PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Peritoneal dialysis solution with 1.5% glucose, Peritoneal dialysis solution with 1.5% glucose low calcium, Peritoneal dialysis solution with 2.5% glucose, Peritoneal dialysis solution with 2.5% glucose low calcium, Peritoneal dialysis solution with 4.25% glucose and Peritoneal dialysis solution with 4.25% glucose low calcium.

This is a summary of the risk management plan for Peritoneal dialysis solution with 1.5% glucose, Peritoneal dialysis solution with 1.5% glucose low calcium, Peritoneal dialysis solution with 2.5% glucose, Peritoneal dialysis solution with 2.5% glucose low calcium, Peritoneal dialysis solution with 4.25% glucose and Peritoneal dialysis solution with 4.25% glucose low calcium. The RMP details important risks of the medicinal product, how these risks can be minimised, and how more information will be obtained about the risks and uncertainties (missing information) of the peritoneal dialysis solutions.

Peritoneal dialysis solution with 1.5% glucose, Peritoneal dialysis solution with 1.5% glucose low calcium, Peritoneal dialysis solution with 2.5% glucose, Peritoneal dialysis solution with 2.5% glucose low calcium, Peritoneal dialysis solution with 4.25% glucose and Peritoneal dialysis solution with 4.25% glucose low calcium's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how the medicinal product should be used.

I. The medicine and what it is used for

The products belong to the group of solution for peritoneal dialysis. In peritoneal dialysis, the proper composition of the dialysis solution allows removal of waste products as well as correction for water-electrolyte and acid-base balance. Peritoneal dialysis solutions are indicated for patients in acute or chronic kidney failure. The products contain glucose monohydrate, sodium chloride, calcium chloride dihydrate, magnesium chloride hexahydrate and sodium lactate as active substances and are intended for intraperitoneal administration only.

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

Important risks of Peritoneal dialysis solution with 1.5% glucose, Peritoneal dialysis solution with 1.5% glucose low calcium, Peritoneal dialysis solution with 2.5% glucose, Peritoneal dialysis solution with 2.5% glucose low calcium, Peritoneal dialysis solution with 4.25% glucose and Peritoneal dialysis solution with 4.25% glucose low calcium, together with measures to minimise such 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.

Further, PSUR shall be submitted for the product Peritoneal dialysis solution with 2.5% glucose low calcium as it is an application based on Article 10(3) of Directive 2001/83/EU as amended, and otherwise is specified in the EURD list. Therefore, 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.

If important information that may affect the safe use of Peritoneal dialysis solution with 1.5% glucose, Peritoneal dialysis solution with 1.5% glucose low calcium, Peritoneal dialysis solution with 2.5% glucose, Peritoneal dialysis solution with 2.5% glucose low calcium, Peritoneal dialysis solution with 4.25% glucose and Peritoneal dialysis solution with 4.25% glucose low calcium is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Peritoneal dialysis solution with 1.5% glucose, Peritoneal dialysis solution with 1.5% glucose low calcium, Peritoneal dialysis solution with 2.5% glucose, Peritoneal dialysis solution with 2.5% glucose low calcium, Peritoneal dialysis solution with 4.25% glucose and Peritoneal dialysis solution with 4.25% glucose low calcium are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 the medicinal product. 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.

List of important risks and missing information	
Important identified risks	• Peritonitis including aseptic peritonitis • Lactic acidosis • Electrolyte disturbances • Protein, amino acid and vitamin deficiencies • Hyperglycaemia, especially in diabetic patients • Over-hydration and dehydration

Important potential risks	• None
Missing information	• Use during pregnancy

II.B Summary of important risks

Important identified risk: Peritonitis including aseptic peritonitis (cloudy peritoneal effluent)	
Evidence for linking the risk to the medicine	Peritonitis is a common and serious complication of peritoneal dialysis. Although less than 5% of peritonitis episodes result in death, peritonitis is the direct or major contributing cause of death in around 16% of peritoneal dialysis patients. In addition, severe or prolonged peritonitis leads to structural and functional alterations of the peritoneal membrane, eventually leading to membrane failure. Peritonitis is a major cause of peritoneal dialysis technique failure and conversion to long-term haemodialysis.
Risk factors and risk groups	Patients with increased blood sugar level, ethnicity, and malnutrition.
Risk minimisation measures	**Routine risk minimisation measures:** This risk is mentioned in relevant informational materials such as the SmPC and PIL. <u>Risk minimisation activities described in the relevant sections of the SmPC:</u> Listed in Section 4.2, 'Posology and method of administration' Listed in Section 4.3, 'Contraindication' Listed in Section 4.4, 'Special warnings and precautions for use' Listed in Section 4.8, 'Undesirable effects' <u>Risk minimisation activities described in the relevant sections of the PIL:</u> Listed in Section 3. How to use <Peritoneal dialysis solution> Listed in Section 4. Possible side effects Routine risk minimisation activities recommending

	specific clinical measures to address the risk: Recommendation to monitor the indicators of peritonitis is present in SmPC Section 4.4. Other routine risk minimisation measures Legal Status: Prescription only product **Additional risk minimisation measures:** None

Important identified risk: Lactic acidosis	
Evidence for linking the risk to the medicine	World-wide, high blood sugar is the most common cause of end-stage kidney disease and approximately 7 to 8% of the total dialysis population undergo peritoneal dialysis as renal replacement therapy. A high number of deaths have been reported due to disease related complication; especially in patients undergoing peritoneal dialysis. Metformin is generally recommended for high blood sugar treatment and rarely causes lactic acidosis. Peritoneal dialysis solution is composed of different electrolytes (chemicals that are important for the cells in the body to function and allow the body to work), e.g., sodium, potassium, chloride, calcium, magnesium, and phosphate; buffer and osmotic agent. Because bicarbonate and calcium may precipitate during storage, lactate is used as a buffer instead. Lactate-based fluids are acidic (approximately pH 5.5), and may exhibit cytotoxic effects.
Risk factors and risk groups	Patients with severe low blood pressure or sepsis (life-threatening complication of an infection) that can be associated with acute kidney failure, inborn errors of metabolism, treatment with drugs such as metformin and nucleoside/nucleotide reverse transcriptase inhibitors.
Risk minimisation measures	**Routine risk minimisation measures:** This risk is mentioned in relevant informational materials such as the SmPC and PIL. Risk minimisation activities described in the relevant section of the SmPC:

	Listed in Section 4.3, 'Contraindication' <u>Risk minimisation activities described in the relevant section of the PIL:</u> Listed in Section 2. What you need to know before you use <Peritoneal dialysis solution> Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures Legal Status: Prescription only product **Additional risk minimisation measures:** None

Important identified risk: Electrolyte disturbances	
Evidence for linking the risk to the medicine	The daily removal of potassium by the dialysate in peritoneal dialysis is approximately 30 to 40 mmoL. Ten to 58% of patients on peritoneal dialysis are known to develop hypokalaemia. In the early stages of kidney failure, hypocalcaemia (low levels of calcium in blood) can occur because of the decrease in calcitriol (active form of vitamin D found in the body) production and a subsequent decrease in the intestinal absorption of calcium. Complications include bone disease. In addition, severe hypocalcaemia may result in cardiovascular collapse, hypotension unresponsive to fluids and vasopressors, dysrhythmias and neurological complications. Although some patients with hypocalcaemia may improve with treatment, the calcification typically is not reversible.
Risk factors and risk groups	The loss of this mineral significantly increases with the use of diuretics; presence of diarrhoea; vomiting; or other underlying illness. Moreover, patients may have low intake of protein and foods rich in potassium, pre-existing malnutrition, and comorbid conditions. The combination of high loss and low reserve or intake may contribute to the severe hypokalaemia in peritoneal dialysis patients. In children, nutritional deficiencies are

	more frequent and adults are more prone to kidney problems.
Risk minimisation measures	**Routine risk minimisation measures:** This risk is mentioned in relevant informational materials such as the SmPC and PIL. <u>Risk minimisation activities described in the relevant sections of the SmPC:</u> Listed in Section 4.3, 'Contraindication' Listed in Section 4.4, 'Special warnings and precautions for use' Listed in Section 4.5, 'Interaction with other medicinal products and other forms of interaction' Listed in Section 4.8, 'Undesirable effects' Listed in Section 4.9, 'Overdose' <u>Risk minimisation activities described in the relevant sections of the PIL:</u> Listed in Section 2. What you need to know before you use <Peritoneal dialysis solution> Listed in Section 3. How to use <Peritoneal dialysis solution> Listed in Section 4. Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for regular monitoring of serum calcium and potassium is present in SmPC Section 4.4. Other routine risk minimisation measures Legal Status: Prescription only product **Additional risk minimisation measures:** None

Important identified risk: Protein, amino acid and vitamin deficiencies	
Evidence for linking the risk	Protein-energy loss is relatively common in patients with

to the medicine	kidney disease treated with haemodialysis or peritoneal dialysis and is associated with worse outcome. Losses of nutrients into dialysate may contribute to malnutrition. Peritoneal dialysis patients are reported to lose 3 to 4 g/day of amino acids and 4 to 15 g/day of proteins.
Risk factors and risk groups	Patients with kidney problems, poor appetite, and taking multiple medicines for other medical problems.
Risk minimisation measures	**Routine risk minimisation measures:** This risk is mentioned in relevant informational materials such as the SmPC and PIL. Risk minimisation activities described in the relevant section of the SmPC: Listed in Section 4.4, 'Special warnings and precautions for use' Risk minimisation activities described in the relevant section of the PIL: Listed in Section 2. What you need to know before you use <Peritoneal dialysis solution> Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for regular monitoring of blood proteins is present in SmPC Section 4.4. Other routine risk minimisation measures Legal Status: Prescription only product **Additional risk minimisation measures:** None

Important identified risk: Hyperglycaemia, especially in diabetic patients	
Evidence for linking the risk to the medicine	Since peritoneal dialysis uses sugar-based solutions (glucose) to perform dialysis, people with high blood sugar level starting peritoneal dialysis often see a rise in

	their blood sugar levels.
Risk factors and risk groups	Patients with high blood sugar level.
Risk minimisation measures	**Routine risk minimisation measures:** This risk is mentioned in relevant informational materials such as the SmPC and PIL. <u>Risk minimisation activities described in the relevant sections of the SmPC:</u> Listed in Section 4.3, 'Contraindication' Listed in Section 4.4, 'Special warnings and precautions for use' Listed in Section 4.5, 'Interaction with other medicinal products and other forms of interaction' Listed in Section 4.8, 'Undesirable effects' <u>Risk minimisation activities described in the relevant sections of the PIL:</u> Listed in Section 2. What you need to know before you use <Peritoneal dialysis solution> Listed in Section 4. Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for regular monitoring of blood sugar is present in SmPC Section 4.4 and PIL Section 2. Other routine risk minimisation measures Legal Status: Prescription only product **Additional risk minimisation measures:** None

Important identified risk: Over-hydration and dehydration	
Evidence for linking the risk to the medicine	Fluid overload is a major concern in dialysis patients, and is associated with increased cardiovascular risk and death. Congestive heart failure, which accounts for approximately 5% of all-cause mortality in prevalent

	dialysis patients, is associated closely with fluid overload, although other major cardiovascular events could also be affected by it.
Risk factors and risk groups	Patients with hypotension, hypertension, diabetes and severe kidney disease.
Risk minimisation measures	**Routine risk minimisation measures:** This risk is mentioned in relevant informational materials such as the SmPC and PIL. <u>Risk minimisation activities described in the relevant sections of the SmPC:</u> Listed in Section 4.4, 'Special warnings and precautions for use' Listed in Section 4.8, 'Undesirable effects' <u>Risk minimisation activities described in the relevant sections of the PIL:</u> Listed in Section 2. What you need to know before you use <Peritoneal dialysis solution> Listed in Section 4. Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for regular monitoring of body weight for the early recognition of conditions of over-hydration and dehydration is present in SmPC Section 4.4 and PIL Section 2. Other routine risk minimisation measures Legal Status: Prescription only product **Additional risk minimisation measures:** None

Important potential risk: None

Missing information: Use during pregnancy	
Risk minimisation measures	**Routine risk minimisation measures:** This risk is mentioned in relevant informational materials such as the SmPC and PIL. <u>Risk minimisation activities described in the relevant sections of the SmPC:</u> Listed in Section 4.6, 'Pregnancy and lactation' Listed in Section 5.3, 'Preclinical safety data' <u>Risk minimisation activities described in the relevant section of the PIL:</u> Listed in Section 2. What you need to know before you use <Peritoneal dialysis solution> Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation to seek advice from doctor is present in SmPC Section 4.6 and PIL Section 2. Other routine risk minimisation measures Legal Status: Prescription only product **Additional risk minimisation measures:** None

II.C Post-authorisation development plan

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

Not applicable

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

Not applicable