VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology (for each indication)

Indication/target population	**Type 1 Gaucher disease**
Incidence and prevalence	The National Gaucher Foundation states that the incidence of GD is about 1 in 20,000 live births. Around 1 in 100 people in the general U.S. population is a carrier for type 1 GD, giving a prevalence of 1 in 40,000.[2,3] European origin; the carrier frequency in these individuals is approximately 1 per 15 population, whereas the disease frequency is 1 per 855 population.[4]
Demographics of the target population – age, sex, race/ethnic origin	All 3 types of GD are inherited as autosomal recessive traits and have an equal sex distribution.[4] All forms of GD are panethnic. Type 1 GD is the most common lysosomal storage disease and is the most prevalent genetic disorder in individuals of Ashkenazi Jewish descent.[4]
Risk factors for the disease	The risk of having type 1 GD or being a carrier is higher if you're of Eastern or Central European Jewish (Ashkenazi) ancestry.[5] A family history of any type of GD increases the risk of being either a carrier of Gaucher's or of developing the disease.[5]
Main treatment options	It is possible to restore the balance by either increasing the amount of enzyme or reducing the amount of substrate.[6,7] Miglustat, the first oral agent for the treatment of individuals with mild to moderate GD for whom ERT is not a therapeutic option.[6,7] Bone marrow transplantation is another therapeutic option to replace damaged blood forming cells.[6,7]
Mortality and morbidity (natural history)	Estimated life expectancy at birth was 68 y, compared with 77 y in reference population; splenectomized patients, 64 y; nonsplenectomized, 72 y.[8]

VI.2.2 Summary of treatment benefits

The clinical efficacy for miglustat is well-established. As this application is made under Article 10(1) of European Directive 2001/83/EC, as amended, no new efficacy study data are provided and information from innovator SmPC is provided below.
A study was carried out by using controlled randomised 36 patients who had received a minimum of 2 years of treatment with ERT, into three treatment groups: continuation with imiglucerase,

imiglucerase in combination with miglustat, or switch to miglustat. This study was conducted over a 6-month randomised comparison period followed by 18 months extension where all patients received miglustat monotherapy. In the first 6 months in patients who were switched to miglustat, liver and spleen organ volumes and haemoglobin levels were unchanged. In some patients there were reductions in platelet count and increases in chitotriosidase activity indicating that miglustat monotherapy may not maintain the same control of disease activity in all patients. 29 patients continued in the extension period. When compared to the measurements at 6 months, disease control was unchanged after 18 and 24 months of miglustat monotherapy (20 and 6 patients, respectively). No patient showed rapid deterioration of type 1 Gaucher disease following the switch to miglustat monotherapy.[1]

VI.2.3 Unknowns relating to treatment benefits

No unknowns relating to treatment benefits have been identified for miglustat.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Involuntary movements (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.	Yes, • Please tell to doctor or pharmacist • Dose reduction may ameliorate the tremor • Discontinuation of treatment may sometimes be required
Three or more loose or liquid bowel movements per day (Diarrhoea and other gastrointestinal ADRs)	• Gastrointestinal events, mainly diarrhoea, have been observed in more than 80% of patients, either at the outset of treatment or intermittently during treatment	Yes, • Doctor may ask you to change your diet • temporarily reduce dose • May prescribe anti-diarrhoeal medicines • Please tell to doctor or pharmacist
Damage to nerves of the peripheral nervous system (Peripheral neuropathy)	• 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.	Yes, • Please report them to doctor as soon as possible • Doctor will perform some tests before and during treatment with of miglustat to assess this.

Risk	What is known	Preventability
Decrease of platelets in blood (Thrombocytopenia)	• Common undesirable effect • Could be due to the underlying disease	Yes, • If the side effect gets serious, please inform to doctor or pharmacist

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Inability of a male to achieve a pregnancy in a fertile female (Impaired fertility in men)	• 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. • Repeated-dose toxicity studies in rats showed effects on the seminiferous epithelium of the testes.

Important missing information

Risk	What is known
Pregnancy and lactation	• 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. • It is not known if miglustat is secreted in breast milk. Miglustat should not be taken during breast-feeding.
Renal or hepatic impairment	• 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. Use in patients with severe renal impairment (creatinine clearance < 30 ml/min/1.73 m2) is not recommended

VI.2.5 Summary of additional risk minimisation measures by safety concern

Not applicable

VI.2.6 Planned post authorisation development plan

Not applicable

VI.2.7 Summary of changes to the risk management plan over time

Major changes to the risk management plan over time