# AUSTRALIAN PRODUCT INFORMATION – PLENVU® POWDER FOR SOLUTION

## 1 NAME OF THE MEDICINE

Macrogol 3350, sodium sulfate, ascorbic acid, sodium ascorbate, sodium chloride, and potassium chloride.

## 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 | 100.0 g |
| Sodium sulfate | 9.0 g |
| Sodium chloride | 2.0 g |
| Potassium chloride | 1.0 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 2 (Sachets A and B)** contains the following active substances:

**Sachet A**:

| | |
|---|---|
| Macrogol 3350 | 40.0 g |
| Sodium chloride | 3.2 g |
| Potassium chloride | 1.2 g |

**Sachet B**:

| | |
|---|---|
| Sodium ascorbate | 48.1 g |
| Ascorbic acid | 7.5 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 |

Dose 1 contains 790 mg of sucralose. Dose 2 (Sachet A) contains 875 mg of aspartame.
The complete treatment contains 10.5 g of sodium and 1.1 g of potassium.
For the full list of excipients, see ‘Section 6.1 List of Excipients’

## 3 PHARMACEUTICAL FORM

Powder for oral solution.

One pack of PLENVU contains a single treatment of three sachets.
Dose 1 (mango flavour) Sachet contains 115.96 g of white to off-white powder.
Dose 2 (fruit punch flavour) Sachet A contains 46.26 g of white to off-white powder and Dose 2 Sachet B contains 55.65 g of white to yellow powder.

# 4 CLINICAL PARTICULARS

## 4.1 THERAPEUTIC INDICATIONS

PLENVU is indicated for bowel cleansing prior to any procedure requiring a clean bowel.

## 4.2 DOSE AND METHOD OF ADMINISTRATION

Adults (18 years of age and over), including the 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 one of the three schedules specified below:

- Two-day split dosing schedule with the first 500 mL dose of PLENVU (including additional 500 mL of clear fluid) taken in the evening before the clinical procedure and the second 500 mL dose (including an additional 500 mL of clear fluid) in the morning of the day of the clinical procedure (approximately 12 hours after the start of the first dose), or

- Morning only dosing schedule with both doses taken in the morning of the day of the clinical procedure (including an additional 500 mL of clear fluid); 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 (including an additional 500 mL of clear fluid); the second dose should be taken a minimum of 2 hours after the start of the first dose.

A time interval of more than 12 hours between preparation administration and colonoscopy may reduce the bowel cleansing efficacy.

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

Patient should be warned to expect frequent, loose bowel movements.

Patients should be reminded of the importance of hydration while taking these products and to seek medical attention if they experience any signs of severe dehydration, such as excessive thirst, dizziness, confusion and decreased urine output or dark coloured urine.

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

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

Use in the elderly
Refer to '4.2 Dosage and Administration'. Elderly patients were included in the clinical trial program, refer to '5.1 Clinical Trials'.

Paediatric use
The safety and efficacy of PLENVU in children below 18 years of age has not yet been established. PLENVU is therefore not recommended for use in this population.

**Preparation Instructions**
Dose 1: The contents of the single sachet for dose 1 should be made up to 500 mL with water (not chilled). 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 the 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 (not chilled). 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 the clear fluid is acceptable.

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

Reconstitution of PLENVU in water (not chilled) may take up to approximately 8 minutes and is best performed by adding the powder to the mixing vessel first followed by the water (not chilled). 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 refrigerated before use.

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

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 8 pm. 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.

## 4.3 CONTRAINDICATIONS

Do not use in patients with known or suspected:

- hypersensitivity to the active or inactive ingredients
- gastrointestinal obstruction or perforation
- ileus
- disorders of gastric emptying (e.g. gastroparesis, gastric retention, etc.)
- phenylketonuria (due to the presence of aspartame)
- glucose-6-phosphate dehydrogenase deficiency (patients may be at risk of acute haemolysis due to the presence of ascorbate)
- unconsciousness
- severe dehydration
- severe inflammatory conditions of the intestinal tract, such as Crohn's disease, ulcerative colitis and toxic megacolon.

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

**Identified precautions**

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

Patients should be advised to hydrate adequately before, during, and after the use of any bowel preparation. If a patient develops significant vomiting or signs of dehydration after taking PLENVU, consider performing post-colonoscopy laboratory tests.

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
- renal impairment whose creatinine clearance is less than 30 mL/minute/1.73 $m^2$
- grade III or IV cardiac failure
- those at risk of arrhythmia, for example those with or on treatment for cardiovascular disease, thyroid disease or electrolyte imbalance.

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.

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.

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.

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

Ischaemic colitis

Post-marketing cases of ischaemic colitis, including serious cases, 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.

**Use in hepatic impairment**

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

**Use in renal impairment**

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

Plenvu should be used with caution in patients with renal impairment whose creatinine clearance is less than 30 mL/minute/1.73 $m^2$

In 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.

**Use in the elderly**

Refer to ‘4.2 Dosage and Administration’. Elderly patients were included in the clinical trial program, refer to ‘5.1 Clinical Trials’.

Caution should be used with the administration of PLENVU to frail or debilitated patients.

**Paediatric use**

The safety and efficacy of PLENVU in children below 18 years of age has not yet been established. PLENVU is therefore not recommended for use in this population.

**Effects on laboratory tests**

No data available

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The interaction of PLENVU with other medicinal products has not been studied. Theoretically, 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.

Medications such as diuretics, calcium channel blockers or corticosteroids, may affect electrolyte levels or may exacerbate hypokalaemia.

Medications such as diuretics may exacerbate volume depletion associated with bowel cleansing.

PLENVU may have a potential interactive effect when used with starch-based food thickeners. The macrogol ingredient counteracts the thickening effect of starch, effectively liquefying preparations that need to remain thick for people with swallowing problems.

Note: For more information, refer to '4.4 Special Warnings and Precautions for Use' section.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

**Effects on fertility**

There are no data on the effects of PLENVU on fertility.

**Use in pregnancy – Pregnancy Category B1**

Macrogol is designated Australian Pregnancy Category B1 Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.

There are no data on the use of PLENVU during pregnancy. The preparation should only be used during pregnancy if considered essential by the physician.

**Use in lactation**

There are no data on the use of PLENVU during lactation. The preparation should only be used during lactation if considered essential by the physician.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

## 4.8 ADVERSE EFFECTS (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.

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 causally related 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 disorders | | | 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,<br>Sinus tachycardia |
| Vascular disorders | | | Transient increase in blood pressure, Hot flush |
| Investigations | | | Transient increase in liver enzymes***<br>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 suspected adverse effects**

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

## 4.9 OVERDOSE

Overdosage may cause severe diarrhoea. In case of overdose, fluid replacement and electrolyte correction may be necessary. For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia) or 0800 764 766 (New Zealand).

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 PHARMACODYNAMIC PROPERTIES

### Mechanism of action

The pharmacodynamic properties of this osmotically-acting bowel preparation are a combination of the direct synergistic osmotic action of the components of PLENVU (macrogol 3350 plus sodium sulfate components in Dose 1 and ascorbate plus macrogol 3350 components in Dose 2) and the induction of propulsive contractions of the smooth muscle of the bowel, which induce the laxative effect. The physiological consequence is a propulsive colonic transportation of the softened stools.

The electrolytes present in the formulation and the supplementary clear fluid intake are included to prevent clinically significant variations of sodium, potassium or water, and thus reduce dehydration risk.

Macrogol 3350 is chemically inert and highly soluble in water. The principal action of macrogol 3350 is to increase the water content of the bowel by exerting an osmotic action. Macrogol 3350 is able to hold water in the ratio of 100 molecules of water to every one molecule of macrogol 3350 and it has been shown that increasing osmotic loads of macrogol 3350 results in a near linear increase in stool weight and stool water output.

The human body usually contains about 1.5 g of ascorbic acid with excess rapidly excreted by glomerular filtration. Unabsorbed ascorbic acid/sodium ascorbate passes into the faecal water.

The bulk of sulfate is not absorbed and remains in the intestine adding to the synergistic osmotic action in Dose 1. The osmotic action of sodium sulfate is brought about by irritation of the intestinal mucosa by high intraluminal concentrations of sulfate ions.

### Clinical trials

The colon cleansing efficacy, safety and tolerability of PLENVU was evaluated in three randomized, parallel group, multi-centre, investigator-blinded, Phase III studies in patients undergoing colonoscopy.

The three studies, NER1006-01/2014 (NOCT), NER1006-02/2014 (MORA) and NER1006-03/2014 (DAYB) were designed with many similarities to allow for optimum comparability of data. The primary focus of the Phase III clinical program was to compare the bowel cleansing ability of PLENVU against a different comparator using different dosing regimen(s):

- Two-Day split-dosing allowing for an overnight gap between doses,
- One-Day Morning dosing giving both doses the morning of the day of colonoscopy and
- One-Day Day Before dosing giving both doses the day before colonoscopy.

Details of which regimen was used in each study for PLENVU and each of the comparators are provided in Table 1.

**Table 1: PLENVU and comparator dosing regimens in NOCT, MORA and DAYB studies**

| Treatment | Phase III Study | | |
|---|---|---|---|
| | NOCT | MORA | DAYB |
| PLENVU | | | |
| Two-Day split-dosing | x | x | |
| One-Day Morning dosing (day of colonoscopy) | | x | |
| One-Day Day Before dosing (day before colonoscopy) | | | x |
| Comparator: | | | |
| Two-Day split-dosing | x (Trisulfate) | x (2L Macrogol+E) MOVIPREP | |
| One-Day Day Before split-dosing (day before colonoscopy) | | | X (SP+MS) |

(SP+MS) = Sodium Picosulfate and Magnesium Salt solution; (Macrogol+E) = Macrogol and Electrolytes

***Design of Studies***

The alternative primary endpoints were the same across all three studies and were as follows:

- The overall bowel cleansing success rate of PLENVU is non-inferior to that of the comparator using the Harefield Cleansing Scale (HCS), wherein success corresponds to Grades A and B, and failure corresponds to Grades C and D.
- The 'Excellent plus Good' cleansing rate in the ascending colon of PLENVU is non-inferior to that of the comparator using the segmental cleansing scoring system of the HCS, wherein the ordinal score of 4 corresponds to Excellent cleansing and score of 3 corresponds to Good cleansing.

The alternative primary efficacy endpoint was judged by blinded central readers (gastroenterologists) on the basis of video recordings of the colonoscopy.

The patient population consisted of male and female patients aged 18 to 85 years inclusive, who were scheduled to undergo a screening, surveillance or diagnostic colonoscopy.

<u>NOCT Study</u>

The NOCT study was a multicentre, randomized, parallel group Phase III study in adults comparing the bowel cleansing efficacy, safety and tolerability of PLENVU versus a trisulfate bowel cleansing solution containing sodium sulfate, potassium sulfate, and magnesium sulfate using an overnight Two-Day split-dosing regimen.

A total of 516 patients [255 patients in the PLENVU treatment group and 261 patients in the trisulfate solution treatment group] completed the study. Overall, the demographic characteristics were well balanced between the two treatment groups.

A similar percentage of patients achieved successful bowel cleansing in the overall colon in both treatment groups (85.1% in the PLENVU treatment group versus 85.0% in the trisulfate solution treatment group). With regard to the cleansing rate in the ascending colon, a greater percentage of patients achieved an "Excellent plus Good" cleansing rate in the PLENVU treatment group (35.9% in the PLENVU treatment group versus 29.3% in the trisulfate solution treatment group). PLENVU was shown to be non-inferior to the trisulfate solution with regard to both alternative primary endpoints of HCS results in the overall colon and the ascending colon.

MORA Study

The MORA study was a multicentre, randomized, parallel group Phase III study in adults comparing the bowel cleansing efficacy, safety and tolerability of PLENVU (Two-Day split-dosing and One-Day Morning dosing regimens) versus a 2 litre Macrogol + electrolytes (MOVIPREP) Two-Day split-dosing regimen.

A total of 781 patients [260 patients in the Two-Day PLENVU split-dosing group, 262 in the One-Day PLENVU morning dosing group and 259 patients in the 2L Macrogol+E treatment group] completed the study. Overall, the demographic characteristics were well balanced between the three treatment groups.

Similar percentages of patients achieved a successful bowel cleansing in the overall colon in the three treatment groups (92.0% in the PLENVU 2-day split-dosing group, 89.1% in the PLENVU 1-day split-dosing group and 87.5% in the 2L Macrogol+E treatment group), confirming non-inferiority for the PLENVU Two-Day split-dosing and PLENVU One-Day split-dosing groups versus the 2L Macrogol+E group. With regard to the cleansing rate in the ascending colon, both PLENVU groups met the criteria for superiority versus the 2L Macrogol+E group. The PLENVU Two-Day and One-Day dosing groups achieved "Excellent plus Good" cleansing rates of 31.6% and 33.8% respectively, whilst the 2L Macrogol+E group achieved a rate of 15.1%.

DAYB Study

The DAYB study was a multicentre, randomized, parallel group Phase III study in adults comparing the bowel cleansing efficacy, safety and tolerability of PLENVU versus a Sodium Picosulfate and Magnesium Salt (SP+MS) solution, using a One-Day Day Before dosing regimen.

A total of 473 patients [233 patients in the PLENVU treatment group, and 240 patients in the SP+MS treatment group] completed the study. Overall, the demographic characteristics were well balanced between the two treatment groups.

The percentage of patients who achieved successful bowel cleansing in the overall colon in the PLENVU group was numerically higher compared to the SP+MS group (62.0% versus 53.8% respectively), this difference did not reach statistical significance. Regarding the cleansing rate in the ascending colon, the percentage of patients achieved an "Excellent plus Good" cleansing rate (4.4% in the PLENVU treatment group versus 1.2% in the SP+MS treatment group). PLENVU was shown to be non-inferior to SP+MS with regard to both alternative primary endpoints in the overall colon and the ascending colon.

***Demographics and Results***

In general, the demographic characteristics were well balanced across the PLENVU patients in all three studies. However, there were two notable differences in 1) patients aged over 65: MORA (26% Two-Day and 22% One-Day), NOCT (18%) and DAYB (17%) and 2) the ratio of female and male patients: MORA (males 42% Two-Day and 46% One-Day), NOCT (males 51%) and DAYB (males 35%).

The alternative primary endpoint results are provided in Table 2.

Table 2: Overall and Ascending Colon Cleansing rates of PLENVU versus Comparator

| **Studies** | | **NOCT** | | **MORA** | | | **DAYB** | |
|---|---|---|---|---|---|---|---|---|
| **Comparators** | | **PLENVU** | **Trisulfate** | **PLENVU 2-Day** | **PLENVU 1-Day** | **2L Macrogol+E** | **PLENVU** | **SP+MS** |
| Regimen | | Two-Day Split-Dosing | Two-Day Split-Dosing | Two-Day Split-Dosing | One-Day Morning of Colonoscopy Dosing | Two-Day Split-Dosing | One-Day Day Before Colonoscopy Dosing | One-Day Day Before Colonoscopy Dosing |
| Alternative Primary Endpoints using HCS | Overall Colon Cleansing Rate | 85.1 % | 85.0% | 92.0% | 89.1% | 87.5% | 62.0% | 53.8% |
| | | (LCL= -8.15, p=0.528) | | (LCL=-4.00, p=0.055) | (LCL=-6.91, p=0.328) | | (LCL=-0.50, p=0.038) | |
| | Ascending Colon Cleansing Rate (Excellent plus Good) | 35.9% | 29.3% | 31.6% | 33.8% | 15.1% | 4.4% | 1.2% |
| | | (LCL=-1.69, p=0.059) | | (LCL=8.11, p<0.001) | (LCL=10.32, p<0.001) | | (LCL=-5.56, p=0.027) | |
| Summary of Primary Endpoints | | Non-inferiority demonstrated - Primary endpoints met | | Non-inferiority demonstrated - Primary endpoints met. Superiority for Excellent + Good ascending colon cleansing demonstrated | | | Non-inferiority demonstrated - Primary endpoints met | |

LCL= 97.5% Lower Confidence Limit
10% NI margin; threshold for statistical significance: p<0.025

## 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.

Ascorbic acid/sodium ascorbate is an essential vitamin in humans with a daily requirement of 50 – 100 mg. At physiological doses, it is actively absorbed from the jejunum, with a bioavailability of 60-75%.

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.

### Genotoxicity

No studies have been carried out on the genotoxicity, or toxic effect on reproduction with this product. However, available data on macrogols of relevant size, sodium sulfate, and ascorbic acid did not reveal any special hazard for humans based on studies of genotoxicity, and reproductive toxicity.

### Carcinogenicity

No studies have been carried out on the carcinogenicity of this product. However, available data on macrogols of relevant size, sodium sulfate, and ascorbic acid did not reveal any special hazard for humans based on studies of carcinogenicity.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

PLENVU contains the following inactive ingredients: aspartame (E951), sucralose (E955), encapsulated citric acid (contains citric acid and maltodextrin), mango flavour and fruit punch flavour.

## 6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

## 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Sachets: Store below 25°C.
Reconstituted solution: Store below 25°C, or store in refrigerator. Keep solution covered. Shelf life of solution 24 hours.

## 6.5 NATURE AND CONTENTS OF CONTAINER

One pack of PLENVU contains a single treatment of three sachets. Dose 1 (mango flavour) Sachet contains 115.96 g of powder. Dose 2 (fruit punch flavour) 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. The cardboard carton also contains the patient information leaflet.

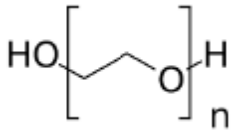
## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

## 6.7 PHYSICOCHEMICAL PROPERTIES

### Chemical structure

Macrogol 3350



| | |
|---|---|
| Ascorbic acid | $C_6H_8O_6$ |
| Sodium chloride | NaCl |
| Sodium sulfate | $Na_2SO_4$ |
| Potassium chloride | KCl |
| Sodium ascorbate | $NaC_6H_7O_6$ |

**CAS number**

| | |
|---|---|
| Ascorbic acid | 50-81-7 |
| Macrogol 3350 | 25322-68-3 |
| Sodium chloride | 7647-14-5 |
| Sodium sulfate | 7757-82-6 |
| Potassium chloride | 7447-40-7 |
| Sodium ascorbate | 134-03-2 |

# 7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 3. Pharmacist Only Medicine

# 8 SPONSOR

Norgine Pty Limited. Suite 3.10 Building A, 20 Rodborough Road, Frenchs Forest NSW 2086.
www.norgine.com.au
Ph 1800 766 936

# 9 DATE OF FIRST APPROVAL

9 January 2018

# 10 DATE OF REVISION

5 August 2024

**SUMMARY TABLE OF CHANGES**

| Section Changed | Summary of new information |
|---|---|
| | |
| **4.5** | Section 4.5 was updated to clarify the theoretical nature of the one-hour time interval between taking macrogol-containing products and taking other oral medicinal products. |