European Union Risk Management Plan
MIGLUSTAT (Zavesca®)

Data lock point for current RMP	19 October 2022	Version number	15.1

CHMP approval date 09/11/2023

QPPV Sign-off Date: 10 November 2023
RMP Version Number: 15.1
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QPPV Name(s):	Dr. Laurence Oster-Gozet, PharmD, PhD
QPPV Signature:	The MAH QPPV has either reviewed and approved this RMP, or approved with an electronic signature appended to this RMP, as applicable.

Details of this RMP Submission	
Version Number	15.1
Rationale for submitting an updated RMP (if applicable)	To reflect updated guidance: Guideline on good pharmacovigilance practices Module V – Risk management systems (Rev 2).
Summary of significant changes in this RMP:	• Safety concerns The following important identified risks were removed: • Peripheral neuropathy. • Growth disturbance in pediatric patients with NP-C disease. The following important potential risks were removed: • Crohn's disease. • Adverse effects on spermatogenesis and sperm parameters, and reducing fertility. • Reproductive toxicity, including dystocia. • Increased incidence of large intestinal inflammation, adenoma and adenocarcinoma. The following missing information was removed: • Use in pediatric patients with GD-1. • Use in elderly patients with GD-1. • Use in patients with a history of significant gastrointestinal disease. • Update of postmarketing exposure data • Conversion of RMP to current company RMP template

Other RMP Versions Under Evaluation:

RMP Version Number	Submitted on	Procedure Number
None		

Details of the Currently Approved RMP:

Version number of last agreed RMP:	14
Approved within procedure	EMA/H/C/435/II/0062/G
Date of approval (Competent authority opinion date)	12 July 2018

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PART I: PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	Miglustat
Pharmacotherapeutic group(s) (ATC Code)	Other alimentary tract and metabolism products (ATC code: A16AX06)
Marketing Authorization Holder	Janssen-Cilag International NV
Medicinal products to which the RMP refers	1
Invented name(s) in the EEA	Zavesca®
Marketing authorization procedure	Centralized procedure
Brief description of the product	**Chemical class:** Other alimentary tract and metabolism products.
	Summary of mode of action: Miglustat is an inhibitor of glucosylceramide synthase, the enzyme responsible for the first step in the synthesis of most glycosphingolipids. This inhibitory action forms the rationale for substrate reduction therapy in Gaucher disease and Niemann-Pick type C disease.
	Important information about its composition: None
Reference to the Product Information	EMA/H/C/453/II/0072/G (Approval date: 01 July 2021)
Indication(s) in the EEA	Current: Zavesca is indicated for the oral treatment of adult patients with mild to moderate type 1 Gaucher disease. Zavesca may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable. Zavesca is indicated for the treatment of progressive neurological manifestations in adult patients and pediatric patients with Niemann-Pick type C disease.
Dosage in the EEA	Current: <u>Dosage in type 1 Gaucher disease</u> The recommended starting dose for the treatment of adult patients with type 1 Gaucher disease is 100 mg three times a day. Temporary dose reduction to 100 mg once or twice a day may be necessary in some patients because of diarrhea. There is no experience with the use of Zavesca in patients with type 1 Gaucher disease under the age of 18. The use of Zavesca is therefore not recommended in children or adolescents with type 1 Gaucher disease. There is no experience with the use of Zavesca in patients over the age of 70. <u>Dosage in Niemann-Pick type C disease</u> The recommended dose for the treatment of adult and adolescent patients

<table>
<tr><td></td><td colspan="2">with Niemann-Pick type C disease is 200 mg three times a day.

Dosing in patients under the age of 12 years should be adjusted on the basis of body surface area as illustrated below:

<table><tr><th>Body surface area (m^2)</th><th>Recommended dose</th></tr><tr><td>> 1.25</td><td>200 mg three times a day</td></tr><tr><td>> 0.88-1.25</td><td>200 mg twice a day</td></tr><tr><td>> 0.73-0.88</td><td>100 mg three times a day</td></tr><tr><td>> 0.47-0.73</td><td>100 mg twice a day</td></tr><tr><td>≤ 0.47</td><td>100 mg once a day</td></tr></table>
Temporary dose reduction may be necessary in some patients because of diarrhea.

The benefit to the patient of treatment with Zavesca should be evaluated on a regular basis.

There is limited experience with the use of Zavesca in Niemann-Pick type C disease patients under the age of 4 years.

Renal impairment

In patients with an adjusted creatinine clearance of 50-70 mL/min/1.73 m^2, administration should commence at a dose of 100 mg twice daily in patients with type 1 Gaucher disease, and at a dose of 200 mg twice daily (adjusted for body surface area in patients below the age of 12) in patients with Niemann-Pick type C disease. In patients with an adjusted creatinine clearance of 30-50 mL/min/1.73 m^2, administration should commence at a dose of 100 mg once daily in patients with type 1 Gaucher disease, and at a dose of 100 mg twice daily (adjusted for body surface area in patients below the age of 12) in patients with Niemann-Pick type C disease. Use in patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73 m^2) is not recommended.</td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td colspan="2">Current: Hard capsule. Each capsule contains 100 mg miglustat.</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU?</td><td>☐ Yes</td><td>☑ No</td></tr>
</table>

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the Indication(s) and Target Population(s)

Indication

Zavesca is indicated for the oral treatment of adult patients with mild to moderate type 1 Gaucher disease. Zavesca may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable.

Incidence and prevalence:

GD-1 has a prevalence of 1 in 40,000 to 1 in 60,000 in the general population with the greatest prevalence in the Ashkenazi Jewish population of Eastern Europe ancestry (1 in 500 to 1 in 800) (Grabowski 2019; Beutler 1993; Zimran 1991; Poupetová 2010).

Demographics of the Population in the Authorized Indication - Age, Sex, Racial and/or Ethnic Origin and Risk Factors for the Disease

Among the 1698 patients enrolled into the Gaucher Registry (Charrow 2000), 46% were male and 54% female. The average age at data snapshot was 34.7 years (SD, 19.5 years), ranging from less than 1 to 90 years. Age at diagnosis ranges from birth to 81 years (mean, 17.4 years), with nearly half of the patients receiving a diagnosis before 10 years of age. Ethnicity was provided for 514 Registry patients (30%). Among this subgroup, 68% identified themselves as Jewish (Ashkenazi and Sephardic combined); 21% were non-Jewish white. Other ethnicities constituting at least 1% of Registry patients were Arabic (5%), Hispanic (2%), and African American (1%) (Charrow 2000).

GD-1 is an inherited metabolic disorder.

Main Existing Treatment Options:

Gaucher disease is an inherited metabolic disorder caused by a failure to degrade glucosylceramide resulting in lysosomal storage of this material and widespread pathology. Miglustat is an inhibitor of GCS, the enzyme responsible for the first step in the synthesis of most glycolipids. The inhibitory action on GCS forms the rationale for SRT in Gaucher disease.

Eliglustat is another SRT indicated in GD-1. It is a potent and specific inhibitor of GCS and, differently from miglustat, eliglustat is not an iminosugar. Eliglustat is administered orally once or twice a day. It is contraindicated in patients who are CYP2D6 intermediate metabolizers or extensive metabolizers taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor, and in patients who are CYP2D6 poor metabolizers taking a strong CYP3A inhibitor.

SRT provides an important alternative to the well-established ERT with imiglucerase, velaglucerase, and taliglucerase in the treatment of GD-1, providing both a different pharmacological mode of action (substrate reduction) and an oral route of administration.

The rationale of ERT is to restore a level of enzyme activity sufficient to clear tissue substrate accumulation, thereby stabilizing the progressive decline in function of affected organs in patients with GD-1. ERTs are administered intravenously every two weeks. As stated in the SmPC, miglustat may be used only in the treatment of patients with GD-1 for whom ERT is unsuitable. Reasons for not receiving ERT may include hypersensitivity to ERT, the burden of intravenous infusions and difficulties in venous access.

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

The estimated life expectancy at birth for GD-1 patients was approximately 9 years below the general population (Weinreb 2008).

Important Co-morbidities:

Recent data on co-morbidity in Gaucher disease emanate from a nationwide enquiry in Spain (Pérez-Calvo 2000).

As a group, Gaucher patients seem to have a greater risk of suffering from other common unrelated diseases than carriers or healthy relatives. This excess of risk appears higher among female patients. Carrier status does not seem to heighten the risk of suffering from other diseases.

The authors of a literature review of Parkinsonism in 10 patients with GD-1 (recorded in the French national GD registry) and in 49 previously published cases, concluded that relative to the general population, Parkinsonism in GD patients was 1) more frequent, 2) occurred at an earlier age, 3) responded less well to levodopa, and 4) was more frequently associated with signs of cortical dysfunction. ERT and SRT were ineffective in GD-associated Parkinsonism (Kraoua 2009).

The incidence of polyneuropathy and Parkinsonism among GD-1 patients is significantly increased compared to general population (Biegstraaten 2010). Presence of demyelinating lesions secondary to Vitamin B12 deficiency has been reported in association with Gaucher disease (Gielchinsky 2001; Pastores 2003; Biegstraaten 2008). Gaucher disease is associated with hyperactivity of the immune system, which is manifested by polyclonal hypergammaglobulinemia and an increased incidence of monoclonal gammopathies (Shoenfeld 1982).

Patients with GD-1 present signs and symptoms of progressive substrate (glucosylceramide) deposition, primarily in cells of the monocyte-macrophage system (i.e., Gaucher cells), which leads to bone marrow replacement causing progressive anemia, thrombocytopenia, bleeding tendency, and decreased white blood cell count with consequent recurrent infection; hepatosplenomegaly, secondary hypersplenism, and progressive bone disease. Bone lesions range from mild osteopenia, medullary expansion, and remodeling defects (e.g., Erlenmeyer flask deformity) to osteonecrosis of the femoral or humeral heads and spinal cord compression from vertebral collapse. Fractures from generalized osteopenia or focal lytic lesions or infarctions and osteoarthritis may also occur. Epidemiological data show that bone manifestations are not limited to GD patients with severe disease (Pastores 2004; Pastores 2009). In the Gaucher Registry (ICGG), 63% of patients reported bone pain and 96% had at least one radiological bone disease (Charrow 2000).

The prevalence of depression was in the range of 8% to 12% in surveys of GD-1 patients carried out in 10 countries in North America, Latin America, Europe and Japan, referring to a total sample size of more than 37,000 subjects.

Indication

Zavesca is indicated for the treatment of progressive neurological manifestations in adult patients and pediatric patients with Niemann-Pick type C disease.

Incidence and prevalence:

1 in 120,000 live births (Vanier 2010).

The ultra-rarity of the disease hinders population-based estimates.

Up to now, no formal epidemiologic studies provided information on the prevalence of NP-C by age at neurological onset. However, two large case series suggest a fairly even distribution between the pre-/peri-natal, infantile, juvenile, and adolescent/adult onset forms. In their cohort of 200 NP-C patients diagnosed between late 1993 and 2002, (Vanier 2003) observed that 22% of patients were diagnosed within the first few months of life, around 45% during childhood (2 to 10 years old) and the remaining 33% were diagnosed during adolescence and adulthood. (Imrie 2007) presented similar findings from a series of 94 patients with NP-C diagnosed in the UK in the preceding 28 years. Around one-third of patients were diagnosed neonatally, one-third during childhood and one-third during adolescence/adulthood.

Demographics of the Population in the Authorized Indication - Age, Sex, Racial and/or Ethnic Origin and Risk Factors for the Disease

The majority of patients with NP-C have progressive neurological disease. Some patients may also exhibit hepatic damage which may be lethal. The classic NP-C phenotype presents in childhood and consists of variable hepatosplenomegaly, vertical supranuclear gaze palsy and progressive ataxia, dystonia, and dementia.

Among the 472 patients with NP-C enrolled in the International NP-C Registry (9th NP-C Registry report [Module 5.3.6]), 51.9% were male and 48.1% were female. The mean (SD) age at enrolment was 21.2 years (14.6) ranging from less than 1 to 72 years. Age at diagnosis ranged from birth to 70 years (mean, 16.9 years, SD 14.9 years), with half of the patients receiving a diagnosis before 13 years of age.

NP-C is an autosomal recessive genetic disorder.

No studies were identified that reported risk factors for NP-C per se. However, information from case series suggests that early prolonged neonatal jaundice may predict for earlier death.

Main Existing Treatment Options:

NP-C disease is a very rare, invariably progressive and eventually fatal neurodegenerative disorder characterized by impaired intracellular lipid trafficking. The neurological manifestations are

considered secondary to the abnormal accumulation of glycosphingolipids in neuronal and glial cells.

Miglustat is currently the only approved disease-specific therapy for NP-C. Treatment of patients with NP-C with miglustat is associated with stabilization of clinically important neurological manifestations of the disease.

As reported in the NP-C Registry, the most frequently used non-drug NP-C therapies include physical therapy, speech therapy, and vitamins.

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

The broad clinical spectrum ranges from a neonatal rapidly fatal disorder to an adult-onset chronic neurodegenerative disease. Neurological features are progressive, and include ambulatory impairment, cerebellar ataxia, dementia, dysarthria, dysphagia, psychotic episodes, seizures, and vertical supranuclear gaze palsy. The neurological involvement defines the disease severity in most patients but is typically preceded by systemic signs (cholestatic jaundice in the neonatal period or isolated spleno- or hepatosplenomegaly in infancy/juvenile forms). The average time from initial symptom to diagnosis is approximately 4 years.

The lifespan of the patients varies between a few days until over 60 years of age. A national US cohort of all patients with NP-C (Garver 2007) reported a median age of death of 12.5 years. Actually, a majority of cases die between 10 and 25 years of age. Aspiration pneumonia is the most common cause of death in neurodegenerative diseases, including NP-C, and dysphagia is a frequent cause of aspiration pneumonia (Walterfang 2012).

Important Co-morbidities:

The broad clinical spectrum ranges from a neonatal rapidly fatal disorder to an adult-onset chronic neurodegenerative disease. The neurological involvement defines the disease severity in most patients but is typically preceded by systemic signs (cholestatic jaundice in the neonatal period or isolated spleno- or hepatosplenomegaly in infancy or childhood).

The disease is dominated clinically by progressive and disabling neurological symptoms such as poor muscle coordination, dysphagia, dysarthria, dystonia, seizures, abnormal saccadic eye movements, impaired gait and balance, and learning, cognitive and psychiatric abnormalities. Psychosis is not an uncommon sign in the presentation of adolescent or adult-onset NP-C, and may present alongside motor symptoms and cognitive impairment as an initial manifestation in perhaps 25–40% of adult-onset cases (Walterfang 2006; Shulman 1995; Tyvaert 2005). In the later stages of the disease patients are frequently bedridden, in need of nasogastric tube feeding, suffering from poor muscle control, and severe cognitive intellectual impairment. Epileptic seizures are a common manifestation of NP-C disease and sometimes are refractory to anti-epileptic treatment. Doses of anti-epileptic drugs should be increased until seizure control is achieved or adverse effects supervene, and it should be taken into consideration that a seizure-free period could signal disease-related changes (e.g., loss of seizure-generating neurons). If 2 or more drugs used in appropriate doses for an adequate period are ineffective in controlling seizures, the likelihood of

achieving control is poor. Patients who develop severe epilepsy generally have a worse prognosis and reduced lifespan compared with otherwise similar patients who are seizure free (Patterson 2012). Disturbed coordination of swallowing resulting from brainstem involvement in NP-C patients represents a clinically relevant, disabling and distressing component of the symptomatology of NP-C disease (Walterfang 2012). Ultimately, the outcome is premature death. The lifespan ranges from days to more than 60 years, with the majority of patients dying between the ages of 10 to 20 years. A national US cohort study of NP-C patients reported a median age of 12.5 years at death (Garver 2007).

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

Miglustat has undergone a complete nonclinical development program. All reports from finalized studies have been submitted to the EMA and the results from the nonclinical toxicology, carcinogenicity, and reproductive/development toxicity studies are reflected in the approved SmPC for Zavesca.

Key Safety Findings	Relevance to Human Usage
Toxicity	
Single and repeat-dose toxicity	
Administration of miglustat to male and female CD1 mice by oral gavage at dose levels of 210, 420 and 840/500 mg/kg/day (dose reduction after half a year) for 2 years resulted in an increased incidence of inflammatory and hyperplastic lesions in the large intestine in both sexes. Based on mg/kg/day and corrected for differences in fecal excretion, the doses corresponded to 8, 16 and 33/19 times the highest recommended human dose (200 mg t.i.d.). Carcinomas in the large intestine occurred occasionally at all doses with a statistically significant increase in the high dose group. There was no drug-related increase in tumor incidence in any other organ.	A relevance of these findings to humans cannot be excluded.
Reproductive toxicity	
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.	
Developmental toxicity	
Miglustat affected embryo/fetal 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.	
Other	Zavesca is indicated for use in the pediatric population with NP-C disease. Though limited, there are adequate clinical safety data in the pediatric population and therefore there is no need for additional nonclinical safety data. These data are also reflected in the SmPC with the appropriate precautions.
Special populations	
Results from a juvenile rat study did not reveal new target organs as compared to studies with adult rats.	

Summary of Nonclinical Safety Concerns

Important identified risks	None
Important potential risks	None
Missing information	None

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Brief Overview of Development

Zavesca has been developed and marketed for the oral treatment of adult patients with mild to moderate GD-1. Zavesca may be used only in the treatment of patients for whom ERT is unsuitable. Zavesca has also been developed and marketed for the treatment of progressive neurological manifestations in adult patients and pediatric patients with NP-C disease.

Early in the clinical development of miglustat, studies in HIV patients were performed, utilizing the ability of miglustat to inhibit α-glucosidase. Development was not pursued in this indication. Therefore these studies were not considered in this RMP.

SIII.2. Clinical Trial Exposure

Table SIII.1 through Table SIII.8 present available integrated exposure data across indications based on the data lock point of 19 October 2022.

The following studies were not included in the integrated exposure data: cystic fibrosis studies AC-056-201 and AC-056A202; Japanese studies AC-056-101, AC-056C301 and AC-056C302; and AC-056C405 as these studies do not contribute significant exposure data nor have any impact on the overall safety profile of miglustat.

Exposure in Randomized Clinical Trials

The randomized clinical trials population includes 3 trials:

- Trial OGT 918-006
- Trial OGT 918-007
- Trial OGT 918-009

Exposure to miglustat in the randomized clinical trials population is summarized in Tables SIII.1 through SIII.4 for all subjects by duration, by age group and sex, by dose, and by variable stratifications relevant to the product (eg, pregnant women, lactating women, renal impairment at baseline, hepatic impairment at baseline).

Table SIII.1: Exposure to Miglustat by Duration of Exposure: Randomized Clinical Trials

Cumulative for all Indications: Trials OGT 918-006 (GD-3), OGT 918-007 (NP-C), OGT 918-009 (GM2 gangliosidosis)

Duration of exposure	Patients	Person time (Years)
<1 Month	3	<0.1
1 - <3 Months	1	0.1
3 - <6 Months	4	1.7
6 - <12 Months	7	5.3
12 – <24 Months	24	39.7
24 - <36 Months	32	79.4
≥36 Months	28	105.9
Total	99	232.1

GD-3 = Gaucher disease type 3; NP-C = Niemann-Pick type C.
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Table SIII.2: Exposure to Miglustat by Age Group and Sex: Randomized Clinical Trials

Cumulative for all Indications: Trials OGT 918-006 (GD-3), OGT 918-007 (NP-C), OGT 918-009 (GM2 gangliosidosis)

Age group and Sex	Patients		Person time (Years)	
	M	F	M	F
0 - <28 days	0	0	0	0
28 days - <2 years	0	0	0	0
2 - <12 years	11	18	25.8	43.4
12 - <18 years	8	8	17.6	19.4
18 years - <65 years	31	23	75.6	50.3
65 years - <75 years	0	0	0	0
75 years - <85 years	0	0	0	0
≥85 years	0	0	0	0
Total	50	49	119.0	113.1

GD-3 = Gaucher disease type 3; NP-C = Niemann-Pick type C.
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Table SIII.3: Exposure to Miglustat by Dose: Randomized Clinical Trials

Cumulative for all Indications: Trials OGT 918-006 (GD-3), OGT 918-007 (NP-C), OGT 918-009 (GM2 gangliosidosis)

Dose of exposure	Patients	Person time (Years)
200 mg t.i.d	99	232.1
Total	99	232.1

GD-3 = Gaucher disease type 3; NP-C = Niemann-Pick type C; t.i.d = 3 times a day.
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Table SIII.4: Exposure to Miglustat by Special Populations: Randomized Clinical Trials

Cumulative for all Indications: Trials OGT 918-006 (GD-3), OGT 918-007 (NP-C), OGT 918-009 (GM2 gangliosidosis)

Special Population	Patients	Person time (Years)
Pregnant Women	0	0
Lactating Women	0	0
Renal Impairment	0	0
Cardiac Impairment	0	0

Table SIII.4: Exposure to Miglustat by Special Populations: Randomized Clinical Trials

Hepatic Impairment	0	0
Genetic Polymorphism	0	0
Total	0	0

GD-3 = Gaucher disease type 3; NP-C = Niemann-Pick type C.
A subject may be counted in more than one category
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Exposure in All Clinical Trials

The all clinical trials population includes 10 trials:

- Trial OGT 918-001
- Trial OGT 918-002
- Trial OGT 918-003
- Trial OGT 918-004
- Trial OGT 918-005
- Trial OGT 918-006
- Trial OGT 918-007
- Trial OGT 918-009
- Trial OGT 918-011
- Trial OGT 918-016

Exposure to miglustat in the all clinical trials population is summarized in Tables SIII.5 through SIII.8 for all subjects by duration, by age group and sex, by dose, and by variable stratifications relevant to the product (eg, pregnant women, lactating women, renal impairment at baseline, hepatic impairment at baseline).

Table SIII.5: Exposure to Miglustat by Duration of Exposure: All Clinical Trial

Cumulative for all indications: Trials OGT 918-001, OGT 918-002, OGT 918-003, OGT 918-004, OGT 918-005, OGT 918-006, OGT 918-007, OGT 918-009, OGT 918-011; OGT 918-016

Duration of exposure	Patients	Person time (Years)
<1 Month	9	0.2
1 - <3 Months	9	1.4
3 - <6 Months	15	5.8
6 - <12 Months	29	20.7
12 – <24 Months	75	116.6
24 - <36 Months	58	135.9
≥36 Months	52	236.8
Total	247	517.5

Table SIII.5: Exposure to Miglustat by Duration of Exposure: All Clinical Trial

Indication: GD-1, Trials OGT 918-001, OGT 918-003, OGT 918-004, OGT 918-005, OGT 918-011; OGT 918-016		
Duration of exposure	**Patients**	**Person time (Years)**
<1 Month	5	0.1
1 - <3 Months	8	1.3
3 - <6 Months	11	4.2
6 - <12 Months	14	9.7
12 – <24 Months	44	69.4
24 - <36 Months	26	56.5
≥36 Months	24	131
Total	132	272.2

Indication: Fabry Disease, Trials OGT 918-002		
Duration of exposure	**Patients**	**Person time (Years)**
<1 Month	1	0.1
1 - <3 Months	0	0
3 - <6 Months	0	0
6 - <12 Months	8	5.7
12 – <24 Months	7	7.5
24 - <36 Months	0	0
≥36 Months	0	0
Total	16	13.2

Indication: Gangliosidosis, Trials OGT 918-006 (GD-3), OGT 918-007 (NP-C), OGT 918-009 (GM2 gangliosidosis)		
Duration of exposure	**Patients**	**Person time (Years)**
<1 Month	3	<0.1
1 - <3 Months	1	0.1
3 - <6 Months	4	1.7
6 - <12 Months	7	5.3
12 – <24 Months	24	39.7
24 - <36 Months	32	79.4
≥36 Months	28	105.9
Total	99	232.1

GD-1 = Gaucher disease type 1; GD-3 = Gaucher disease type 3; NP-C = Niemann-Pick type C.
Trial -016 comprises patients previously enrolled in Trials -001, -003, and -004.
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Table SIII.6: Exposure to Miglustat by Age Group and Sex: All Clinical Trials

Cumulative for all Indications: Trials OGT 918-001, OGT 918-002, OGT 918-003, OGT 918-004, OGT 918-005, OGT 918-006, OGT 918-007, OGT 918-009, OGT 918-011; OGT 918-016

Age group	Patients		Person time (Years)	
	M	F	M	F
0 - <28 days	0	0	0	0
28 days - <2 years	0	0	0	0
2 - <12 years	11	18	25.8	43.4
12 - <18 years	8	8	17.6	19.4
18 years - <65 years	109	90	190.2	216.9
65 years - <75 years	2	1	2.3	2.0
75 years - <85 years	0	0	0	0
≥85 years	0	0	0	0
Total	130	117	235.9	281.7

Indication: GD-1, Trials OGT 918-001, OGT 918-003, OGT 918-004, OGT 918-005, OGT 918-011; OGT 918-016

Age group	Patients		Person time (Years)	
	M	F	M	F
0 - <28 days	0	0	0	0
28 days - <2 years	0	0	0	0
2 - <12 years	0	0	0	0
12 - <18 years	0	0	0	0
18 years - <65 years	62	67	101.3	166.6
65 years - <75 years	2	1	2.3	2.0
75 years - <85 years	0	0	0	0
≥85 years	0	0	0	0
Total	64	68	103.6	168.6

Indication: Fabry Disease, Trials OGT 918-002

Age group	Patients		Person time (Years)	
	M	F	M	F
0 - <28 days	0	0	0	0
28 days - <2 years	0	0	0	0
2 - <12 years	0	0	0	0
12 - <18 years	0	0	0	0
18 years - <65 years	16	0	13.2	0
65 years - <75 years	0	0	0	0
75 years - <85 years	0	0	0	0
≥85 years	0	0	0	0
Total	16	0	13.2	0

Indication: Gangliosidosis, Trials OGT 918-006 (GD-3), OGT 918-007 (NP-C), OGT 918-009 (GM2 gangliosidosis)

Age group	Patients		Person time (Years)	
	M	F	M	F
0 - <28 days	0	0	0	0
28 days - <2 years	0	0	0	0
2 - <12 years	11	18	25.8	43.4
12 - <18 years	8	8	17.6	19.4
18 years - <65 years	31	23	75.6	50.3
65 years - <75 years	0	0	0	0
75 years - <85 years	0	0	0	0
≥85 years	0	0	0	0
Total	50	49	119.0	113.1

GD-1 = Gaucher disease type 1; GD-3 = Gaucher disease type 3; NP-C = Niemann-Pick type C.
Trial -016 comprises patients previously enrolled in Trials -001, -003, and -004.

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Table SIII.7: Exposure to Miglustat by Dose: All Clinical Trials

Cumulative for all indications: Trials OGT 918-001, OGT 918-002, OGT 918-003, OGT 918-004, OGT 918-005, OGT 918-006, OGT 918-007, OGT 918-009, OGT 918-011; OGT 918-016		
Dose of exposure	**Patients**	**Person time (Years)**
100 mg t.i.d.	148	285.4
200 mg t.i.d.	99	232.1
Total	247	517.5
Indication: GD-1, Trials OGT 918-001, OGT 918-003, OGT 918-004, OGT 918-005, OGT 918-011; OGT 918-016		
Dose of exposure	**Patients**	**Person time (Years)**
100 mg t.i.d.	132	272.2
Total	132	272.2
Indication: Fabry Disease, Trial OGT 918-002		
Dose of exposure	**Patients**	**Person time (Years)**
100 mg t.i.d.	16	13.2
Total	16	13.2
Indication: Gangliosidosis, Trials OGT 918-006 (GD-3), OGT 918-007 (NP-C), OGT 918-009 (GM2 gangliosidosis)		
Dose of exposure	**Patients**	**Person time (Years)**
200 mg t.i.d.	99	232.1
Total	99	232.1

GD-1 = Gaucher disease type 1; GD-3 = Gaucher disease type 3; NP-C = Niemann-Pick type C; t.i.d = 3 times a day.
Trial -016 comprises patients previously enrolled in Trials -001, -003, and -004.

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Table SIII.8: Exposure to Miglustat by Special Populations: All Clinical Trials

Cumulative for all indications: Trials OGT 918-001, OGT 918-002, OGT 918-003, OGT 918-004, OGT 918-005, OGT 918-006, OGT 918-007, OGT 918-009, OGT 918-011; OGT 918-016		
Special Population	**Patients**	**Person time (Years)**
Pregnant Women	1	7.2
Lactating Women	1	7.2
Renal Impairment	16	13.2
Cardiac Impairment	0	0
Hepatic Impairment	0	0
Genetic Polymorphism	0	0
Total	17	20.4
Indication: GD-1, Trials OGT 918-001, OGT 918-003, OGT 918-004, OGT 918-005, OGT 918-011; OGT 918-016		
Special Population	**Patients**	**Person time (Years)**
Pregnant Women	1	7.2
Lactating Women	1	7.2
Renal Impairment	0	0
Cardiac Impairment	0	0
Hepatic Impairment	0	0
Genetic Polymorphism	0	0
Total	1	7.2

Table SIII.8: Exposure to Miglustat by Special Populations: All Clinical Trials

Indication: Fabry Disease, Trial OGT 918-002		
Special Population	**Patients**	**Person time (Years)**
Pregnant Women	0	0
Lactating Women	0	0
Renal Impairment	16	13.2
Cardiac Impairment	0	0
Hepatic Impairment	0	0
Genetic Polymorphism	0	0
Total	16	13.2

Indication: Gangliosidosis, Trials OGT 918-006 (GD-3), OGT 918-007 (NP-C), OGT 918-009 (GM2 gangliosidosis)		
Special Population	**Patients**	**Person time (Years)**
Pregnant Women	0	0
Lactating Women	0	0
Renal Impairment	0	0
Cardiac Impairment	0	0
Hepatic Impairment	0	0
Genetic Polymorphism	0	0
Total	0	0

GD-1 = Gaucher disease type 1; GD-3 = Gaucher disease type 3; NP-C = Niemann-Pick type C.
Trial -016 comprises patients previously enrolled in Trials -001, -003, and -004.
A subject may be counted in more than one category

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PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table SIV.1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 1	**Subjects who were pregnant or breast-feeding**
Reason for being an exclusion criterion	Miglustat crosses the placenta. Studies in animals have shown reproductive toxicity, including dystocia.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	SmPC, Section 4.6 (Fertility, pregnancy and lactation) adequately addresses this potential risk.
Criterion 2	**Fertile subjects who did not agree to use adequate contraception throughout the study, and for 3 months after cessation of treatment.**
Reason for being an exclusion criterion	Miglustat crosses the placenta. Studies in animals have shown reproductive toxicity, including dystocia.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	SmPC Section 4.6 (Fertility, pregnancy and lactation) adequately addresses this potential risk.
Criterion 3	**Subjects who were suffering from clinically significant diarrhea (more than three liquid stools per day for more than 7 days) without definable cause within 6 months of screening visit, or who had a history of significant gastrointestinal disorders.**
Reason for being an exclusion criterion	A life-time carcinogenicity study in mice showed increased incidence of large intestinal inflammation, adenoma and adenocarcinoma.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	SmPC, Section 4.4 (Special warning and precautions for use) adequately addresses this potential risk.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The safety profile of miglustat has been investigated in clinical trials.

The limitations of the safety data pertain mainly to the restrictions imposed by the orphan nature of the disease conditions treated, which impacts on the overall size of the database as well as on the representativity of the data for all aspects of demographic and baseline disease characteristics. For the currently approved indications for miglustat, these limitations are described in the approved SmPC.

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program(s)

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Children and adolescents	In the all clinical trials population, a total of 29 patients aged 2 to <12 years (69.2 patient years) and 16 patients aged 12 to <18 years (37.0 patient years) have been exposed to miglustat (Table SIII.6).
Pregnant or breastfeeding women	There are no adequate data from the use of miglustat in pregnant women in clinical trials. Miglustat crosses the placenta and should not be used during pregnancy. Male patients should maintain reliable contraceptive methods while taking Zavesca. In addition, before seeking to conceive, male patients should cease Zavesca and maintain reliable contraceptive methods for 3 months thereafter. In the all clinical trials population, 1 patient (7.2 patient years) was exposed to miglustat while pregnant and 1 patient (7.2 patient years) was exposed to miglustat while lactating (Table SIII.8). Cumulatively to 19 October 2021, 15 post-marketing reports of pregnancy exposure were received (maternal and paternal exposure). The estimated reporting frequency for post-marketing cases is 0.02% (1 case/5,073 person-years of exposure).
Population with relevant different ethnic origin	Not applicable
Subpopulations carrying relevant genetic polymorphisms	In the all clinical trials population, no patients with genetic polymorphisms have been exposed to miglustat (Table SIII.8).

Type of Special Population	Exposure
Elderly	In the all clinical trials population, a total of 3 patients aged 65 to <75 years (4.3 patient years) have been exposed to miglustat. No patients aged 75 to <85 years or aged ≥85 years have been exposed to miglustat (Table SIII.6).
Patients with relevant comorbidities:	
Patients with hepatic impairment	Zavesca has not been evaluated in patients with hepatic impairment. Miglustat is mainly eliminated by renal excretion
Patients with renal impairment	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 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. Based on the above data, specific recommendations are addressed in the SmPC. In the all clinical trials population, a total of 16 patients (13.2 patient years) with renal impairment have been exposed to miglustat (Table SIII.8).
Patients with cardiovascular impairment	Not included in the clinical development program.
Immunocompromised patients	Not included in the clinical development program.
Patients with other relevant co-morbidity	There is no limitation for patients with other co-morbidities relevant to the target population.
Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable

Summary of Missing Information Due to Limitations of the Clinical Trial Program

Important identified risks	None
Important potential risks	None
Missing information	None

PART II: SAFETY SPECIFICATION

Module SV: Postauthorization Experience

SV.1. Postauthorization Exposure

SV.1.1. Method used to Calculate Exposure

Post-approval (non-clinical trial) exposure

Reporting frequencies calculated using exposure data do not reflect occurrence rates. Multiple factors influence the reporting of spontaneous experiences and therefore, caution must be exercised in the analysis and evaluation of spontaneous reports. In addition, product exposure is estimated at the time of distribution, not at the time of usage. There is a delay between the time a medication is distributed until it is used by a patient.

Patient exposure

Exposure (in terms of number of patients exposed) was calculated based on number of tablets and average duration of exposure of 365 days for the interval (based on the assumption that all patients took the medication for the entire reporting period.

SV.1.2. Exposure

Cumulative exposure estimates

Cumulatively, since the IBD, based on 1,622,509,533.0 milligrams of miglustat distributed worldwide by the Company from launch to 31 October 2021, the estimated patient exposure is 5,073 person-years.

Additional stratifications for miglustat

Additional stratifications are provided using IQVIA (formerly IMS MIDASTM) data where possible and appropriate. Market research sources for non-study exposure data are unavailable for breakdowns such as: usage in pregnant or breast feeding women, usage in hepatic impairment population, and usage in renal impairment population.

<u>Exposure by age and sex presented as a percentage of prescription sales:</u>

Prescription sales stratified by age available from IQVIA are presented below (as a percentage of total prescriptions). Data only available for 282 prescriptions, of which 100% were male.

Further splits such as sex within age group are not provided since it is not appropriate to stratify to this level of detail based on prescription information available from IQVIA for these subcategories. Prescription units are reported as absolute values.

Table SV.1.2: Post-marketing (Non-study) Exposure for Miglustat by Age Group in Europe (01 July 2018 to 30 June 2021)

Age group (years)[a]	EU (282 prescriptions[b])
0 to 17	47.2%
18 to 35	52.8%

EU=European Union.

a: Regional prescription data by age are only available for the last 3 years ending June 2021.

b: Includes retail channels.

Post-authorization use in special populations

There is no available information on post-authorization use of miglustat in special populations.

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

The abuse potential of miglustat has not been evaluated in human studies. Miglustat is not expected to be subject to abuse and no evidence of an abuse potential for miglustat has been observed.

PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Not applicable as this is not the first RMP for miglustat.

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

Reason for not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Not applicable.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

No safety concerns have been added or reclassified since this RMP was last submitted (Version 14.0 dated 27 March 2018).

In total, 9 safety concerns (2 important identified risks, 4 important potential risks, and 3 classified as missing information) have been removed from the RMP since Version 14.0.

Peripheral neuropathy and growth disturbance in pediatric patients with NP-C disease, previously classified as important identified risks, are removed from the list of safety concerns. Crohn's disease, adverse events on spermatogenesis and sperm parameters, and reducing fertility, reproductive toxicity, including dystocia, and increased incidence of large intestinal inflammation, adenoma and adenocarcinoma, previously classified as important potential risks, are removed from the list of safety concerns. These important identified risks and potential risks have been monitored and characterized for 20 years since the IBD (20 November 2002), with 5,073 patient years estimated exposure to commercial miglustat. No additional pharmacovigilance activities are ongoing or planned for any of the risk topics, and the SmPC adequately addresses the risks.

Use in pediatric patients with GD-1, use in elderly patients with GD-1, and use in patients with a history of significant gastrointestinal disease, previously classified as missing information, are removed from the list of safety concerns. These missing information categories have also been monitored and characterized for 20 years since the IBD (20 November 2002), with 5,073 patient years estimated exposure to commercial miglustat. The anticipated safety profile is not expected to be different in pediatric and elderly populations, or those with a history of significant gastrointestinal disease, compared with the target population. No additional pharmacovigilance activities are ongoing or planned in these populations.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

Not applicable.

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Not applicable.

SVII.3.2. Presentation of the Missing Information

Not applicable.

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

Important Identified Risks	None
Important Potential Risks	None
Missing Information	None

PART III: PHARMACOVIGILANCE PLAN (Including Postauthorization Safety Studies)

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific Follow-up Questionnaires for Safety Concerns	
Safety Concern	Purpose/Description
Not applicable as there are no important identified risks, important potential risks or missing information for miglustat.	

Other Forms of Routine Pharmacovigilance Activities		
Activity	**Objective/Description**	**Milestones**
Not applicable		

III.2. Additional Pharmacovigilance Activities

None.

III.3. Summary Table of Additional Pharmacovigilance Activities

None.

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable.				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable.				
Category 3 - Required additional pharmacovigilance activities				
Not applicable.				

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Table Part IV.1: Planned and Ongoing Postauthorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy Studies which are conditions of the marketing authorizations				
Not applicable				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				

PART V: RISK MINIMIZATION MEASURES (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Not applicable as there are no important identified risks, important potential risks or missing information for miglustat.

V.2. Additional Risk Minimization Measures

Not applicable.

V.2.1. Removal of Additional Risk Minimization Activities

None.

V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Not applicable.		

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Zavesca (Miglustat)

This is a summary of the risk management plan (RMP) for Zavesca. The RMP details important risks of Zavesca, how these risks can be minimized, and how more information will be obtained about Zavesca's risks and uncertainties (missing information).

Zavesca's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Zavesca should be used.

This summary of the RMP for Zavesca should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Zavesca's RMP.

I. The Medicine and What it is Used For

Zavesca is authorized for the treatment of adult patients with mild to moderate type 1 Gaucher disease and the treatment of progressive neurological manifestations in adult patients and pediatric patients with Niemann-Pick type C disease (see SmPC for the full indication). It contains miglustat as the active substance and it is given by a hard capsule.

Further information about the evaluation of Zavesca's benefits can be found in Zavesca's EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/Zavesca.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Zavesca, together with measures to minimize such risks and the proposed studies for learning more about Zavesca's risks, are outlined below.

Measures to minimize 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 authorized 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 (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including periodic safety update report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A. List of Important Risks and Missing Information

Important risks of Zavesca are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. 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 Zavesca. 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 (eg, on the long-term use of the medicine);

List of Important Risks and Missing Information

Important identified risks	None
Important potential risks	None
Missing information	None

II.B. Summary of Important Risks

Not applicable.

II.C. Postauthorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Zavesca.

II.C.2. Other Studies in Postauthorization Development Plan

There are no studies required for Zavesca.

PART VII: ANNEXES

Annex 4: Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 6: Details of Proposed Additional Risk Minimization Activities (if applicable)

Not applicable.