electrolyte, renal function test and ECG as appropriate. If patients develop any symptoms indicating arrhythmia or shifts of fluid/electrolytes (e.g. oedema, shortness of breath, increasing fatigue, cardiac failure), plasma electrolytes should be measured, ECG monitored and any abnormality treated appropriately*.'

Convulsions are a well-known symptom of severe hyponatremia, patients who develop symptoms of electrolyte imbalance should be monitored and treated appropriately. No additional risk minimization measures are put in place for this risk.

Cardiac failure/decompensation previously classified as an important potential risk has been removed as it has been evaluated that there are sufficient warnings for caution in this group of patients and no additional measures are deemed necessary currently. Section 4.4 of the RSI states: '*MOVIPREP® should be used with caution in patients with: grade III or IV cardiac failure. If patients develop any symptoms indicating arrhythmia or shifts of fluid/electrolytes (e.g. oedema, shortness of breath, increasing fatigue, cardiac failure), plasma electrolytes should be measured, ECG monitored and any abnormality treated appropriately*.'

Acute renal failure/decompensation previously classified as an important potential risk has been removed as it has been evaluated that there are sufficient warnings for caution in this group of patients and no additional measures are deemed necessary currently. Section 4.4 of the RSI states: '*MOVIPREP®*

should be used with caution in patients with: renal impairment whose creatinine clearance is less than 30 mL/minute. In debilitated fragile patients, patients with poor health, those with clinically significant renal impairment, arrhythmia and those at risk of electrolyte imbalance, the physician should consider performing a baseline and post-treatment electrolyte, renal function test and ECG as appropriate. This medicinal product contains 28.4 mmol (1.1 g) potassium per course of treatment. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.'

Perforation of toxic megacolon secondary to severe IBD previously classified as an important potential risk has been removed as it has been evaluated that there is adequate wording in the RSI describing this risk. Section 4.4 of the RSI warns: '*MOVIPREP® should be used with caution in patients with: severe acute inflammatory bowel disease. If a patient experiences severe bloating, abdominal distension, or abdominal pain, administration should be slowed or temporarily discontinued until the symptoms abate*.' MOVIPREP® is contraindicated for use in patients with known or suspected toxic megacolon. No additional risk minimization measures are put in place for this risk.

Aspiration (in unconscious patients especially if prepared with a nasogastric tube) previously classified as an important potential risk has been removed as it has been evaluated that there is adequate wording in the RSI describing this risk. Section 4.4 of the RSI states: '*MOVIPREP® should be used with caution in patients with: impaired gag reflex, with the possibility of regurgitation or aspiration, or with diminished levels of consciousness*.' Additionally, it is also expected that unconscious patients or patients prone to aspiration or regurgitation will be closely observed during administration, especially if this is via a nasogastric route. No additional risk minimization measures are put in place for this risk.

Atrial fibrillation previously classified as an important potential risk has been removed as '*Cardiac disorders: Arrhythmia, palpitations*' is listed in section 4.8 of the MOVIPREP® RSI. There is extensive wording in section 4.4 of the RSI which notes: '*MOVIPREP® should be used with caution in patients with: those at risk of arrhythmia, for example those on treatment for cardiovascular disease or who have thyroid disease. In debilitated fragile patients, patients with poor health, those with clinically significant renal impairment, arrhythmia and those at risk of electrolyte imbalance, the physician should consider performing a baseline and post-treatment electrolyte, renal function test and 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 (e.g. oedema, shortness of breath, increasing fatigue, cardiac failure), plasma electrolytes should be measured, ECG monitored and any abnormality treated appropriately*.' No additional risk minimization measures are put in place for this risk.

Patients with G6PD deficiency (there are no studies in this patient population due to the ascorbate content of MOVIPREP®) previously classified as missing information has been removed as there is an adequate warning in section 4.4 of the MOVIPREP® RSI that states: '*Patients with glucose-6-phosphate dehydrogenase deficiency may be at risk of acute haemolysis due to the presence of ascorbate*.' It is also known to healthcare professionals that various drugs can precipitate a haemolytic crisis in G6PD-deficient individuals.

Use in paediatric population previously classified as missing information has been removed as MOVIPREP® is not indicated for use in children <18 years of age. Section 4.2 of the RSI states: '*Children: Not recommended for use in children below 18 years of age as MOVIPREP® has not been studied in the paediatric population*.' No further characterization or risk minimization through additional risk management activities are considered necessary. In the absence of any additional actions for the risk (ongoing aRMM, aPhV) the safety concern is removed.

Use in pregnant/lactating women previously classified as missing information has been removed as MOVIPREP® is not indicated for use in pregnant and lactating women. Section 4.6 of the MOVIPREP® RSI states: '*Pregnancy: There are no data on the use of MOVIPREP® during pregnancy. The preparation should only be used during pregnancy if considered essential by the physician. Breastfeeding: There are no data on the use of MOVIPREP® during lactation. The preparation should only be used during lactation if considered essential by the physician. Fertility: There are no data on the effects of MOVIPREP® on fertility*.' No further characterization or risk minimization through additional risk management activities are considered necessary. In the absence of any additional actions for the risk (ongoing aRMM, aPhV) the safety concern is removed.

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

N/A – there are no important identified or important potential risks in the updated list of safety concerns.

SVII.3.2. Presentation of the missing information

N/A – there is no missing information in the updated list of safety concerns.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

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 MOVIPREP®.

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.

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

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

There are no important identified risks, important potential risks or missing information currently for MOVIPREP®.

V.2. Additional Risk Minimisation Measures

There are no important identified risks, important potential risks or missing information currently for MOVIPREP®, therefore there are no additional risk minimisation measures.

V.3 Summary of risk minimisation measures

There are no important identified risks, important potential risks or missing information currently for MOVIPREP®.

Part VI: Summary of the risk management plan

Summary of risk management plan for MOVIPREP® (macrogol 3350).

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

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

I. The medicine and what it is used for

MOVIPREP® is authorised in adults over the age of 18 years for bowel cleansing prior to any clinical procedures requiring a clean bowel, e.g., bowel endoscopy or radiology, or digestive tract surgery. It contains macrogol 3350 as the active substance and it is given orally.

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

Important risks of MOVIPREP®, together with measures to minimise such risks and the proposed studies for learning more about MOVIPREP®'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 MOVIPREP® 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 MOVIPREP®. 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	None

List of important risks and missing information	
Important potential risks	None
Missing information	None

II.B Summary of important risks

There are no important identified risks or important potential risks currently for MOVIPREP®.

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 MOVIPREP®.

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

There are no studies required for MOVIPREP®.

Part VII: Annexes

Table of contents

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

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)

1. Zavoral et al. World J Gastroenterol. 2009 Dec 21; 15(47): 5907–5915. Published online 2009 Dec 21.
2. Peery AF, Dellon ES, Lund J, et al. Burden of gastrointestinal disease in the United States. Gastroenterology. 2012;143:1179–87.
3. A Ruigómez et al. Incidence of chronic atrial fibrillation in general practice and its treatment pattern. Journal of Clinical Epidemiology 2002 55: 358-363.
4. V. L. Roger et al. Trends in Heart Failure Incidence and Survival in a Community-Based population. JAMA 2004; 292 (3): 344-50.
5. Australian Institute of Health and Welfare. AIHW and AACR, AIHW National Mortality Database, Australia's Health 2004, AIHW.
6. M J Carter, A J Lobo, S P L Travis. Guidelines for the management of inflammatory bowel disease in adults. Gut 2004;53(V):1–16.

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

Version	Approval date Procedure	Change
3.0	02 Jul 2009	**Identified Risks:** • Dehydration and electrolyte abnormalities • Anaphylaxis/ significant allergic reactions **Potential Risks** • Perforation/aggravation of the condition in patients with toxic megacolon as a result of severe IBD • Aspiration in unconscious patients especially if prepared with a nasogastric tube • Cardiac failure • Renal failure • Atrial fibrillation **Missing information** • Patients with G6PD deficiency
3.1	02 Nov 2009	Following risk were added as identified risks: • Transient increase in blood pressure • Convulsions in association with severe hyponatremia
4.0	10-Feb-2016	• RMP prepared in the latest GVP-template • Safety specifications were updated • Risk characterisation updated with cumulative analysis of post authorisation reports in the MAH's safety database • Following text added to the missing information: Use in paediatric population Use in pregnant and lactating women
4.1	06-May-2016 UK/H/0891/001-002/IB/053	• Updated to V.1 Risk minimisation measures by safety concern to remove 'other routine risk minimisation measures' • Administrative updates to Part II: Module SVI – Additional EU requirements for the safety specification
4.2	26-Nov-2018	• Change of QPPV details • Additional information included in VI.2 Elements for a Public Summary (Ukraine Only)
4.3	04-Apr-2022 SE/H/1800/02/II/80	• Updated to EMA Revision 2 RMP template Revision of safety concerns <u>All the below safety concerns have been removed:</u> <u>Important identified risk:</u> • Dehydration and electrolyte abnormalities

		• Anaphylaxis/ significant allergic reactions • Transient increases in blood pressure • Convulsions in association with severe hyponatremia <u>Important potential risk:</u> • Cardiac failure/decompensation • Acute renal failure/decompensation • Perforation of toxic megacolon secondary to severe IBD • Aspiration (in unconscious patients especially if prepared with a nasogastric tube) • Atrial fibrillation <u>Missing information:</u> • Patients with G6PD deficiency (there are no studies in this patient population due to the ascorbate content of MOVIPREP® • Use in paediatric population • Use in pregnant/lactating women
5.0		Approved, Signed version of updates made to version 4.3. Approval date 4-Apr-2022.