Part VI: Summary of activities in 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	• Peripheral Neuropathy • Tremor • Thrombocytopenia • Gastro-intestinal disturbance Weight loss and decreased appetite.
Important potential risks	• Effect on male fertility • Use in patients with renal impairment • Use in patients with hepatic impairment
Missing information	• Use during pregnancy • Use during breastfeeding

VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Not Applicable

VI.1.3 Summary of Post authorisation efficacy development plan

Not Applicable

VI.1.4 Summary table of risk minimisation measures

Safety concern **(Identified)**	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Peripheral Neuropathy	*SmPC Section 4.4: Special warnings and precautions for use* Cases of peripheral neuropathy have been reported in patients treated with miglustat with or without concurrent conditions such as vitamin B_{12} deficiency and monoclonal gammopathy. Peripheral neuropathy seems to be more common in patients with type 1 Gaucher disease compared to the general population. All patients should undergo baseline and repeat neurological evaluation. *SmPC Section 4.8 Undesirable effects:* The most common serious adverse reaction reported with miglustat treatment in clinical studies was peripheral neuropathy Nervous system disorders: Common: Peripheral neuropathy Legal Status: Prescription only product.	Not Applicable
Tremors	*SmPC Section 4.4: Special warnings and precautions for use*	Not Applicable

Safety concern (Identified)	**Routine risk minimisation measures**	**Additional risk minimisation measures**
	Tremor Approximately 37% of patients in clinical trials in type 1 Gaucher disease reported tremor on treatment. In type 1 Gaucher disease, these tremors were described as an exaggerated physiological tremor of the hands. Tremor usually began within the first month, and in many cases resolved during treatment after between 1 and 3 months. Dose reduction may ameliorate the tremor, usually within days, but discontinuation of treatment may sometimes be required. *SmPC Section 4.8 Undesirable effects:* The most common adverse reactions reported in clinical studies with miglustat was tremor Nervous system disorders Very common: tremor Legal Status: Prescription only product.	
Thrombocytopenia	*SmPC Section 4.8: Undesirable effects:* Blood and lymphatic disorders:	Not Applicable

Safety concern (Identified)	**Routine risk minimisation measures**	**Additional risk minimisation measures**
	Common: Thrombocytopenia Miglustat has been studied in indications where certain events reported as adverse reactions, such as thrombocytopenia could also be due to the underlying conditions. Legal Status: Prescription only product.	
Gastro-intestinal disturbance	*SmPC Section 4.4 Special warnings and precautions for use.*Gastrointestinal disturbancesGastrointestinal events, mainly diarrhoea, have been observed in more than 80% of patients, either at the start of treatment or intermittently during treatment. The mechanism is most likely inhibition of disaccharidases such as sucrase-isomaltase in the gastrointestinal tract leading to reduced absorption of dietary disaccharides. In clinical practice, miglustat-induced gastrointestinal events have been observed to respond to individualised diet modification (for example reduction of sucrose, lactose and other carbohydrate intake), to taking miglustat between meals, and/or to anti-diarrhoeal medicinal	Not Applicable

Safety concern (Identified)	Routine risk minimisation measures	Additional risk minimisation measures
	products such as loperamide. In some patients, temporary dose reduction may be necessary. Patients with chronic diarrhoea or other persistent gastrointestinal events that do not respond to these interventions should be investigated according to clinical practice. Miglustat has not been evaluated in patients with a history of significant gastrointestinal disease, including inflammatory bowel disease. *SmPC Section 4.8 Undesirable effects:* The most common adverse reactions reported in clinical studies with miglustat were diarrhoea, flatulence and abdominal pain. . Gastrointestinal disorders: Very common: Diarrhoea, flatulence, abdominal pain Common: Nausea, vomiting, abdominal distension/discomfort, constipation, dyspepsia Legal Status: Prescription only product.	

Safety concern (Identified)	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Weight loss and decreased Appetite.	*SmPC Section 4.8 undesirable effects:* The most common adverse reactions reported in clinical studies with miglustat was weight loss. Metabolism and nutrition disorders Very common: Weight loss, decreased appetite Weight loss has been reported in 55% of patients. The greatest prevalence was observed between 6 and 12 months. *SmPC Section 5.3 Preclinical safety data:* The main effects common to all species was weight loss. Legal Status: Prescription only product.	Not Applicable

Safety concern (Potential)	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Effect on male fertility	*SmPC Section 4.4 Special warnings and precautions for use* Effects on spermatogenesis	Not Applicable

Safety concern (Potential)	Routine risk minimisation measures	Additional risk minimisation measures
	Male patients should maintain reliable contraceptive methods while taking miglustat. Studies in the rat have shown that miglustat adversely affects spermatogenesis and sperm parameters, and reduces fertility. Until further information is available, before seeking to conceive, male patients should cease miglustat and maintain reliable contraceptive methods for a further 3 months. *SmPC Section 4.6: Fertility, pregnancy and lactation:* Studies in the rat have shown that miglustat adversely affects sperm parameters (motility and morphology) thereby reducing fertility. Until further information is available, it is advised that before seeking to conceive, male patients should cease miglustat and maintain reliable contraceptive methods for 3 months thereafter. Contraceptive measures should be used by women of childbearing potential. Male patients should maintain reliable contraceptive	

Safety concern (Potential)	Routine risk minimisation measures	Additional risk minimisation measures
	methods while taking miglustat. SmPC Section 5.3 Preclinical safety data Repeated-dose toxicity studies in rats showed effects on the seminiferous epithelium of the testes. Other studies revealed changes in sperm parameters (motility and morphology) consistent with an observed reduction in fertility. These effects occurred at exposure levels similar to those in patients, but showed reversibility. Miglustat affected embryo/foetal survival in rats and rabbits, dystocia was reported, post-implantation losses were increased, and an increased incidence of vascular anomalies occurred in rabbits. These effects may be partly related to maternal toxicity. Legal Status: Prescription only product.	
Use in patients with renal impairment	*SmPC Section 4.2 Posology and method of administration* *Renal impairment* Pharmacokinetic data indicate increased systemic exposure to	Not Applicable

Safety concern (Potential)	Routine risk minimisation measures	Additional risk minimisation measures
	miglustat in patients with renal impairment. In patients with an adjusted creatinine clearance of 50–70 ml/min/1.73 m2, administration should commence at a dose of 100 mg twice daily in patients with type 1 Gaucher disease. In patients with an adjusted creatinine clearance of 30–50 ml/min/1.73 m2, administration should commence at a dose of 100 mg once daily in patients with type 1 Gaucher disease. Use in patients with severe renal impairment (creatinine clearance < 30 ml/min/1.73 m2) is not recommended *SmPC Section 4.4 Special warnings and precautions for use:* Special populations Due to limited experience, miglustat should be used with caution in patients with renal impairment. There is a close relationship between renal function and clearance of miglustat, and exposure to miglustat is markedly increased in patients with severe renal	

Safety concern (Potential)	Routine risk minimisation measures	Additional risk minimisation measures
	impairment. At present, there is insufficient clinical experience in these patients to provide dosing recommendations. Use of miglustat in patients with severe renal impairment (creatinine clearance < 30 ml/min/1.73 m2) is not recommended. SmPC Section 5.2 Posology and method of administration Miglustat is mainly eliminated by renal excretion, with urinary recovery of unchanged drug accounting for 70-80% of the dose. Apparent oral clearance (CL/F) is 230 ± 39 ml/min. The average half-life is 6–7 hours. Limited data in patients with Fabry disease and impaired renal function showed that CL/F decreases with decreasing renal function. While the numbers of subjects with mild and moderate renal impairment were very small, the data suggest an approximate decrease in CL/F of 40% and 60% respectively, in mild and moderate renal impairment. Data in severe renal impairment are limited to two patients with creatinine	

Safety concern (Potential)	Routine risk minimisation measures	Additional risk minimisation measures
	clearance in the range 18 – 29 ml/min and cannot be extrapolated below this range. These data suggest a decrease in CL/F by at least 70% in patients with severe renal impairment. Legal Status: Prescription only product.	
Use in patients with hepatic impairment	*SmPC Section 4.2 Posology and method of administration* *Hepatic impairment* Miglustat has not been evaluated in patients with hepatic impairment. *SmPC Section 4.4 Special warnings and precautions for use:* Special populations Due to limited experience, miglustat should be used with caution in patients with hepatic impairment. At present, there is insufficient clinical experience in these patients to provide dosing recommendations. Legal Status: Prescription only product.	Not Applicable

Safety concern **(Missing information)**	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Use during pregnancy	*SmPC Section 4.6 Fertility, pregnancy and lactation:* Pregnancy There are no adequate data from the use of miglustat in pregnant women. Studies in animals have shown reproductive toxicity, including dystocia. The potential risk for humans is unknown. Miglustat crosses the placenta and should not be used during pregnancy. SmPC Section 5.3 Preclinical safety data Miglustat affected embryo/foetal survival in rats and rabbits, dystocia was reported, post-implantation losses were increased, and an increased incidence of vascular anomalies occurred in rabbits. These effects may be partly related to maternal toxicity. Legal Status: Prescription only product.	Not Applicable
Use during breastfeeding	*SmPC Section 4.6 Fertility,*	Not Applicable

Safety concern (Missing information)	Routine risk minimisation measures	Additional risk minimisation measures
	pregnancy and lactation: *Breastfeeding* It is not known if miglustat is secreted in breast milk. Miglustat should not be taken during breast-feeding. *SmPC Section 5.3 Preclinical safety data* Changes in lactation were observed in female rats in a 1-year study. The mechanism for this effect is unknown. Legal Status: Prescription only product.	

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Type 1 Gaucher disease (GD)

Gaucher disease is an inherited condition in which there is deficiency of an enzyme called glycocerebrosidase (enzyme responsible for breaking down the fatty substances in body). Hence the fatty substance do not break down properly and accumulate around different organs like liver, spleen, lungs, bones and brain. Type I is the most common form and does not affect the brain. The prevalence of GD is approximately 1/57,000 to 1/75,000 births worldwide, but the disease is more prevalent in individuals of Ashkenazi Jewish descent in whom the incidence is 1/800 births).. The severity of type 1 is extremely variable; some patients present in childhood with virtually all the complications of GD, while others are asymptomatic into

the eighth decade. Patients diagnosed in the first five years of life are frequently non-Jewish and typically have a more malignant disease course.

VI.2.2 Summary of treatment benefits

During the review procedure of Zavesca® the CPMP agreed that although Enzyme Replacement Therapy (ERT) is the standard of care for patients with type 1 Gaucher disease, there is a population of patients, however few, for whom ERT is not suitable and where there is an unmet medical need. Miglustat has shown clinically relevant efficacy in such patients. An acceptable benefit/risk ratio would apply only to those patients for whom ERT is deemed unsuitable. Assessment of the benefit/risk ratio is the responsibility of a physician knowledgeable in the management of these patients. Diligent prospective monitoring has to be put in place to anticipate the adverse neurological events. **(Zavesca EPAR summary 2005)**.

VI.2.3 Unknowns relating to treatment benefits

Not Applicable

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Peripheral Neuropathy (Damage to nerves which leads to weakness, numbness and pain, usually in hands and feet)	Peripheral neuropathy is the common (≥ 1/100 and < 1/10) side effect with miglustat. Some patients have had tingling or numbness in the hands and feet. Peripheral neuropathy seems to be more common in patients with type 1 Gaucher disease compared to the general population.	All patients should undergo neurological evaluation frequently during treatment and before start of treatment.
Tremors (unintentional	Tremor is the most common	Dose adjustment/reduction

Risk	What is known	Preventability
trembling/shaking of one or more body parts)	(≥ 1/10) side effect with Miglustat. Tremor usually began within the first month of treatment, and in many cases resolved during treatment after between 1 and 3 months.	may help to reduce the tremor.
Thrombocytopenia (Reduced levels of blood platelets)	Low platelet count in blood is the common (≥ 1/100 and < 1/10) side effect with miglustat.	Regular platelet count check-up can identify early detection of this condition.
Gastro-intestinal disturbance	The most common (≥ 1/10) side effects are diarrhoea, flatulence (wind), abdominal (stomach) pain, weight loss and decreased appetite.	Miglustat can be taken between meals, and/or to anti-diarrhoeal medicinal products such as loperamide. In some patients, temporary dose reduction may be necessary.
Weight Loss and decreased Appetite.	The most common (≥ 1/10) side effects are weight loss and decreased appetite.	Patient should observe these effects carefully and healthcare provider should frequently check the weight and diet habit history.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Effect on male fertility	Studies in rats have shown that miglustat adversely affects sperm parameters (motility and morphology) thereby

Risk	What is known (Including reason why it is considered a potential risk)
	reducing fertility. Data from human study is not available hence it is considered as potential risk to human population
Use in patients with renal impairment	Due to limited experience, miglustat should be used with caution in patients with renal impairment. There is a close relationship between renal function and clearance of miglustat, and exposure to miglustat is markedly increased in patients with severe renal impairment. At present, there is insufficient clinical experience in renal impaired patients to provide dosing recommendations. Use of miglustat in patients with severe renal impairment (creatinine clearance < 30 ml/min/1.73 m2) is not recommended. Due to limited information use of miglustat in renal impairment is considered as potential risk.
Use in patients with hepatic impairment	Due to limited experience, miglustat should be used with caution in patients with hepatic impairment. At present, there is insufficient clinical experience in hepatic impaired patients to provide dosing recommendations. Due to limited information use of miglustat in hepatic impairment is considered as potential risk.

Missing information

Risk	What is known
Use during pregnancy	*Pregnancy:* Adequate data regarding the use of miglustat in pregnant women is not available. Studies in animals have shown reproductive toxicity, including dystocia . The potential risk for humans is unknown. Miglustat crosses the placenta and

Risk	What is known
	should not be used during pregnancy.
Use during breastfeeding	*Breastfeeding:* It is not known if miglustat is secreted in breast milk. Miglustat should not be taken during breast-feeding. Preclinical safety data Changes in lactation were observed in female rats in a 1-year study. The mechanism for this effect is unknown.

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 minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine 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

Version	Date	Safety Concern	Comment
2.0	24-Nov-2015	The name of below safety concerns has been updated in the RMP: Important identified risks: Gastro-intestinal disturbance (Diarrhoea, flatulence, abdominal	As per regulatory comments from portugal INFARMED, dated 26 October 2015, RMP has been updated.

		pain, Nausea, vomiting, abdominal distension/discomfort, constipation, dyspepsia) changed to Gastro-intestinal disturbance. Important Potential risks: Use of miglustat in patients with hepatic and/or renal impairment changed to • Use in patients with renal impairment • Use in patients with hepatic impairment Missing information: Pregnancy and Breast Feeding changed to • Use during pregnancy • Use during breastfeeding	