PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Summary of safety concerns	
Important identified risks	• Electrolyte disturbances, particularly hyperkalaemia and hypokalaemia • Hypersensitivity (including anaphylactic reactions)
Important potential risks	• Decreased efficacy with some concomitantly administered medicinal products
Missing information	• None

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Not Applicable

VI.1.3 Summary of Post authorisation efficacy development plan

Not Applicable

VI.1.4 Summary table of Risk Minimization Measures

Safety concern	**Routine risk minimization measures**	**Additional risk minimization measures**
Electrolyte disturbances, particularly hyperkalaemia and hypokalaemia	***For Compound Macrogol 6.86 g Paediatric powder for oral solution in sachet:*** Risk minimization activities described in the relevant section of the SPC: Listed in *Section 4.4 Special warnings and precautions for use* Rare symptoms indicating shifts of fluid/electrolytes e.g. oedema, shortness of breath, increasing fatigue, dehydration, and cardiac failure have been reported in	None proposed

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	adults when using preparations containing Macrogol. If this occurs Macrogol 3350 should be stopped immediately, electrolytes measured, and any abnormality should be treated appropriately. Listed in *Section 4.8 Undesirable effects Metabolism and nutrition disorders*: • Not known: Electrolyte disturbances, particularly hyperkalaemia and hypokalaemia. <u>Risk minimization activities described in the relevant section of the PL</u>: Listed in *Section 4 Possible side effects* Like all medicines, Macrogol can have side effects. Other side effects reported include: • High or low levels of potassium in the blood ***For Compound Macrogol 13.72 g powder for oral solution in sachet:*** <u>Risk minimization activities described in the relevant section of the SPC</u>: Listed in *Section 4.4 Special warnings and precautions for use* Mild adverse drug reactions are possible, as indicated in „Section 4.8 Undesirable effects". If patients develop any symptoms indicating shifts of fluids/electrolytes (e.g. oedema, shortness of breath, increasing fatigue, dehydration, cardiac failure) Macrogol 3350 should be	

Safety concern	**Routine risk minimization measures**	**Additional risk minimization measures**
	stopped immediately and electrolytes measured, and any abnormality should be treated appropriately. Listed in *Section 4.8 Undesirable effects* The frequency of the adverse effects is not known as it cannot be estimated from the available data. • *Metabolism and nutrition disorders:* Electrolyte disturbances, particularly hyperkalaemia and hypokalaemia. <u>Risk minimization activities described in the relevant section of the PL</u>: Listed in *Section 2 What you need to know before you take Compound Macrogol* Warning and precautions: If you develop any symptoms indicating shifts of fluids/electrolytes (e.g. oedema, shortness of breath, increasing fatigue, dehydration, cardiac failure), consult your doctor. Listed in *Section 4 Possible side effects* Like all medicines, Macrogol can have side effects. Other side effects reported include: • High or low levels of potassium in the blood Other routine risk minimization measures Legal Status: Prescription only product.	
•Hypersensitivity (including anaphylactic reactions)	***For Compound Macrogol 6.86 g Paediatric powder for oral solution in sachet:***	None proposed

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	Risk minimization activities described in the relevant section of the SPC: Listed in *Section 4.3 Contraindications* Hypersensitivity to the active substances. Tabulated in *Section 4.8 Undesirable effects* Immune system disorders: Rare: Anaphylaxis. Not known: Angioedema, dyspnoea, rash, erythema, urticaria and pruritus. Risk minimization activities described in the relevant section of the PL: Listed in *Section 2 What you need to know before you give Compound Macrogol Paediatric to your child* Do not give Macrogol if your doctor has told you that your child is: Allergic to Macrogol 3350, sodium chloride, sodium hydrogen carbonate, potassium chloride, or any of the other ingredients in this medicine Listed in *Section 4 Possible side effects* Other side effects include: Allergic reactions which may cause a skin rash, itching, reddening of the skin or a nettle rash, swollen hands, feet or ankles, headaches, and high and low levels of potassium in the blood. ***For Compound Macrogol 13.72 g powder for oral solution in sachet:***	

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	Risk minimization activities described in the relevant section of the SPC: Listed in *Section 4.3 Contraindications* Hypersensitivity to the active ingredients or to any of the excipients. Tabulated in *Section 4.8 Undesirable effects* Immune system disorders: Allergic reactions, including anaphylaxis, angioedema, dyspnoea, rash, erythema, urticaria, and pruritus. Risk minimization activities described in the relevant section of the PL: Listed in *Section 2. What you need to know before you take Compound Macrogol* Do not take Macrogol if your doctor has told you that you are allergic (hypersensitive) to Macrogol 3350, sodium chloride, sodium hydrogen carbonate, potassium chloride or acesulfame potassium Listed in *Section 4. Possible side effects* Other side effects include: Allergic reactions which may cause a skin rash, itching, reddening of the skin or a nettle rash, swollen hands, feet or ankles, headaches, and high and low levels of potassium in the blood.	

Safety concern	**Routine risk minimization measures**	**Additional risk minimization measures**
	Other routine risk minimization measures Legal Status: Prescription only product.	
Decreased efficacy with some concomitantly administered medicinal products	***For Compound Macrogol 6.86 g Paediatric powder for oral solution in sachet:*** <u>Risk minimization activities described in the relevant section of the SPC</u>: Listed in *Section 4.4 Special warnings and precautions for use* The absorption of other medicinal products could be transiently reduced due to an increase in gastro-intestinal transit rate induced by Macrogol 3350. Listed in *Section 4.5 Interaction with other medicinal products and other forms of interaction* Medicinal products in solid dose form taken within one hour of administration of large volumes of Macrogol preparations (as used when treating faecal impaction) may be flushed from the gastrointestinal tract and not absorbed. Macrogol raises the solubility of medicinal products that are soluble in alcohol and relatively insoluble in water. There is a possibility that the absorption of other medicinal products could be transiently reduced during use with Macrogol 3350. There have been isolated reports of decreased efficacy with some concomitantly administered medicinal products, e.g. anti-epileptics.	None proposed

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	Risk minimization activities described in the relevant section of the PL: Listed in *Section 2 What you need to know before you give Compound Macrogol Paediatric to your child* Taking other medicines Some medicines, e.g. anti-epileptics, may not work as effectively during use with Macrogol. Tell your doctor about any other medicines your child is taking. When taking large volumes of Macrogol (e.g. for faecal impaction), your child should not take other medicines within one hour of taking Macrogol. ***For Compound Macrogol 13.72 g powder for oral solution in sachet:*** Risk minimization activities described in the relevant section of the SPC: Listed in *Section 4.4 Special warnings and precautions for use* The absorption of other medicinal products could be transiently reduced due to an increase in gastro-intestinal transit rate induced by Macrogol 3350 Listed in *Section 4.5 Interaction with other medicinal products and other forms of interaction* Macrogol raises the solubility of	

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	medicinal products that are soluble in alcohol and relatively insoluble in water. There is a possibility that the absorption of other medicinal products could be transiently reduced during use with Macrogol 3350.There have been isolated reports of decreased efficacy with some concomitantly administered medicinal products, e.g. anti-epileptics. <u>Risk minimization activities described in the relevant section of the PL</u>: Listed in *Section 2. What you need to know before you take Compound Macrogol* Taking other medicines Some medicines, e.g. anti-epileptics, may not work as effectively during use with Macrogol. Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicines, including medicines obtained without a prescription Other routine risk minimization measures Legal Status: Prescription only product.	

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Constipation:
Constipation (difficulty to pass stools regularly) is a common problem worldwide. It is estimated that approximately 1 to 30 out of every 100 children, and 2 to 35 out of every 100 adults in Europe, Oceania, and North America suffer from constipation. Constipation is more likely to happen after the age of 60 years, being common after 70 years, but it can occur in all age groups, from young age (18 to 23 years) to middle age (45 to 50 years). Constipation is more likely to

happen in women than in men. Constipation cases range widely between countries and continents, but in general Asian countries seem to have a lower rate of occurrence of constipation compared to North America, Europe, and Oceania. This worldwide variation in the number of cases of constipation comes from diverse cultural, dietary, genetic, social and economic conditions and different health care systems[2].

Faecal impaction:
A faecal impaction is a large lump of dry, hard stool that stays stuck in the rectum. Faecal impaction is a common and potentially serious medical condition that occurs in long term or severe constipation or other digestive diseases. This condition is common in the elderly, particularly in those who are hospitalized. However, this condition can occur at any age, although it is most common in children and the elderly. The occurrence rate of this condition in older adults appears to range between 5 to 40 people out of 100. Risk factors for this condition include immobility, motility-slowing medications, poor fibre and fluid intake etc. A study showed that factors thought to be responsible for this condition are heart disease (36%), nerve related disease (28%), complete bed rest (27%), diabetes (23%), and tumours (21%)[3].

VI.2.2 Summary of treatment benefits
Clinical studies in patients for evaluating effective and safe use of Macrogol 3350 were not conducted, considering this is a generic medicine (generic medicine means a medicine that is developed to be the same as a reference medicine that has already been authorized). The available medical literature is considered sufficient to evaluate the safety of Macrogol in the proposed therapeutic indications for Compound Macrogol Paediatric 6.86 g powder for oral solution in sachet and Compound Macrogol 13.72 g powder for oral solution in sachet.

VI.2.3 Unknowns relating to treatment benefits
None.

VI.2.4 Summary of safety concerns

Important identified risks:

Risk	What is known	Preventability
Electrolyte disturbances, particularly hyperkalaemia and hypokalaemia (disturbances in the normal levels of electrolytes in the body like potassium)	Electrolyte disturbances (altered levels of substances like potassium and sodium) in the blood have been reported with treatment of Macrogol. Symptoms of this side effect have been reported on rare occasions. Swelling, shortness	Yes, if the patient suffers from any of the symptoms indicating disturbances in the normal levels of electrolytes in the body like potassium, he or she should consult the treating physician immediately. Macrogol should be stopped

Risk	What is known	Preventability
	of breath, tiredness, dehydration, and heart problems have been reported in adults when using preparations containing Macrogol.	immediately and electrolytes measured, and any abnormality should be treated appropriately.
Allergy to the active substance or to any of the excipients (Hypersensitivity to the active substance or to any of the excipients).	Allergic reactions (Hypersensitivity) with manifestations such as giant hives (angioedema), chest tightness, difficulty in breathing (dyspnoea) and flushing fatal allergic reactions (anaphylaxis) have been reported in clinical trials.	Yes. The patient should not be given Macrogol if he or she is allergic to rasagiline or to any of the other ingredients of this medicine. The patient should talk to the treating physician or pharmacist before taking Macrogol if he or she has any signs of allergy or intolerance.

Important potential risks:

Risk	What is known
Some drugs taken with Macrogol may not work (Decreased efficacy with some concomitantly administered medicinal products)	The absorption of other medicines could be reduced because of increased bowel movements induced by Macrogol 3350. Medicinal products like tablets or capsules taken within one hour after macrogol preparations (as used when treating faecal impaction) may be flushed from the gastrointestinal tract and not absorbed. There is a possibility that the absorption of other medicinal products could be transiently reduced during use with Macrogol 3350.There have been isolated reports of decreased efficacy with some medicinal products, e.g. anti-epileptics.

Missing information:
None

VI.2.5 Summary of additional risk minimization measures by safety concern
Summary of Product Characteristics (SPC) of Compound Macrogol 6.86 g Paediatric powder for oral solution in sachet and Compound Macrogol 13.72 g powder for oral solution in sachet provides physicians, pharmacists, and other health care professionals with details on how to use

the medicine, the risks, and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). All of these risk minimization measures are given in the SPC and PL of Compound Macrogol 6.86 g Paediatric powder for oral solution in sachet and Compound Macrogol 13.72 g powder for oral solution in sachet.
No additional risk minimization measures have been proposed for this generic medicine.

VI.2.6 Planned post authorisation development plan
No post authorisation study is planned for this product.

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

Version	**Date (dd-mm-yyyy)**	**Safety Concerns**	**Comment**
01 (first version)	22/04/2015	*Important identified risks*: Diarrhoea Electrolyte disturbances *Important potential risks*: Use in patients with impaired cardiovascular function *Missing information*: Use in patients with renal insufficiency	Nil
02	19/02/2016	*Important identified risks:* Electrolyte disturbances, particularly hyperkalaemia and hypokalaemia Hypersensitivity (including anaphylactic reactions). *Important potential risks*: Decreased efficacy with some concomitantly administered medicinal products *Missing information:* None	Product name also changed from: Macrogol 6.86 g, powder for oral solution Macrogol 13.72 g, powder for oral solution. To Compound Macrogol 6.86 g Paediatric powder for oral solution in sachet Compound Macrogol 13.72 g powder for oral solution in sachet