Part VI: Summary of the risk management plan

Summary of risk management plan for Pombiliti (cipaglucosidase alfa)

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

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

This summary of the RMP for Pombiliti should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of 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 Pombiliti's RMP.

I. The medicine and what it is used for

Pombiliti is a type of enzyme replacement therapy (ERT) authorised for the treatment of late-onset Pompe disease in adults. Pombiliti is always used with another medicine called "Opfolda" (miglustat 65 mg hard capsules). Pombiliti is given as an intravenous infusion and Opfolda is given orally.

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

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

Important risks of Pombiliti, together with measures to minimise such risks and the proposed studies for learning more about Pombiliti's 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 (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Pombiliti, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (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 Pombiliti is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Pombiliti 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 Pombiliti. 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	• Infusion-associated reactions including hypersensitivity and anaphylactic reactions with or without development of immunoglobulin G (IgG) and immunoglobulin E (IgE) antibodies
Important potential risks	• Immune complex related reaction • Medication error in home infusion setting
Missing information	• Use in pregnant and lactating women • Long-term use (> 24 months)

II.B Summary of important risks

Important identified risk: Infusion-associated reactions including hypersensitivity and anaphylactic reactions with or without development of IgG and IgE antibodies

Evidence for linking the risk to the medicine	Infusion-associated reactions (IARs) are a known issue with alglucosidase alfa (another ERT similar in structure to cipaglucosidase alfa), which in some instances have included life-threatening anaphylaxis or other severe allergic reactions. Serious and life-threatening anaphylactic reactions, including anaphylactic shock were reported in infantile- and late-onset patients during alglucosidase alfa infusions. In the cipaglucosidase alfa/miglustat clinical development programme, IARs occurred in 28.5% of subjects and were associated with 2.4% of all cipaglucosidase alfa infusions. The most frequent IARs (occurring in ≥ 2.0% of subjects) were headache, pyrexia, chills, dizziness, urticaria, diarrhoea, dyspnoea, nausea, pruritus, abdominal distension, abdominal pain, fatigue, flushing, and rash. The proportion of cipaglucosidase alfa/miglustat-treated subjects who experienced IARs was similar for ERT-experienced subjects versus ERT-naïve subjects (28.2% versus 29.4%, respectively). The IARs were generally mild to moderate and were usually manageable with reduction or temporary stopping of infusion flow, premedications with corticosteroids, antihistamines, and/or paracetamol, and/or treatment with corticosteroids or antihistamines. Most IARs were medically managed such that subjects were able to continue treatment with cipaglucosidase alfa. Few IARs were serious. No life-threatening or fatal IARs were observed. Hypersensitivity reactions including anaphylaxis were reported in cipaglucosidase alfa/miglustat clinical studies. One subject experienced an event reported as an anaphylactoid reaction, which occurred during the cipaglucosidase alfa infusion. Other potential hypersensitivity/anaphylaxis events, reported in ≥ 2% of subjects, were asthma, chest discomfort, cough, dyspnoea, flushing, mouth ulceration, pruritus, rash, seasonal allergy, and urticaria. Most of the reported hypersensitivity/anaphylaxis events were nonserious and did not lead to discontinuation of study drug. Serious hypersensitivity/anaphylaxis events reported in 1 or more subjects included bradycardia, cough, dizziness, dyspnoea, flushing, hypotension, pharyngeal oedema, pruritus, urticaria and wheezing. No life-threatening or fatal cases of hypersensitivity or anaphylaxis were observed.
Risk factors and risk groups	Infusion-associated reactions are more likely to occur with higher infusion rates. Pompe disease patients not previously treated with ERT or those who have a prior history of IARs, hypersensitivity/allergies, and/or anaphylaxis may be more at risk. Although no consistent association was demonstrated in clinical trials, patients who develop antibodies to cipaglucosidase alfa may be at a higher risk to experience IARs when cipaglucosidase alfa is re-administered.

Important identified risk: Infusion-associated reactions including hypersensitivity and anaphylactic reactions with or without development of IgG and IgE antibodies

Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.2, 4.3, 4.4, and 4.8; • PL Sections 2 and 4; • As stated in the SmPC (Section 4.3) and PL (Section 2), treatment is contraindicated in patients with history of life-threatening IARs (eg, anaphylaxis and severe cutaneous reactions) to the active substance or any of the excipients when rechallenge was unsuccessful; • As stated in the SmPC (Section 4.2), premedication used for patients that have switched from another ERT to Pombiliti in combination with miglustat should be continued when starting Pombiliti; • As stated in the PL (Section 2), patients are instructed to tell their doctor if they notice any signs of IARs or allergic events and such signs are listed in Section 4; • Recommendations for managing IARs including hypersensitivity and anaphylactic reactions are provided in the SmPC, including rate reduction or stoppage of infusion, guidance on resumption or re-initiating, recommendations regarding corrective treatment and premedications, and cardiopulmonary resuscitation equipment. Other routine risk minimisation measures beyond the Product Information: • Prescription only. Additional risk minimisation measures: • Home infusion guide; • Patient/caregiver's guide including an infusion diary.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • ATB200-02; • ATB200-07; • Prospective observational registry. See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviations: ERT = enzyme replacement therapy; IAR = infusion-associated reaction; IgE = immunoglobulin E; IgG = immunoglobulin G; PL = package leaflet; SmPC = Summary of Product Characteristics.

Important potential risk: Immune complex related reaction

Evidence for linking the risk to the medicine	Immune complex related reactions are an established safety risk with alglucosidase alfa (another ERT similar in structure to cipaglucosidase alfa), which in some instances have included severe skin reactions and chronic systemic reactions affecting the kidney and joints, such as severe inflammatory arthropathy (a severe disease of a joint, in which the joint is inflamed), and proteinuria (protein loss in urine) and nephrotic syndrome(a kidney disorder that causes the body to pass too much protein in the urine, resulting in swelling of lower limbs and generalised swelling). No events consistent with immune complex related reactions were identified in patients treated with cipaglucosidase alfa in combination with miglustat in clinical trials; however, a potential class effect cannot be excluded as the formation of antibodies to cipaglucosidase alfa is well-established and such reactions have been reported with alglucosidase alfa.
Risk factors and risk groups	Persistently high IgG antibody titres (ie, formation of a large number of antibodies to cipaglucosidase alfa) is a risk factor for experiencing an immune complex related reaction.
Risk minimisation measures	Routine risk minimisation measures: • As stated in the SmPC (Section 4.4), patients should be monitored for clinical signs and symptoms of systemic immune complex related reactions; • Recommendations for managing immune complex related reactions are provided in the SmPC (Section 4.4), including discontinuation of Pombiliti in combination with miglustat and appropriate medical treatment. Other routine risk minimisation measures beyond the Product Information: • Prescription only.
Additional pharmacovigilance activities:	Additional pharmacovigilance activities: • ATB200-02; • ATB200-07; • Prospective observational registry. See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviations: ERT = enzyme replacement therapy; IgG = immunoglobulin G; PL = package leaflet; SmPC = Summary of Product Characteristics.

Important potential risk: Medication error in home infusion setting

Evidence for linking the risk to the medicine	Adverse events may occur due to incorrect dose calculation, preparation, reconstitution, or administration of cipaglucosidase alfa in the home or clinic setting. It is expected and understood that the healthcare professionals administering cipaglucosidase alfa in the home setting are experienced in the management of the Pompe disease, as well as in the management of other ERTs. An overdose could place a patient at a higher risk for adverse events, while an underdose could result in lack of therapeutic effect. The risk for medication errors may be greater when the product is administered at the patient's home rather than at a healthcare facility, and the risk for more serious or severe outcomes due to cipaglucosidase alfa-related adverse events may be greater when administered in this setting due to the lack of available emergency medical support. In the cipaglucosidase alfa/miglustat clinical development programme, a total of 80 subjects have received home infusion(s). Some IARs have been reported from clinical trials in association with home infusions, however, the majority of these have been nonserious and mild. No medication errors have occurred in the home setting. Nonetheless, as for other ERTs for which home infusion is possible, there is a possible risk of medication errors in the home infusion setting, and the consequences of such medication errors outside of a clinical setting could be more severe for the patient.
Risk factors and risk groups	Patients administered cipaglucosidase alfa in the home setting.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.2 and 6.6; • PL Section 3; • As stated in the SmPC (Section 4.2), infusions should be supervised by healthcare professionals experienced in the management of Pompe disease; • As stated in the SmPC (Section 4.2), home infusions may be considered for patients who are tolerating their infusions well and have no history of moderate or severe IARs for a few months, and recommendations regarding a decision to move to home infusions are described in the SmPC (Section 4.2); • As stated in the SmPC (Section 4.4), for patients who experience anaphylaxis or severe allergic reactions in the home setting, if they continue on treatment, their next infusions must occur in a clinical setting equipped to deal with such medical emergencies; • The SmPC (Section 6.6) contains detailed instruction regarding preparation of the medicinal product (including calculating the dose, activities before reconstitution, reconstituting the lyophilised cake/powder, dilution and preparation of the infusion bag, and preparing for administration); • Recommendations for managing IARs including hypersensitivity and anaphylactic reactions are provided in the SmPC. Other routine risk minimisation measures beyond the Product Information: • Prescription only. Additional risk minimisation measures: • Home infusion guide; • Patient/caregiver's guide including an infusion diary.

Important potential risk: Medication error in home infusion setting

Additional pharmacovigilance activities	Additional pharmacovigilance activities: • ATB200-02; • ATB200-07; • Prospective observational registry. See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviations: ERT = enzyme replacement therapy; IAR = infusion-associated reaction; PL = package leaflet; SmPC = Summary of Product Characteristics.

Missing information: Use in pregnant and lactating women

Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.6 and 5.3; • PL Section 2; • Recommendations regarding use in pregnant women and use in breastfeeding women are provided in the SmPC (Section 4.6) and PL (Section 2); • As stated in the SmPC (Section 4.6) and PL (Section 2), female patients of childbearing potential are advised to maintain reliable contraceptive methods prior, during, and for 4 weeks after stopping Pombiliti in combination with miglustat; • As stated in the PL (Section 2), Pombiliti in combination with miglustat should not be used during pregnancy, and patients are instructed to tell their doctor if they are pregnant, may be pregnant, or are planning to become pregnant; • As stated in the PL (Section 2), Pombiliti in combination with miglustat should not be used in breastfeeding women, and patients are instructed to tell their doctor if they are breastfeeding. Other routine risk minimisation measures beyond the Product Information: • Prescription only.
Additional pharmacovigilance activities:	Additional pharmacovigilance activities: • Prospective observational registry. See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviations: PL = package leaflet; SmPC = Summary of Product Characteristics.

Missing information: Long-term use (> 24 months)

Risk minimisation measures	Routine risk minimisation measures: • None. Other routine risk minimisation measures beyond the Product Information: • Prescription only.
Additional pharmacovigilance activities:	Additional pharmacovigilance activities: • ATB200-02; • ATB200-07; • Prospective observational registry. See Section II.C of this summary for an overview of the post-authorisation development plan.

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 the post-authorisation development plan

Study name	Purpose of the study
ATB200-02 – A Phase 1/2 open-label, fixed-sequence, ascending-dose, first-in-human study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of intravenous infusions of cipaglucosidase alfa co-administered with oral miglustat in adult subjects with Pompe disease	Objectives from the open-label extension portions of the study (ie, Stage 3 and Stage 4) include evaluations of long-term efficacy, safety, and tolerability of cipaglucosidase alfa/miglustat in all subjects from Stage 3. This study will allow continued collection of high-quality clinical trial data on IARs, hypersensitivity, anaphylaxis, potential immune complex related reaction, and medication error in home infusion setting related to cipaglucosidase alfa and help to characterise the impact of the missing information of Long-term use (> 24 months) on the safety profile of miglustat.
ATB200-07 – A Phase 3, open-label extension study to assess the long-term safety and efficacy of intravenous cipaglucosidase alfa co-administered with oral miglustat in adult subjects with late-onset Pompe disease	The primary objective is to assess the long-term safety and tolerability of cipaglucosidase alfa/miglustat. Secondary objectives include assessments of long-term efficacy (as measured by various parameters), long-term effect on biomarkers of muscle injury and disease substrate, and immunogenicity. This study will allow continued collection of high-quality clinical trial data on IARs, hypersensitivity, anaphylaxis, potential immune complex related reactions, and medication error in home infusion setting related to cipaglucosidase alfa and help to characterise the impact of the missing information of Long-term use (> 24 months) on the safety profile of miglustat.

Study name	Purpose of the study
Prospective observational registry – A prospective observational registry of patients with Pompe disease	The goal of the registry is to assess long-term safety and effectiveness of Pompe disease treatments in patients with late-onset Pompe disease (LOPD) and infantile-onset Pompe disease (IOPD). Eligible patients include those who are currently receiving a medical therapy for Pompe disease (regardless of dose/dosing frequency) and those who are not currently receiving any medical therapy for Pompe disease. The objectives are to evaluate long-term safety of Pompe disease treatments through collection of adverse events (AEs) and serious adverse events (SAEs) occurring in patients with Pompe disease, including infusion-associated reactions (IARs), hypersensitivity reactions (including anaphylaxis), immune complex related reactions, and pregnancy exposures; to evaluate long-term real-world effectiveness of Pompe disease treatments through collection of functional outcomes assessments; to evaluate long-term real-world impact of Pompe disease treatments on quality of life (QOL) using patient reported outcome measures. This study will help to characterise the impact of the missing information of Use in pregnant and lactating women and Long-term use (> 24 months) on the safety profile of cipaglucosidase alfa and miglustat, and to help better characterise the important risks for cipaglucosidase alfa associated with IARs, hypersensitivity, anaphylaxis, immune complex related reactions, and medication errors in the home infusion setting.