Part VI: Summary of the risk management plan

Summary of risk management plan for Myalepta (metreleptin)solution for injection)

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

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

This summary of the RMP for Myalepta 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 Myalepta's RMP.

I. The medicine and what it is used for

Myalepta is authorised as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in LD patients:

with confirmed congenital generalised LD (Berardinelli-Seip syndrome) or acquired generalised LD (Lawrence syndrome) in adults and children 2 years of age and above

with specialist-confirmed familial partial LD or acquired partial LD (Barraquer-Simons syndrome), in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control.

It contains metreleptin as the active substance and it is given by SC injection.

Further information about the evaluation of Myalepta's benefits can be found in Myalepta's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004218/human_med_002251.jsp&mid=WC0b01ac058001d124].

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

Important risks of Myalepta, together with measures to minimise such risks and the proposed studies for learning more about Myalepta'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 HCPs;
- 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 (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Myalepta, 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 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 Myalepta is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Myalepta 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 Myalepta. 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 (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks:	Hypersensitivity (Anaphylaxis, Urticaria and Generalised Rash) Acute Pancreatitis Associated with Discontinuation of Metreleptin Hypoglycaemia with Concomitant Use with Insulin and Other Antidiabetics Medication Errors
Important potential risks:	Lymphoma Serious and Severe Infections Secondary to Nabs Unplanned Pregnancy Loss of Efficacy, Potentially Due to Nabs Autoimmune disorder progression
Missing information:	Use in Pregnancy and Lactation

List of important risks and missing information	
	Use in the Elderly Effect of Metreleptin on Brain Development Effect of Metreleptin on Bone Metabolism Effect of increased levels of LH above normal ranges in the paediatric population

II.B Summary of important risks

Important identified risk: Hypersensitivity (anaphylaxis, urticaria, and generalised rash)	
Evidence for linking the risk to the medicine	**Non-clinical trials:** SC mass/necrosis associated with local inflammatory response was noted at the injection site in animals receiving FCA. Severe anaphylaxis occurred in all BSA and metreleptin 2.5 and 5 mg/mL sensitised groups. **Clinical trials:** hypersensitivity events were reported in 16-27% of the patients. Few of the cases were serious. 19 patients had hypersensitivity events concurrent with ADAs. **Post-marketing**: 24 cases reporting hypersensitivity–related Aes were received from spontaneous sources; anaphylactic reaction was reported twice in 1 serious case.
Risk factors and risk groups	Some drug-related, treatment regimen-related, and patient-related risk factors (such as age, sex, concurrent illnesses and previous reactions to related drugs), have been identified as having an important role in drug hypersensitivity (Gomes and Demoly 2005). Drug related factors that affect its immunogenicity include its ability to act as a hapten, a prohapten or to bind covalently to immune receptors. Thus, certain classes of drugs tend to be associated with a higher frequency of drug allergies compared with others (Thong and Tan 2011). Females appear more likely to develop drug allergies than males, but this may be attributable to the overall female predominance in ADRs. Concomitant disease states may predispose to the development of allergic drug reactions by altering metabolic pathways and inducing variations in the immunologic responses to drugs. Ethnicity and genetics appear to be increasingly important in the predisposition to certain types of drug allergy (Thong and Tan 2011).

	Patients with prior severe hypersensitivity reactions to metreleptin or to any of the product components are at higher risk.
Risk minimisation measures	**Routine risk communication**: 4.3 Contraindications 4.4 Special warnings and precautions for use 4.8 Undesirable effects PIL Prescription only medicine Use restricted to physicians experienced in the management of metabolic disorders **Additional risk minimisation measures**: Educational materials for HCPs and patients/caregivers.
Additional pharmacovigilance activities	MEASuRE Registry
Important identified risk: Acute pancreatitis associated with discontinuation of metreleptin	
Evidence for linking the risk to the medicine	**Clinical trials:** A small number of patients experienced pancreatitis however, all patients had a history of pancreatitis and hypertriglyceridaemia and were thus predisposed to pancreatitis and all events were deemed unrelated to study treatment. **Post-marketing experience:** Cumulatively through to 24Jul2016, 16 cases of pancreatitis-related ADRs were received from spontaneous sources. Only 4 (of 16) cases were determined to potentially represent reports of pancreatitis.
Risk factors and risk groups	Patient with a medical history of pancreatitis and/or severe hypertriglyceridaemia, especially those with triglycerides level exceeding 500-1000 mg/dL are at higher risk. Cessation of treatment will result in elevation of hypertriglyceridaemia and hence an increased risk of pancreatitis.
Risk minimisation measures	**Routine risk communication:** 4.2 Posology and method of administration 4.4 Special warnings and precautions for use 4.8 Undesirable effects

	PIL Prescription only medicine Use restricted to physicians experienced in the management of metabolic disorders **Additional risk minimisation measures:** Educational materials for HCPs and patients/caregivers.
Additional pharmacovigilance activities	MEASuRE Registry
Important identified risk: Hypoglycaemia with concomitant use with Insulin and other antidiabetics	
Evidence for linking the risk to the medicine	**Clinical trials:** In Study NIH991265/20010769, hypoglycaemia was reported in 10 (15%) of the 66 GL patients. Events were drug-related in 8 patients (12%). In the PL subgroup, hypoglycaemia was reported in 6 (19%) patients. Events were drug-related in 3 (10%). Events were drug-related in 10-12%. In Study FHA101, hypoglycaemia was reported in 22% of the GL patients and in 43% of the PL subgroup. **Post-marketing:** Cumulative through 24Jul2016, 4 cases reporting hypoglycaemia were received from spontaneous sources. Concomitant use of insulin and metformin was reported in 2 and 3 cases, respectively. In all of the cases retrieved, the analysis was non-conclusive as other confounding factors were present.
Risk factors and risk groups	Patients receiving metreleptin concomitantly with insulin with or without an oral antidiabetic drug that causes hypoglycaemia may be at increased risk of hypoglycaemia, especially those on high dose insulin who have marked improvements in insulin sensitivity with metreleptin treatment.
Risk minimisation measures	**Routine risk communication:** 4.2 Posology and method of administration 4.4 Special warnings and precautions for use 4.5 Interaction with other medicinal products and other forms of interaction 4.8 Undesirable effects PIL

	Prescription only medicine Use restricted to physicians experienced in the management of metabolic disorders **Additional risk minimization measures:** Educational materials for HCPs and patients/caregivers.
Additional pharmacovigilance activities	MEASuRE Registry
Important identified risk: Medication errors	
Evidence for linking the risk to the medicine	**Clinical trials:** No medication errors were reported in clinical trials. **Post marketing experience:** Cumulatively, up to 24Jul2017, there were 17 events of medication errors in 16 patients.
Risk factors and risk groups	Lack of training and lack of adipose tissue due to LD are potential risk factors.
Risk minimisation measures	Routine risk communication: 4.2 Posology and Method of Administration 4.9 Overdose 6.3 Shelf life 6.4 Special precautions for storage 6.6 Special precautions for disposal and other handling PIL **Prescription only medicine** Use restricted to physicians experienced in the management of metabolic disorders The 3 mg and 5.8 mg vials will address the concern of medication errors patients who require a lower maximum daily dose (injection volume) **Additional risk minimisation measures:** Medication errors can be minimised by a comprehensive approach that includes the following elements: Packaging Design

	The package is designed as a compact carton containing 30 vials which is equivalent to a month's supply. **Educational and Training Activities** The sponsor will initiate a programme of educational activities for prescribers and patients (and their care-givers) containing key elements as follows: Reminders on key prescribing information Responsibility of the prescribing physician to provide appropriate training to the patient/care-giver Requirement to perform regular follow-ups with the patient/care-giver to ensure continued correct and compliant Myalepta reconstitution and treatment Guidance on the appropriate syringe size ancillary administration set to prescribe according to the dosage of Myalepta Copies of the SmPC and PIL/IFU HCPs, patients, and care-givers will also be provided access to further materials, including training videos in multiple languages that will demonstrate each step to in preparing and administering Myalepta.
Additional pharmacovigilance activities	MEASuRE Registry
Important potential risk: Lymphoma	
Evidence for linking the risk to the medicine	**Clinical trials**: There have been 2 reports of PTCL both of which were reported as not related to treatment and 1 cases of ALCL which was considered to be related to treatment. All occurred in patients with AGL, which is known to be associated with autoimmune disease. In the two cases of PTCL, there was evidence of pre-existing lymphoma and/or bone marrow/haematological abnormalities.
Risk factors and risk groups	Patients with significant haematologic abnormalities (including leukopenia, neutropenia, bone marrow abnormalities, lymphoma, and/or lymphadenopathy) and/or patients with acquired forms of LD may be at an increased risk. Also patients with diabetes have an increased risk of developing non-Hodgkin's lymphoma compared with those without diabetes (Mitri, Castillo et al. 2008). A meta-analysis showed that (1) patients with diabetes mellitus

	type 2 have mild-to-moderate increased odds of developing non-Hodgkin's lymphoma but not Hodgkin lymphoma; (2) when evaluating non-Hodgkin's lymphoma subtypes, patients with diabetes mellitus type 2 was associated with increased odds of PTCL in a small subset analysis. (Castillo, Mull et al. 2012). Gallagher reported a significant association between diabetes and the risk for developing non-Hodgkin's lymphoma (Relative risk of 1.22 (95% CI: 1.07–1.39)) (Gallagher and LeRoith 2013).
Risk minimisation measures	**Routine risk communication:** 4.4 Special warnings and precautions for use 4.8 Undesirable effects PIL Prescription only medicine Use restricted to physicians experienced in the management of metabolic disorders **Additional risk minimisation measures:** Educational materials for HCPs and patients/caregivers
Additional pharmacovigilance activities	MEASuRE Registry
Important potential risk: Serious and severe infections secondary to NABs	
Evidence for linking the risk to the medicine	**Non-clinical trials:** Repeated-dose studies in mice showed that increases in serum metreleptin concentrations were consistent with the development of circulating antibodies. However, the results lack clinical relevance since most foreign proteins can elicit similar responses. **Clinical trials:** Most patients develop an ADA response to metreleptin (96.1%). Nac was observed in 37.3% of the patients tested. There were 34 Aes of infection in 16 patients which were potentially temporally associated with Nac. Serious and/or severe infections that were temporally associated with Nac occurred in 5 GL patients.
Risk factors and risk groups	Patients with GL between ≥6 to <18 years were more likely to report serious infections (6 patients, 15%), primarily reports of sepsis/septic shock/bacteraemia (3 patients) and pneumonia (2 patients); no adult patients had serious infections.

Risk minimisation measures	**Routine risk communication:** 4.4 Special warnings and precautions for use 4.8 Undesirable effects PIL **Prescription only medicine** Use restricted to physicians experienced in the management of metabolic disorders **Additional risk minimisation measures:** Educational materials for HCPs and patients/caregivers.
Additional pharmacovigilance activities	MEASuRE Registry Metreleptin SOB003 Protocol (Integrated immunogenicity report)
Important potential risk: Unplanned Pregnancy	
Evidence for linking the risk to the medicine	**Clinical trials**: A small number of patients became pregnant during clinical trials however it is not clear whether they were unplanned or planned.
Risk factors and risk groups	Women of childbearing potential
Risk minimisation measures	**Routine risk communication:** 4.4 Special warnings and precautions for use 4.6 Fertility, pregnancy and lactation PIL Prescription only medicine Use restricted to physicians experienced in the management of metabolic disorders **Additional risk minimisation measures:** Educational materials for HCPs and patients/caregivers.
Additional pharmacovigilance activities	MEASuRE Registry
Important potential risk: Lack of efficacy, potentially due to NABs	
Evidence for linking the risk to the medicine	**Clinical trials:** Based on the limited number of patients that were assessed, metreleptin does not appear to negatively impact the

	primary efficacy indicators in either GL or PL patients, including those PL patients with more severe metabolic abnormalities at baseline.
Risk factors and risk groups	Unknown
Risk minimisation measures	**Routine risk communication:** Prescription only medicine Use restricted to physicians experienced in the management of metabolic disorders **Additional risk minimisation measures:** Educational materials for HCPs and patients/caregivers.
Additional pharmacovigilance activities	MEASuRE Registry Metreleptin SOB003 Protocol (Integrated immunogenicity report)
Important potential risk: Auto-immune disorder progression	
Evidence for linking the risk to the medicine	Post-marketing reports and medical literature have outlined cases where patients have developed auto-immune flares and disease progression.
Risk factors and risk groups	Patients with a pre-existing auto-immune disease
Risk minimisation measures	**Routine risk communication:** 4.4 Special warnings and precautions for use PIL Prescription only medicine Use restricted to physicians experienced in the management of metabolic disorders **Additional risk minimisation measures:** Educational materials for HCPs and patients/caregivers.
Additional pharmacovigilance activities	MEASuRE Registry
Missing information: Use in Pregnancy and Lactation	
Risk minimisation measures	**Routine risk communication:** 4.6 Fertility, Pregnancy and Lactation

	5.3 Preclinical Safety Data PIL Prescription only medicine Use restricted to physicians experienced in the management of metabolic disorders **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	MEASuRE Registry
Missing information: Use in Elderly	
Risk minimisation measures	**Routine risk communication:** 4.2 Posology and Method of Administration Prescription only medicine Use restricted to physicians experienced in the management of metabolic disorders **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	MEASuRE Registry
Missing information: Effect of Metreleptin on Brain Development	
Risk minimisation measures	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** Prescription only medicine Use restricted to physicians experienced in the management of metabolic disorders **Additional risk minimization measures:** None

Additional pharmacovigilance activities	MEASuRE Registry
Missing information: Effect of Metreleptin on Bone Metabolism	
Risk minimisation measures	**Routine risk communication:** Prescription only medicine Use restricted to physicians experienced in the management of metabolic disorders **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	MEASuRE Registry
Missing information: Effect of Increased Levels of LH Above Normal Ranges in the Paediatric Population	
Risk minimisation measures	**Routine risk communication:** Prescription only medicine Use restricted to physicians experienced in the management of metabolic disorders **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	MEASuRE Registry

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

STUDY NAME	**PURPOSE OF THE STUDY**
MEASuRE Registry	This registry will seek to further characterise these safety concerns in routine clinical practice.
APL-22: A 24-Month, Multi-Centre, Open Label Phase IV Post Authorisation Efficacy Study to Evaluate the Efficacy, Safety and Immunogenicity of Daily Subcutaneous Metreleptin Treatment in Patients with Partial Lipodystrophy	To further characterise efficacy of metreleptin in PL patients
Metreleptin SOB003 Protocol (Integrated immunogenicity report)	To further characterise the effect of metreleptin treatment on ADA formation and on endogenous leptin levels, using validated immunogenicity assays and mass spectrometry.

II.C.2 Other studies in post-authorisation development plan

STUDY NAME	**PURPOSE OF THE STUDY**
AEGR-734-401: A 36-Month, Multicentre, Open Label Phase 4 Study to Evaluate the Immunogenicity of Daily SC Metreleptin Treatment in Patients with Generalised Lipodystrophy (US)	Primary objective: Evaluate the immunogenicity associated with daily SC metreleptin treatment in patients with congenital or acquired GL. Secondary objective: Assess 2 methods of measuring *in vitro* Nac to metreleptin. Safety objectives: Evaluate the safety and tolerability in relation to the development of or absence of anti-metreleptin or anti-huL antibodies, and/or *in vitro* Nac to metreleptin in patients with congenital or acquired GL. Measure *in vitro* Nac in all patients with suspected loss of response (worsening of metabolic control) or

STUDY NAME	PURPOSE OF THE STUDY
	endogenous leptin action (severe infections or sepsis) at time of AE report. Exploratory objective: Evaluate the efficacy achieved with daily SC metreleptin treatment in patients with congenital or acquired GL.