VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

PLENVU is intended for bowel cleansing prior to any procedures requiring a clean bowel.
Bowel cleansing is most often performed prior to a colonoscopy. In Europe, about 15 million colonoscopies are performed every year. This means approximately 5% of the overall European population goes through the procedure of colonoscopy at some stage in life. Although all segments of population could need a large intestine procedure, the majority is expected to be in the population over 50 years of age. It has been calculated that approximately 80% colon procedures take place in the adult patient population over 50 years of age while the remaining 20% are carried in patients between 18 to 49 years of age. Some specific inter-country variations are expected, because of the setup of large intestine cancer screening programmes. Germany is one of these countries with screening programme properly implemented. Repeat colonoscopies are rare and are conducted only in special circumstances in certain patients, or if the bowel was not fully cleansed and the surface of the bowel could not be fully visualised. Overall, bowel preparation/cleansing for procedures such as colonoscopy is a safe process with minimal side effects when bowel preparations are taken as directed. Colonoscopy is also a safe procedure with a rare chance of complications (only in 1-5% cases) and the rate of death in this procedure is calculated to be less than 0.1%.

VI.2.2 Summary of treatment benefits

NER1006 (the name for PLENVU in the clinical studies) is available as powder for oral solution and is aimed to be used by adults 18 years of age and older to clean the bowel (colon) before any procedure requiring a clean bowel. PLENVU cleans the bowel by causing diarrhoea (loose stools). Cleaning the bowel helps the healthcare provider see the inside of the bowel more clearly during the procedure. Clinical studies have been performed to evaluate the safety of PLENVU and the ability of this medication to clean the bowel. Over a thousand adults, who were scheduled to undergo colonoscopy, received PLENVU in the clinical studies. Overall, the gender/age characteristics were well balanced between the people participating in each study.
In each study, NER1006 was compared with other similar products/comparators with the below results:

- The overall bowel cleansing success rate of NER1006 was non-inferior to that of the comparator.
- High quality cleansing of the colon ascendens (i.e. the first section of the large bowel) of NER1006 was non-inferior to that of two comparators (Trisulfate and Sodium Picosulfate + Magnesium Salt) and superior to another (MOVIPREP®).

Overall, the benefit-risk balance of PLENVU is positive, with the added benefit that patients have the flexibility with regards to how the medication can be taken.

VI.2.3 Unknowns relating to treatment benefits

There are no data available on efficacy or safety of PLENVU in pregnant and breast-feeding women. Similarly no data are available for efficacy and safety in children under 18 years of age.

There are limited data available in non-Caucasian populations. However given the mechanism of action of PLENVU, the efficacy and safety profile of PLENVU is expected to be similar to that in the Caucasian population. There are limited data available in special populations, such as those with hepatic, renal or cardiac disease.

1349 adults have been exposed to PLENVU in clinical studies. Assuming no background incidence, rare adverse drug reactions (those with a frequency of <1 in 1,000) would be unlikely to have been detected in this clinical trial population.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Excessive loss of fluids from the body	Due to profound diarrhoea that PLENVU™ causes to clean the bowel and since it may cause vomiting in some patients, there have been reports of excessive loss of fluids and minerals from the body especially in some patients with generally poor health, poor nutritional status or with a serious medical condition. Symptoms of excessive loss of fluids can range from thirst, dry/sticky mouth, dry skin, dark urine, headache, dizziness and muscle cramps to irritability, confusion, sunken eyes, low blood pressure, rapid heart rate/breathing or in most severe cases unconsciousness. Severe cases of excessive loss of fluids from the body were not seen in clinical trials.	Each dose of PLENVU™ is prepared as 500 ml solution. 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. These fluids can be taken at any time after taking PLENVU™. 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.
Mineral disturbance in the body	Due to profound diarrhoea that PLENVU™ causes to clean the bowel and since it may cause vomiting in some patients, there is a potential that some patients may develop disturbed levels of minerals in the body, especially very high sodium levels, or even very low potassium levels. If severe disturbance of these mineral levels occur, it has the potential to be dangerous and can affect blood pressure, kidney, heart, brain and so on. Symptoms may range from dark urine or little urine, nausea/vomiting, irregular heartbeat, fatigue, muscle cramps to irritability, confusion and even unconsciousness.	PLENVU™ contains sufficient minerals to minimise the possibility of minerals disturbance. However it is very important to prepare the solution correctly as per the instructions provided and take at least 500 ml of additional clear fluids as advised to prevent minerals disturbance. If possible, when symptoms of mineral disturbance are experienced, contact your doctor urgently.
Temporary increase in blood pressure	Since PLENVU™ produces profound diarrhoea to clean the bowel (also vomiting in some patients), excessive loss of fluid from the body may result in a temporary salt retention in the body. Therefore it may increase blood pressure temporarily.	Using the product as advised by the doctor and as detailed in the package leaflet (PL) and taking plenty of clear fluids can help reduce this risk. Patients with high blood pressure should discuss the precautions with the doctor in advance.

Risk	What is known	Preventability
	Temporary rise in blood pressure has been reported in some patients. Patients with known hypertension could be more at risk of this temporary increase in blood pressure.	
Temporary increase in liver enzymes	PLENVU™ is not absorbed into the body and therefore direct effect on liver is highly unlikely. Temporary raised levels of some liver enzymes however have been reported in very few patients during the clinical trials. Patients with background liver disease (e.g. fatty liver, hepatitis), obesity, excessive use of alcohol and diabetic patients are more prone to have this risk. However, this temporary raise in liver enzymes is reversible and settles down within few days.	Using the product as advised by the doctor and as detailed in the package leaflet and taking plenty of clear fluids can help reduce this risk. Patients with risk factors such as known liver disease (e.g. fatty liver, hepatitis), obesity, excessive use of alcohol and diabetic patients should discuss the precautions with the doctor in advance.
Severe allergic reactions	The contents of PLENVU™ may rarely produce allergic reaction in some patients. This can range from a simple rash or itching to severe reactions for example, swelling of eyes and face, ankles or other part of the body, very rapid heart rate, extreme fatigue and shortness of breath. In rare and extreme circumstances some patients may develop low blood pressure and collapse.	In case of known allergies to any factors or medicines, the patient should discuss with the doctor and use PLENVU™ with caution only. If there is known hypersensitivity or allergy to any of its contents, the product should not be used.

Important potential risks

Risk	What is known (including reason why it is considered a potential risk)
Irregular and/or very fast heart rate	Very fast heart rate (palpitations) and irregular heart rhythm (often called atrial fibrillation) are the conditions that are common in elderly population. A potential imbalance of fluids and minerals in the body owing to the profound diarrhoea caused by PLENVU™ may cause or increase this condition in some patients, especially the elderly and patients with poor general health. Patients with previous episodes of fast heart rate/irregular heart rhythm or patients with pre-treatment mineral abnormalities would be more likely to experience arrhythmias. Some known risk factors that can increase the chance of developing this risk include: heart disease, high blood pressure, diabetes, smoking, high cholesterol, obesity and high-fat diet, excessive use

	of alcohol (more than 2 drinks per day), drug abuse, anxiety/stress and family history of heart disease. Such patients must discuss with their doctors before using this product.
Perforation/aggravation of the condition in patients with toxic megacolon as a result of severe IBD	Toxic megacolon is a rare, life-threatening widening of the large intestine that develops within a few days. It is usually a complication of inflammatory bowel disease (IBD) such as Ulcerative colitis or Crohn's disease. Toxic megacolon occurs when IBD causes the large intestine to expand abnormally. When this happens, the large intestine is unable to remove gas or faeces from the body. If gas and faeces build up in the large intestine over a period of time, it may eventually rupture. Since PLENVU™ produces profound diarrhoea with strong propelling movement of the intestinal wall, the possibility of rupture increases many folds. Use of PLENVU™ therefore should not be considered in such patients. However, Patients with toxic megacolon are likely to be symptomatic so this should be identified before bowel preparation.
Aspiration in patients with diminished levels of consciousness/severely debilitated patients especially if prepared with a nasogastric tube	PLENVU™ is prepared as a solution and taken orally with additional clear fluids. In unconscious patients stomach movements are very slow and sometimes may even be absent. When 500 ml of the product solution and 500 ml of the clear fluids are given to such patients, in some patients, due to slow movements of the stomach, fluid may remain in the stomach and with persistent burping and hiccups such patients can inhale the solution in to the lungs and get pneumonia. In the unconscious patients therefore use of PLENVU™ is not recommended. Extreme caution must be exercised if absolutely necessary to use the product in such patients.
Heart failure	PLENVU™ produces profound diarrhoea by exchanging water and salts with the blood in the large intestine wall and is used as 2 doses of 500 ml each. Another 500 ml of clear fluids must be taken with each dose (at least 2 litres in total). Patients with risk factors for heart failure therefore may have the potential to develop fluid overload and hence their heart may not be able to handle/pump enough fluid entering the blood vessels. Such patients may develop a condition called heart failure. Patients with known risks of heart disease must discuss with their doctors before using this product.
Kidney failure	PLENVU™ produces profound diarrhoea by exchanging water and salts with the blood in the large intestine wall and is used as 2 doses of 500 ml each. Another 500 ml of clear fluids must be taken with each dose (at least 2 litres in total). Patients with known kidney disease (especially history of kidney failure) may develop fluid overload and their condition may be aggravated. Similarly patients with

	pre-existing risk factors of kidney disease may develop kidney failure due to excessive loss of fluids and minerals due to the profound diarrhoea caused by PLENVU™. Such patients must discuss with their doctors before using this product.
Potential to alter absorption and decrease efficacy of other medicinal products (drug interaction)	As with any laxative or other factor which might increase bowel transit time, there may be a potential for reduced absorption, concentration and effectiveness of some medications when taken at the same time as PLENVU™.

Missing information

Risk	What is known
Hereditary abnormality of not having enough of the enzyme glucose-6-phosphate dehydrogenase, or G6PD in the body which helps red blood cells function normally and may produce anaemia.	This hereditary condition is a rare event and patients are usually not aware that they have it. If known, PLENVU™ is not recommended to be used. This is because PLENVU™ contains ascorbic acid (Vitamin C), high doses of which may damage red blood cells in such patients and may cause severe anaemia. However, it is worth mentioning here that no associated cases have been reported with the Applicant's other macrogol/PEG 3350 and ascorbic acid containing products.
Use in children (under 18 years of age)	Safety and efficacy of PLENVU™ has not been tested in children under the age of 18 years. Therefore PLENVU™ is not recommended to be used in children.
Use in pregnant or breast feeding women	There are no data on the use of PLENVU™ in pregnant women or breast-feeding women. It should only be used in pregnant/breast feeding women if considered absolutely essential by the physician. If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before taking PLENVU™.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them.
A shortened version of this in layman's language is provided in the form of the package leaflet/patient information leaflet (PIL) for the patients. The measures in these documents are known as routine risk minimisation measures.
PLENVU™ has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable. This is the first EU-RMP for NER1006.

Summary EU-Risk Management Plan