Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Plenvu powder for oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The ingredients of Plenvu are contained in three separate sachets. The first dose is supplied in one sachet and the second dose is supplied in two sachets, A and B.

Dose 1 sachet contains the following active substances:

Macrogol 3350	100 g
Sodium sulfate anhydrous	9 g
Sodium chloride	2 g
Potassium chloride	1 g

The concentration of electrolyte ions when the first dose is made up to 500 ml of solution is as follows:

Sodium	160.9 mmol/500 ml
Sulfate	63.4 mmol/500 ml
Chloride	47.6 mmol/500 ml
Potassium	13.3 mmol/500 ml

Dose 1 also contains 0.79 g of sucralose (E955).

Dose 2 (Sachets A and B) contains the following active substances:

Sachet A:

Macrogol 3350	40 g
Sodium chloride	3.2 g
Potassium chloride	1.2 g

Sachet B:

Sodium ascorbate	48.11 g
Ascorbic acid	7.54 g

The concentration of electrolyte ions when the second dose (Sachets A and B) is made up to 500 ml of solution is as follows:

Sodium	297.6 mmol/500 ml
Ascorbate	285.7 mmol/500 ml
Chloride	70.9 mmol/500 ml
Potassium	16.1 mmol/500 ml

Excipients with known effect

Dose 2 (Sachet A) also contains 0.88 g of aspartame (E951).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral solution.

White to yellow powders.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Plenvu is indicated in adults for bowel cleansing prior to any procedure requiring a clean bowel.

4.2 Posology and method of administration

Posology

Adults and elderly

A course of treatment consists of two separate non-identical 500 ml doses of Plenvu. 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 a two-day or one-day dosing schedules as specified below:
Two-day dosing schedule:

- The first dose taken in the evening before the clinical procedure and the second dose in the morning of the day of the clinical procedure, approximately 12 hours after the start of the first dose.

One-day dosing schedules:

- Morning only dosing schedule with both doses taken in the morning of the day of the clinical procedure; the second dose should be taken a minimum of 2 hours after the start of the first dose, or
- Day before dosing schedule with both doses taken in the evening before the clinical procedure; the second dose should be taken a minimum of 2 hours after the start of the first dose.

The appropriate dosing schedule should be selected according to the timing of the clinical procedure.

Paediatric population

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.

Patients with renal impairment

No special dosage adjustment is deemed necessary in patients with mild to moderate renal impairment. Patients with mild to moderate renal impairment were included in clinical studies.

Patients with hepatic impairment

No special dosage adjustment is deemed necessary in patients with mild to moderate hepatic impairment. Patients with elevated liver function tests were included in clinical studies.

Method of administration

For oral use.

Dose 1: The contents of the single sachet for dose 1 should be made up to 500 ml with water. The reconstituted solution, plus an additional 500 ml of clear fluid, should be taken over a period of 60 minutes. Alternating between the reconstituted solution and clear fluid is acceptable.

Dose 2: The contents of the two sachets (sachets A and B together) for dose 2 should be made up to 500 ml with water. The reconstituted solution, plus an additional 500 ml of clear fluid should be taken over a period of 60 minutes. Alternating

between the reconstituted solution and clear fluid is acceptable.

In some instances, the intake of the reconstituted solution may be slowed or temporarily discontinued (see section 4.4).

In addition to the fluids taken as part of the course of treatment, any amount of supplementary clear fluid (e.g. water, clear soup, fruit juice without pulp, soft drinks, tea and/or coffee without milk) may be taken throughout the bowel preparation process. Note: Avoid any fluid coloured red or purple (e.g. blackcurrant juice) as this can stain the bowel.

Consumption of all fluids should be stopped at least;

- two hours before the clinical procedure when under general anaesthesia, or
- one hour before the clinical procedure without general anaesthesia.

Information regarding meals

No solid food should be taken from the start of the course of treatment until after the clinical procedure.

Patients should be advised to allow adequate time after bowel movements have subsided to travel to the clinical unit.

Two-day split dosing schedule **and** day before dosing schedule:
The day before the clinical procedure, patients can have a light breakfast followed by a light lunch which must be completed at least 3 hours prior to the start of the first dose.

Morning only dosing schedule:

The day before the clinical procedure, patients can have a light breakfast followed by a light lunch, and clear soup and/or plain yogurt for dinner, which should be completed by approximately 20.00H.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Do not use in patients with known or suspected:

· hypersensitivity to the active substances or to any of the excipients listed in section 6.1
· gastrointestinal obstruction or perforation
· ileus
· disorders of gastric emptying (e.g. gastroparesis, gastric retention, etc.)
· phenylketonuria (due to presence of aspartame)
· glucose-6-phosphate dehydrogenase deficiency (due to presence of ascorbate)
· toxic megacolon

4.4 Special warnings and precautions for use

The fluid content of Plenvu when reconstituted with water does not replace regular fluid intake and adequate fluid intake must be maintained.

As with other macrogol containing products, allergic reactions including rash, urticaria, pruritus, angioedema and anaphylaxis are a possibility.

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
- severe renal impairment (creatinine clearance less than 30 ml/minute/1.73 m^2)

- cardiac failure (grade III or IV of NYHA)
- those at risk of arrhythmia, for example those with or on treatment for cardiovascular disease, thyroid disease or electrolyte imbalance
- dehydration
- severe acute inflammatory bowel 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. Any suspected dehydration should be corrected for before use of Plenvu.

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.

If patients experience severe bloating, abdominal distension, or abdominal pain, administration should be slowed or temporarily discontinued until the symptoms subside.

In people with swallowing problems, who need the addition of a thickener to solutions to enhance an appropriate intake, interactions should be considered, see section 4.5.

Ischaemic colitis

Post-marketing cases of ischaemic colitis, including serious, have been reported in patients treated with macrogol for bowel preparation. Macrogol should be used with caution in patients with known risk factors for ischaemic colitis or in case of concomitant use of stimulant laxatives (such as bisacodyl or sodium picosulfate). Patients presenting with sudden abdominal pain, rectal bleeding or other symptoms of ischaemic colitis should be evaluated promptly.

Plenvu contains 458.5 mmol (10.5 g) sodium per course of treatment. This should be taken into consideration for patients on a controlled sodium diet. Only a proportion of the sodium is absorbed, see section 5.2.

Plenvu contains 29.4 mmol (1.1 g) potassium per course of treatment. This should be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

4.5 Interaction with other medicinal products and other forms of interaction

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. The therapeutic effect of drugs with a narrow therapeutic index or short half-life may be particularly affected.

Plenvu may result in a potential interactive effect if used with starch-based food thickeners. Macrogol ingredient counteracts the thickening effect of starch, effectively liquefying preparations that need to remain thick for people with swallowing problems.

4.6 Fertility, pregnancy and lactation

Pregnancy

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 (see section 5.3). 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.

Breast-feeding

It is unknown whether Plenvu active ingredients/metabolites are excreted in human milk. There is insufficient information on the excretion of Plenvu active ingredients/metabolites in human milk.

A risk to the 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.

Fertility
There are no data on the effects of Plenvu on fertility in humans. There were no effects on fertility in studies in male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Plenvu has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Diarrhoea is an expected outcome of bowel preparation. Due to the nature of the intervention, undesirable effects occur in the majority of patients during the process of bowel preparation. Whilst these vary between preparations, nausea, vomiting, bloating, abdominal pain, anal irritation and sleep disturbance commonly occur in patients undergoing bowel preparation. Dehydration may occur as a result of diarrhoea and/or vomiting.

Data from clinical studies are available in a population of over a thousand subjects treated with Plenvu in which undesirable effect data were actively elicited.

The table below is a list of treatment emergent adverse events reported in the clinical studies of Plenvu.

The frequency of adverse reactions to Plenvu is defined using the following convention:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

	Very common (≥1/10) #	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Gastrointestinal disorders		Vomiting, Nausea	Abdominal distension, Anorectal discomfort, Abdominal pain, Abdominal pain upper, Abdominal pain lower
Immune system disorder			Drug hypersensitivity
Metabolism and nutrition disorders		Dehydration	
Nervous system disorders			Headache, Migraine, Somnolence
General disorders and administration site conditions			Thirst*, Fatigue, Asthenia, Chills**, Pains, Aches
Cardiac disorders			Palpitation, Sinus tachycardia
Vascular disorders			Transient increase in blood pressure, Hot flush
Investigations			Transient increase in liver enzymes***

			Hypernatraemia, Hypercalcaemia, Hypophosphataemia, Hypokalaemia, Decreased bicarbonate, Anion gap increased/ decreased, Hyperosmolar state

*Thirst includes the Preferred Terms; Thirst, Dry mouth and Dry throat
**Chills includes the Preferred Terms; Chills, Feeling hot and Feeling cold
***Transient increase in liver enzymes includes the Preferred Terms; ALT increased, AST increased, GGT increased, Hepatic enzymes increased, Transaminases increased
No adverse events with a frequency of "very common" were reported during the clinical trials.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

In case of gross accidental overdose, where diarrhoea is severe, fluid replacement and electrolyte correction may be necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Osmotically acting laxative. ATC code: A06A D65

The oral administration of macrogol-based electrolyte solutions causes moderate diarrhoea and results in rapid emptying of the colon.

Macrogol 3350, sodium sulfate and high doses of ascorbic acid exert an osmotic action in the gut, which induce a laxative effect.

Macrogol 3350 increases the stool volume, which triggers colon motility via neuromuscular pathways.

The physiological consequence is a propulsive colonic transportation of the softened stools.

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.

5.2 Pharmacokinetic properties

The vast majority (>99.7%) of macrogol 3350 is not absorbed by the gastro-intestinal tract and is excreted in faeces. Literature reports that any macrogol 3350 that is absorbed, is excreted via the urine.

Absorption of ascorbate occurs by a sodium-dependant active transport process of limited capacity; a single oral dose above 2 g is reported to saturate jejunal absorption. The unabsorbed ascorbate remains in the gut lumen, it is estimated approximately 96% (48 g) of the ascorbate component is excreted in faeces. Ascorbate is a normal constituent of the blood, however when plasma concentrations exceed approximately 15µg/mL, excess ascorbic acid is eliminated, mainly unchanged, in the urine.

The bulk of oral sulfate is not absorbed, and by establishing an electrochemical gradient, prevents the absorption of accompanying sodium ions. Small amounts of sulfate ions are absorbed throughout the gastrointestinal tract, which adds to the pool of essential inorganic sulfate formed from the breakdown of sulfur containing amino acids. The bulk of absorbed inorganic sulfate is eliminated unchanged by glomerular filtration and is subject to saturable tubular reabsorption.

Osmotically-acting bowel preparations lead to a copious diarrhoea, resulting in extensive elimination of most of the product via the faeces. They can also lead to changes in electrolyte balance in the body, often with depletion of sodium and potassium. The additional sodium and potassium included in Plenvu formulation help to balance the electrolytes. While some absorption of sodium takes place, the bulk of sodium is expected to be excreted in the faeces as the sodium salts of sulfate and ascorbate, the osmotic active ingredients included in the Plenvu composition.

No pharmacokinetic studies were performed in patients with renal or hepatic insufficiency.

5.3 Preclinical safety data

Preclinical studies provide evidence that macrogol 3350, ascorbic acid and sodium sulfate have no significant systemic toxicity potential, based on conventional studies of pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity.

No studies have been carried out on the genotoxicity, carcinogenicity or toxic effect on reproduction with this product.

In reproductive toxicity studies with Movicol (a macrogol 3350 product), there were no direct embryotoxic or teratogenic effects in rats even at maternally toxic levels that are a multiple of 20x the maximum recommended dose of Plenvu in humans. Indirect embryofetal effects, including reduction in fetal and placental weights, reduced fetal viability, increased limb and paw hyperflexion and abortions, were noted in the rabbit at a maternally toxic dose that is the same as the maximum recommended dose of Plenvu in humans. Rabbits are a sensitive animal test species to the effects of GI-acting substances and the studies were conducted under exaggerated conditions with high dose volumes administered, which are not clinically relevant. The findings may have been a consequence of an indirect effect of Movicol related to poor maternal condition as the result of an exaggerated pharmacodynamic response in the rabbit. There was no indication of a teratogenic effect.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucralose (E955)
Aspartame (E951)
Encapsulated citric acid containing citric acid (E330) and maltodextrin (E1400)
Mango flavour containing glycerol (E422), flavouring preparations, gum acacia (E414), maltodextrin (E1400) and natural flavouring substances
Fruit punch flavour containing flavouring preparations, gum acacia (E414), maltodextrin (E1400) and flavouring substances

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Sachets: 2 years
Reconstituted solutions: 24 hours

6.4 Special precautions for storage

Sachets: Do not store above 25°C

Reconstituted solutions: Keep prepared solutions below 25°C and drink it within 24 hours. The solutions may be stored in a refrigerator. The solutions must be covered.

6.5 Nature and contents of container

Each sachet comprises a laminate with the following materials of construction: polyethylene terephthalate (PET), polyethylene, aluminium and extrusion resin.

Dose 1 contains 115.96 g of powder, Dose 2 Sachet A contains 46.26 g of powder and Dose 2 Sachet B contains 55.65 g of powder.

The three sachets are contained in a clear secondary overwrap within a cardboard carton, and comprise a single treatment of Plenvu. The cardboard carton also contains the patient information leaflet.

Plenvu is available in packs containing 1 treatment and in packs containing 40, 80, 160 and 320 treatments. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution of Plenvu in water may take up to approximately 8 minutes and is best performed by adding the powder to the mixing vessel first followed by the water. The patient should wait until all the powder has dissolved before drinking the solution.

After reconstitution in water Plenvu consumption may begin immediately or if preferred, it may be cooled before use.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Norgine B.V.
Antonio Vivaldistraat 150
1083 HP Amsterdam
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA1336/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st December 2017
Date of last renewal: 30th November 2022

10 DATE OF REVISION OF THE TEXT

June 2023