ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Myalepta 3 mg powder for solution for injection.
Myalepta 5.8 mg powder for solution for injection.
Myalepta 11.3 mg powder for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Myalepta 3 mg powder for solution for injection
Each vial contains 3 mg of metreleptin*.

After reconstitution with 0.6 mL water for injections (see section 6.6), each mL contains 5 mg of metreleptin.

Myalepta 5.8 mg powder for solution for injection
Each vial contains 5.8 mg of metreleptin*.

After reconstitution with 1.1 mL water for injections (see section 6.6), each mL contains 5 mg of metreleptin.

Myalepta 11.3 mg powder for solution for injection
Each vial contains 11.3 mg of metreleptin*.

After reconstitution with 2.2 mL water for injections (see section 6.6), each mL contains 5 mg of metreleptin.

*Metreleptin is a recombinant human leptin analogue (produced in Escherichia coli cells by recombinant DNA technology to form recombinant methionyl-human leptin).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection (powder for injection).

White lyophilised cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Myalepta is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (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 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.

4.2 Posology and method of administration

Treatment should be initiated and monitored by a healthcare professional experienced in the diagnosis and management of metabolic disorders.

Posology

The recommended daily dose of metreleptin is based on body weight as provided in Table 1.

In order to ensure patients and carers understand the correct dose to be injected, the prescriber should prescribe the appropriate dose both in milligrams and the volume in millilitres. In order to avoid medication errors including overdose, dose calculation and dose adjustment guidelines below should be followed. A review of the patient's self-administration technique is recommended every 6 months whilst using Myalepta.

Actual body weight at initiation of treatment should always be used when calculating the dose.

Table 1 Metreleptin recommended dose

Baseline weight	**Starting daily dose (injection volume)**	**Dose adjustments (injection volume)**	**Maximum daily dose (injection volume)**
Males and females ≤ 40 kg	0.06 mg/kg (0.012 mL/kg)	0.02 mg/kg (0.004 mL/kg)	0.13 mg/kg (0.026 mL/kg)
Males > 40 kg	2.5 mg (0.5 mL)	1.25 mg (0.25 mL) to 2.5 mg (0.5 mL)	10 mg (2 mL)
Females > 40 kg	5 mg (1 mL)	1.25 mg (0.25 mL) to 2.5 mg (0.5 mL)	10 mg (2 mL)

Dose adjustments

Based on clinical response (e.g. inadequate metabolic control) or other consideration (e.g. tolerability issues, excessive weight loss especially in paediatric patients), the dose may be decreased, or increased to the maximum dose listed in Table 1. The maximum tolerated dose may be less than the maximum daily dose, outlined in Table 1, as evidenced by excessive weight loss, even if metabolic response is incomplete.

A minimum clinical response is defined as at least:

- 0.5% HbA1c reduction and/or 25% reduction in insulin requirements
  and / or
- 15% reduction in triglycerides (TGs)

If clinical response is not seen after 6 months of treatment the physician should ensure that the patient is compliant with the administration technique, is receiving the correct dose and is adherent to diet. Consider dose increase before stopping treatment.
Metreleptin dose increases in adults and children based on incomplete clinical response can be considered after a minimum of 6 months of treatment, allowing for lowering concomitant insulin, oral anti-diabetic and/or lipid lowering medication.

Reductions in HbA1c and TG may not be seen in children as metabolic abnormalities may not be present at the start of treatment. It is anticipated that most children will require increasing per kg dose, especially as they reach puberty. Increasing abnormalities of TG and HbA1c may be seen which may require a dose increase. Dose adjustments in children without metabolic abnormalities should primarily be made according to weight change.

Dose increases should not be made more frequently than every 4 weeks. Dose decreases based on weight loss may be made weekly.

There is a risk of hypoglycaemia in patients treated with Myalepta who are on anti-diabetic therapy. Large dose reductions of 50% or more of baseline insulin requirements may be needed in the initial phases of treatment. Once insulin requirements have stabilised, dose adjustments of other anti-diabetic therapies may also be needed in some patients to minimise the risk of hypoglycaemia (see section 4.4 and 4.8).

Discontinuation in patients at risk for pancreatitis

When discontinuing Myalepta in patients with risk factors for pancreatitis (e.g. history of pancreatitis, severe hypertriglyceridaemia), tapering of the dose over a two-week period is recommended in conjunction with a low-fat diet. During tapering, monitor triglyceride levels and consider initiating or adjusting the dose of lipid-lowering medicinal products as needed. Signs and/or symptoms consistent with pancreatitis should prompt an appropriate clinical evaluation (see section 4.4).

Missed dose

If a patient misses a dose, the dose should be administered as soon as the omission is noticed and the normal dosing schedule resumed the next day.

Special populations

Elderly

Clinical trials of metreleptin did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients. In general, dose selection and modification for an elderly patient should be cautious, although no specific dose adjustment is recommended.

Renal and hepatic impairment

Metreleptin has not been studied in patients with impaired renal or hepatic function. No dose recommendations can be made.

Paediatric population

The safety and efficacy of metreleptin in children aged 0 to 2 years with generalised LD and children aged 0 to 12 years with partial LD has not been established. Very limited data are available for children, especially less than 6 years, with generalised LD.

Method of administration

Subcutaneous use.

Healthcare professionals should provide patients and carers with training on the reconstitution of the product and proper subcutaneous injection technique, so as to avoid intramuscular injection in patients with minimal subcutaneous adipose tissue.

Patients and/or carers should prepare and administer the first dose of the medicinal product under the supervision of a qualified healthcare professional.

The injection should be administered at the same time every day. It can be administered any time of the day without regard to the timing of meals.

The reconstituted solution should be injected into the abdomen, thigh or upper arm tissue. It is recommended that patients should use a different injection site each day when injecting in the same region. Doses exceeding 1 mL can be administered as two injections (the total daily dose divided equally) to minimise potential injection site discomfort due to injection volume. When dividing doses due to volume, doses can be administered one after the other at different injection sites.

When small doses/volumes are prescribed (e.g. in children), the vials will remain almost completely filled with product after withdrawal of the required dose. Remaining reconstituted product should be discarded after use.

For instructions on reconstitution of the medicinal product before administration, see section 6.6 and the information intended for patients in the package leaflet (section 7).

Table 2 Dose calculation

Weight and gender	**Starting dose calculation**
For males and females ≤ 40 kg once daily dose	Weight (kg) x 0.06 mg/kg = Individual patient daily starting dose in mg Weight (kg) x 0.012 mL/kg = Individual patient daily starting volume to inject in mL Example: 25 kg patient is initiated at 0.06 mg/kg of Myalepta. The individual patient dose = 1.5 mg 25 kg patient is initiated at 0.012 mL/kg = 0.3 mL of Myalepta solution to inject
For males > 40 kg once daily dose	Individual patient once daily dose in mg = 2.5 mg Amount to inject once daily dose = 0.5 mL
For females > 40 kg once daily dose	Individual patient once daily dose in mg = 5 mg Amount to inject once daily dose = 1 mL

Table 3 Required syringe for Myalepta reconstitution with water for injection

Syringe	**Needle gauge and length**
<u>Myalepta 3 mg powder for solution for injection</u>	
1.0 mL	21 gauge 40 mm needle
<u>Myalepta 5.8 mg powder for solution for injection</u>	
3.0 mL	21 gauge 40 mm needle
<u>Myalepta 11.3 mg powder for solution for injection</u>	
3.0 mL	21 gauge 40 mm needle

Table 4 Required administration syringe per Myalepta dose

Syringe	**Needle gauge and length**	**Myalepta dose range to be administered**
0.3 mL U100 Insulin Syringe	31 gauge 8 mm needle	For doses of: ≤ 1.5 mg /≤ 0.3 mL volume daily
1.0 mL	30 gauge 13 mm needle	For doses of: > 1.5 mg - 5 mg / 0.3 - 1.0 mL volume daily
2.5 mL	30 gauge 13 mm needle	For doses of: > 5 mg - 10 mg / > 1.0 mL volume daily

For patients weighing less than 40 kg, actual body weight at initiation of therapy should be used to calculate dose; of these, in patients weighing less than or equal to 25 kg, refer to Table 5 for the starting dose.

Table 5 Conversion table for the 0.3 mL U100 insulin syringe

Weight of child	Dose of Myalepta	Actual amount of solution*	Rounded amount of solution	'Unit' measurement volume in 0.3 mL syringe to inject
9 kg	0.54 mg	0.108 mL	0.10 mL	10
10 kg	0.60 mg	0.120 mL	0.12 mL	12
11 kg	0.66 mg	0.132 mL	0.13 mL	13
12 kg	0.72 mg	0.144 mL	0.14 mL	14
13 kg	0.78 mg	0.156 mL	0.15 mL	15
14 kg	0.84 mg	0.168 mL	0.16 mL	16
15 kg	0.90 mg	0.180 mL	0.18 mL	18
16 kg	0.96 mg	0.192 mL	0.19 mL	19
17 kg	1.02 mg	0.204 mL	0.20 mL	20
18 kg	1.08 mg	0.216 mL	0.21 mL	21
19 kg	1.14 mg	0.228 mL	0.22 mL	22
20 kg	1.20 mg	0.240 mL	0.24 mL	24
21 kg	1.26 mg	0.252 mL	0.25 mL	25
22 kg	1.32 mg	0.264 mL	0.26 mL	26
23 kg	1.38 mg	0.276 mL	0.27 mL	27
24 kg	1.44 mg	0.288 mL	0.28 mL	28
25 kg	1.50 mg	0.300 mL	0.30 mL	30

*Note: Initial and dose increments should be rounded down to the nearest 0.01 mL

The once daily dose of Myalepta can be increased by increments as shown in Table 6 to a maximum daily dose.

Table 6 Dose adjustment calculation

Adjust dose as follows (if necessary)	**Action**
Males and females ≤ 40 kg	Weight (kg) x 0.02 mg/kg = amount of dose adjustment in mg Example: A 15 kg patient is initiated at 0.06 mg/kg of Myalepta. The individual patient dose = 0.9 mg. A dose increment of 0.02 mg/kg increases the daily dose to 0.08 mg/kg = 1.2 mg. Total daily volume to be injected is total dose in mg/5, in this case it is 1.2 mg/5 = 0.24 mL which equals 24 units on the 0.3 mL insulin syringe.
Both males and females > 40 kg	For all patients weighing more than 40 kg an incremental adjustment increase in daily dose would be 1.25 mg or 0.25 mL injection volume. Total daily volume to be injected is total dose in mg/5. Example: A male patient is initiated at 2.5 mg of Myalepta daily. A dose increment of 1.25 mg increases the daily dose to 3.75 mg. Total daily volume to be injected is 3.75 mg/5 = 0.75 mL. The maximum daily dose in males and females is 10 mg or 2 mL injection volume

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Data from clinical trials do not support safety and efficacy in patients with HIV-related LD.

Hypersensitivity reactions

There have been reports of generalised hypersensitivity (e.g. anaphylaxis, urticaria or generalised rash) in patients using Myalepta. Anaphylactic reactions may follow immediately after administration of the medicine. If an anaphylactic reaction or other serious allergic reaction occurs, administration should be permanently discontinued immediately and appropriate therapy initiated.

Acute pancreatitis associated with discontinuation of Myalepta

Non-compliance with, or abrupt discontinuation of, Myalepta may result in worsening hypertriglyceridaemia and associated pancreatitis, particularly in patients with risk factors for pancreatitis (e.g. history of pancreatitis, severe hypertriglyceridaemia) (see section 4.8). If a patient develops pancreatitis whilst being treated with metreleptin, it is advised that metreleptin be continued uninterrupted, as stopping treatment abruptly may exacerbate the condition. If metreleptin must be stopped for any reason, tapering of the dose over a two-week period is recommended in conjunction with a low fat diet, see section 4.2. During tapering, monitor triglyceride levels and consider initiating or adjusting the dose of lipid-lowering medicinal products as needed. Signs and/or symptoms consistent with pancreatitis should prompt an appropriate clinical evaluation.

Hypoglycaemia with concomitant use of insulin and other anti-diabetics

There is a risk of hypoglycaemia in patients treated with Myalepta who are on anti-diabetic medicinal products, in particular insulin or insulin secretagogues (e.g. sulphonylureas). Large dose reductions of 50% or more of baseline insulin requirements may be needed in the first 2 weeks of treatment. Once

insulin requirements have stabilised, dose adjustments of other anti-diabetics may also be needed in some patients to minimise the risk of hypoglycaemia.

Closely monitor blood glucose in patients on concomitant insulin therapy, especially those on high doses, or insulin secretagogues and combination treatment. Patients and carers should be advised to be aware of the signs and symptoms of hypoglycaemia.

In clinical studies, hypoglycaemia has been managed with food/drink intake and by modifying the dose of anti-diabetic medicinal product. In case of hypoglycaemic events of a non-severe nature, food intake management may be considered as an alternative to dose-adjustment of anti-diabetics according to the treating physician's opinion.

Rotation of injection sites is recommended in patients co-administering insulin (or other subcutaneous medicinal products) and Myalepta.

T-cell lymphoma

Cases of T-cell lymphoma (see section 4.8) have been reported while using Myalepta in clinical studies. A causal relationship between the medicinal product treatment and the development and/or progression of lymphoma has not been established.

The benefits and risks of treatment should be carefully considered in patients with acquired generalised LD and/or in patients with significant haematological abnormalities (including leukopenia, neutropenia, bone marrow abnormalities, lymphoma, and/or lymphadenopathy).

Immunogenicity

In clinical trials, antidrug antibodies (ADA) to metreleptin occurred very commonly (88%) in patients. A blocking activity of the reaction between metreleptin and a recombinant leptin receptor has been observed *in vitro* in the blood of the majority of patients but the impact on the efficacy of metreleptin could not be clearly established (see section 4.8).

In patients with serious and severe infections, continuation of metreleptin should be at the discretion of the prescriber. An association between the development of a blocking activity against metreleptin and serious and severe infections cannot be excluded (see section 4.8).

Though not confirmed in clinical trials, neutralising antibodies could in theory affect the activity of endogenous leptin.

Autoimmune Diseases

Autoimmune disorder progression / flares, including severe autoimmune hepatitis, have been observed in some patients treated with Myalepta but a causal relationship between Myalepta treatment and progression of autoimmune disease has not been established. Close monitoring for underlying autoimmune disorder flares (sudden and severe onset of symptoms) is recommended. The potential benefits and risks of Myalepta treatment should be carefully considered in patients with autoimmune diseases.

Pregnancy

Unplanned pregnancies may occur due to restoration of luteinizing hormone (LH) release, see section 4.6.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium free".

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed in humans.

Leptin is a cytokine and has the potential to alter the formation of cytochrome P450 (CYP450) enzymes. Since it cannot be excluded that metreleptin may reduce exposure to substrates of CYP3A through enzyme induction, the efficacy of hormonal contraceptives may be reduced if co-administered with metreleptin. Therefore, an additional non-hormonal contraceptive method should be considered during treatment. The effect of metreleptin on CYP450 enzymes may be clinically relevant for CYP450 substrates with narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of metreleptin, in patients being treated with these types of agents, therapeutic monitoring of effect (e.g., warfarin), or drug concentrations (e.g. cyclosporin or theophylline) should be performed and the individual dose of the agent adjusted as needed. When starting therapy with Myalepta there is a risk of hypoglycaemia in patients who are on anti-diabetic medicinal products, in particular insulin or insulin secretagogues (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Myalepta is not recommended during pregnancy and in women of childbearing potential not using contraception. Abortions, stillbirths and preterm deliveries have been reported in women exposed to metreleptin during pregnancy, though there is currently no evidence to suggest a causal relationship with the treatment. Studies in animals have shown some evidence of reproductive toxicity (see section 5.3).

Breast-feeding

It is unknown whether metreleptin or its metabolites are excreted in human milk. Endogenous leptin is present in human milk.

A risk to newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Myalepta therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are data to suggest metreleptin may increase fertility, due to effects on LH, with the consequent potential for unplanned pregnancy (see section 4.4).

Animal studies showed no adverse effects on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Myalepta has minor influence on the ability to drive and use machines due to fatigue and dizziness.

4.8 Undesirable effects

Summary of the safety profile

A total of 148 patients with generalised and partial LD received metreleptin during clinical studies.

Safety and efficacy data were analysed in a subgroup of partial LD patients with the following characteristics: 12 years of age and above with leptin levels < 12 ng/mL, TG ≥ 5.65 mmol/l and/or HbA1c ≥ 8%.

The adverse reactions reported in generalised LD and this subgroup of partial LD patients are listed in Table 7. Additionally, adverse reactions from post-marketing sources are also presented. The most frequently occurring adverse reactions from the clinical studies were hypoglycaemia *(*14%) and weight decreased (17%).

Tabulated list of adverse reactions

Adverse reactions are classified by MedDRA System Organ Class and absolute frequency in Table 7. Frequencies are defined as very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from available data). Due to the number of patients with generalised and partial LD treated in clinical trials, it is not possible to detect with certainty, events which occur at a frequency of < 1%.

Table 7 Adverse reactions reported with Myalepta in > 1 patient during clinical studies in generalised LD and the subgroup of partial LD patients and post-marketing experience

System Organ Class	Very common	Common	Frequency not known*
Infections and infestations			Influenza, Pneumonia
Immune system disorders			Anaphylactic reaction
Metabolism and nutrition disorders	Hypoglycaemia	Decreased appetite	Diabetes mellitus, Hyperphagia, Insulin resistance
Nervous system disorders		Headache	
Cardiac disorders			Tachycardia
Vascular disorders			Deep vein thrombosis
Respiratory, thoracic and mediastinal disorders			Cough, Dyspnoea Pleural effusion
Gastrointestinal disorders		Abdominal pain, Nausea	Abdominal pain upper, Diarrhoea, Pancreatitis, Vomiting
Skin and subcutaneous tissue disorders		Alopecia	Pruritus, Rash, Urticaria
Musculoskeletal and connective tissue disorders			Arthralgia, Myalgia
Reproductive system and breast disorders		Menorrhagia	
General disorders and administration site conditions		Fatigue, Injection site bruising, Injection site erythema, Injection site reaction	Fat tissue increased, Injection site haemorrhage, Injection site pain, Injection site pruritus, Injection site swelling, Malaise, Peripheral swelling
Investigations	Weight decreased	Neutralising antibodies	Blood glucose abnormal, Blood triglycerides increased, Drug specific antibody present, Glycosylated haemoglobin increased, Weight increased

*Global post marketing experience

Acute pancreatitis associated with discontinuation of metreleptin

In clinical studies, 6 patients (4 with generalised LD and 2 with partial LD), experienced treatment-emergent pancreatitis. All patients had a history of pancreatitis and hypertriglyceridaemia. Abrupt interruption and/or non-compliance with metreleptin dosing was suspected to have contributed to the occurrence of pancreatitis in 2 patients. The mechanism for pancreatitis in these patients was presumed to be return of hypertriglyceridaemia and therefore increased risk of pancreatitis in the setting of discontinuation of effective therapy for hypertriglyceridaemia.

Hypoglycaemia

Metreleptin may decrease insulin resistance in diabetic patients, resulting in hypoglycaemia in patients with LD and co-existing diabetes. Hypoglycaemia, deemed as related to metreleptin treatment, occurred in 14.2% of patients studied. All reports of hypoglycaemia in patients with generalised LD and in the subgroup of partial LD patients, have been mild in nature with no pattern of onset or clinical sequelae. Generally the majority of events could be managed by food intake with only relatively few modifications of anti-diabetic medicinal product dose occurring.

T-cell lymphoma

Three cases of T-cell lymphoma have been reported while using metreleptin in clinical studies. All three patients had acquired generalised LD. Two of these patients were diagnosed with peripheral T-cell lymphoma while receiving the medicinal product. Both had immunodeficiency and significant haematological abnormalities including severe bone marrow abnormalities before the start of treatment. A separate case of anaplastic large cell lymphoma was reported in a paediatric patient receiving the medicinal product who did not have haematological abnormalities before treatment.

Immunogenicity

In clinical trials (Studies NIH 991265/20010769 and FHA101), the rate of ADAs for generalised LD and the partial LD patients studied and with data available were 88% (65 out of 74 patients). A blocking activity of the reaction between metreleptin and a recombinant leptin receptor has been observed *in vitro* in the blood of the majority of an extended set of patients (98 out of 102 patients or 96%) but the impact on the efficacy of metreleptin could not be clearly established.
Serious and/or severe infections that were temporally associated with > 80% blocking activity against metreleptin occurred in 5 generalised LD patients. These events included 1 episode in 1 patient of serious and severe appendicitis, 2 episodes in patients of serious and severe pneumonia, a single episode of serious and severe sepsis and non-serious severe gingivitis in 1 patient and 6 episodes of serious and severe sepsis or bacteraemia and 1 episode of non-serious severe ear infection in 1 patient. One serious and severe infection of appendicitis was temporally associated with blocking activity against metreleptin in a patient with partial LD who was not in the subgroup of partial LD patients. Though temporally associated, it is not possible to unequivocally confirm or deny a direct relation to metreleptin treatment based on the currently available body of evidence. LD patients with a blocking activity against metreleptin and concurrent infections responded to standard of care treatment (see section 4.4).

Injection site reactions

Injection site reactions were reported in 3.4% of patients with LD treated with metreleptin. All events reported in clinical studies in patients with LD have been mild or moderate in severity and none have led to treatment discontinuation. Most events occurred during the initial 1-2 months of initiation of treatment.

Paediatric population

Across two completed clinical studies (NIH 991265/20010769 and FHA101), there were 52 paediatric patients (4 in the subgroup of partial LD patients and 48 with generalised LD) enrolled and exposed to

metreleptin. Limited clinical data exists in children less than 2 years old for generalised LD patients and less than 12 years old in partial LD patients.

Overall, the safety and tolerability of metreleptin are similar in children and adults.

In generalised LD patients, the overall incidence of adverse reactions was similar regardless of age. Serious adverse reactions were reported in 2 patients, worsening hypertension and anaplastic large cell lymphoma.

In partial LD patients, assessment across age groups is limited, due to the small sample size. No adverse reactions were reported in paediatric patients in the subgroup of partial LD patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

Ireland
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

In one post-marketing case, an infant was exposed to a 10-fold overdose of metreleptin for 8 months. In this case, prolonged overdose was associated with severe anorexia causing vitamin and zinc deficiencies, iron deficiency anaemia, protein calorie malnutrition, and poor weight gain, which resolved following supportive treatment and dose adjustment.

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions and supportive treatment initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, amino acids and derivatives, ATC code: A16AA07

Mechanism of action

Metreleptin mimics the physiological effects of leptin by binding to and activating the human leptin receptor, which belongs to the Class I cytokine family of receptors that signals through the JAK/STAT transduction pathway.

Only the metabolic effects of metreleptin have been studied. No effects on the distribution of subcutaneous fat are expected.

Clinical efficacy and safety

The efficacy and safety of treatment with metreleptin was evaluated in an open-label, single-arm study (Study NIH 991265/20010769) in patients with congenital or acquired generalised LD or familial or

acquired partial LD. Patients were eligible for inclusion if they were > 6 months old, with a leptin level of < 12 ng/mL, and had at least 1 of the following 3 metabolic abnormalities:

- Presence of diabetes mellitus, or
- Fasting insulin concentration > 30 μU/mL, or
- Fasting TG concentration > 2.26 mmol/L or postprandially elevated triglycerides > 5.65 mmol/L

The co-primary efficacy endpoints in this study were defined as:

- Actual change from baseline in HbA1c at Month 12, and
- Percent change from baseline in fasting serum TGs at Month 12

Study NIH 991265/20010769 was conducted over 14 years, with the primary efficacy assessments being made in both generalised LD and partial LD patients after 12 months of treatment. Multiple dosing regimens were explored during the NIH study, which led to the posology recommended in section 4.2.

Concomitant anti-diabetic and lipid-lowering dose regimens were not held constant during the study, but analyses showed no significant difference in efficacy between patients who had no increases or additions to their anti-diabetic or lipid-lowering treatments versus the overall study population.

Generalised LD

Of the 66 generalised LD patients enrolled, 45 (68%) had congenital generalised LD and 21 (32%) had acquired generalised LD. Overall, 51 (77%) patients were female, 31 (47%) were Caucasian, 11 (17%) Hispanic, and 16 (24%) Black. The median age at baseline was 15 years (range: 1–68 years), with 45 (68%) patients being less than 18 years of age. The median fasting leptin concentration at baseline was 1.0 ng/mL in males (range: 0.3–3.3 ng/mL) and 1.1 ng/mL in females (range: 0.2-5.3 ng/mL) using the LINCO RIA test method.

The median duration of metreleptin treatment was 4.2 years (range: 3.4 months–13.8 years). The medicinal product was administered subcutaneously either once daily or twice daily (in two equal doses). The weighted average daily dose (i.e., the average dose taking into account duration of treatment at different doses) for the 48 patients with baseline body weight greater than 40 kg was 2.6 mg for males and 5.2 mg for females during the first year of treatment, and 3.7 mg for males and 6.5 mg for females over the entire study period. For the 18 patients with baseline body weight less than or equal to 40 kg, the weighted average daily dose was 2.0 mg for males and 2.3 mg for females in the first year of treatment, and 2.5 mg for males and 3.2 mg for females over the entire study period.

Table 8 Primary outcome results in an open-label, single-arm study (NIH 991265/20010769) in evaluable patients with generalised LD treated with metreleptin at 12 months

Parameter	**n**	**Baseline**	**Change from Baseline at Month 12**
HbA1c (%)	59		
Mean (SD)		8.6 (2.33)	-2.2 (2.15)
P			< 0.001
Fasting TGs (mmol/L)	58		
Mean (SD)		14.7 (25.6)	-32.1% (71.28)
P			0.001

SD = standard deviation

Among 45 patients with generalised LD who had a baseline HbA1c of 7% or greater and data available at Month 12, the mean (SD) baseline HbA1c was 9.6% (1.63) and the mean reduction in

HbA1c at Month 12 was 2.8%. Among 24 patients with generalised LD who had a baseline TG level 5.65 mmol/l or greater and data available at Month 12, the mean (SD) baseline TG level was 31.7 mmol/l (33.68) and the mean percent reduction in triglycerides at Month 12 was 72%.

Among the 39 patients with generalised LD who were receiving insulin at baseline, 16 (41%) were able to discontinue insulin use altogether after starting metreleptin. Most of these patients (13 of 16) were able to stop insulin use within the first year of metreleptin. For the 32 patients with generalised LD who were receiving oral anti-diabetic medicinal products at baseline, 7 (22%) were able to discontinue their use. A total of 8 (24%) of the 34 patients with generalised LD who were receiving lipid-lowering therapies at baseline discontinued their use during metreleptin treatment.

There was evidence of improvement in renal and hepatic function in patients with generalised LD treated with metreleptin. In 24 patients with renal data available, the mean change at Month 12 in protein excretion rate versus baseline (1,675.7 mg/24hr) was -906.1 mg/24 hr. In 43 patients with hepatic data available, the mean changes at Month 12 in alanine aminotransferase, versus baseline (112.5 U/L) was -53.1 U/L, and aspartate aminotransferase versus baseline (75.3 U/L) was -23.8 U/L.

Partial LD subgroup

A subgroup of partial LD patients is analysed for whom TG ≥ 5.65 mmol/l and/or HbA1c ≥ 6.5% at baseline. Of the 31 partial LD subgroup patients evaluated, 27 (87%) had familial partial LD and 4 (13%) had acquired partial LD. Overall, 30 (97%) patients were female, 26 (84%) were Caucasian, 2 (7%) Hispanic, and 0 Black. The median age at baseline was 38 years (range: 15-64 years), with 5 (16%) patients being less than 18 years of age. The median fasting leptin concentration at baseline was 5.9 ng/mL (1.6-16.9) using the LINCO RIA test method.

The median duration of metreleptin treatment was 2.4 years (range: 6.7 months-14.0 years). The medicinal product was administered subcutaneously either once daily or twice daily (in two equal doses). The weighted average daily dose (i.e., the average dose taking into account duration of treatment at different doses) for all 31 patients with baseline body weight greater than 40 kg was 7.0 mg during the first year of treatment, and 8.4 mg over the entire study period.

Table 9 Primary outcome results in study (NIH 991265/ 20010769) of evaluable patients in the partial LD subgroup treated with metreleptin at 12 months

Parameter	n	Baseline	Change from Baseline at Month 12
HbA1c (%)	27		
Mean (SD)		8.8 (1.91)	-0.9 (1.23)
P			< 0.001
Fasting Triglycerides (mmol/L)	27		
Mean (SD)		15.7 (26.42)	-37.4% (30.81)
P			< 0.001

SD = standard deviation

Among 15 patients in the partial LD subgroup who had a baseline TG level 5.65 mmol/L or greater and data available at Month 12, the mean (SD) baseline triglyceride level was 27.6 mmol/L (32.88) and the mean percent reduction in TGs at Month 12 was 53.7%.

Among 18 patients in the partial LD subgroup who had a baseline HbA1c level 8% or greater and data available at Month 12, the mean (SD) baseline HbA1c level was 9.9% (1.59) and the mean reduction in HbA1c at Month 12 was 1.3%.

Paediatric population

In the generalised LD group, the number of patients according to age group was as follows: 5 patients < 6 years (including a single patient < 2 years), 12 patients ≥ 6 to < 12 years and 28 patients aged ≥ 12 to < 18 years; in the partial LD subgroup, there were no patients < 12 years of age and 4 patients ≥ 12 to < 18 years.

In the generalised LD group, mean decreases from baseline in HbA1c were noted in all age groups ≥ 6 years; the mean decreases to Month 12/last observation carried forward LOCF were similar in the two older age groups (-1.1% and -2.6%). Mean change among the 5 patients < 6 years of age was 0.2%. These differences across age groups are likely related to differences in mean HbA1c at baseline, which was in the normal range for patients < 6 years (5.7%) and lower in patients ≥ 6 to < 12 years (6.4%) compared to the older age group (9.7%). Mean decreases from baseline to Month 12/LOCF in TGs for the generalised LD group were noted in all age groups with larger mean changes observed in the older age group (-42.9%) compared to the younger age groups (-10.5% and -14.1%).

Among the 4 patients in the partial LD subgroup between 12 and 18 years of age, mean change to Month 12/LOCF for HbA1c was -0.7% and for TGs was -55.1%.

The European Medicines Agency has deferred the obligation to submit the results of studies with Myalepta in one or more subsets of the paediatric population in the treatment of lipodystrophy (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under 'exceptional circumstances'. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product.
The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

There are limited data on the pharmacokinetics of metreleptin in patients with lipodystrophy and therefore no formal exposure-response analysis has been performed.

Absorption

Peak serum leptin (endogenous leptin and metreleptin) concentration (C_{max}) occurred approximately 4.0 hours after subcutaneous administration of single doses ranging from 0.1 to 0.3 mg/kg in healthy adult subjects. In a supportive trial in LD patients, the median T_{max} was 4 hours (range: 2 to 6 hours; N = 5) following single-dose administration of metreleptin.

Distribution

In studies of healthy adult subjects, following intravenous administration of metreleptin, leptin volume of distribution (endogenous leptin and metreleptin) was approximately 4 to 5 times plasma volume; volumes (mean ± SD) were 370 ± 184 mL/kg, 398 ± 92 mL/kg, and 463 ± 116 mL/kg for 0.3, 1.0, and 3.0 mg/kg/day doses, respectively.

Biotransformation

No formal metabolism studies have been conducted.

Elimination

Non-clinical data indicate renal clearance is the major route of metreleptin elimination, with no apparent contribution of systemic metabolism or degradation. Following single subcutaneous doses of 0.01 to 0.3 mg/kg metreleptin in healthy adult subjects, the half-life was 3.8 to 4.7 hours. After IV

administration, metreleptin clearance was shown to be 79.6 mL/kg/h in healthy volunteers. The clearance of metreleptin appears to be delayed in the presence of ADAs. A higher accumulation is observed with higher ADA levels. Dose adjustments should be made based on clinical response (see section 4.4).

Pharmacokinetics in special populations

Hepatic Impairment

No formal pharmacokinetic studies were conducted in patients with hepatic impairment.

Renal Impairment

No formal pharmacokinetic studies were conducted in patients with renal impairment. Non-clinical data indicate renal clearance is the major route of metreleptin elimination, with no apparent contribution of systemic metabolism or degradation. Hence, the pharmacokinetics may be altered in patients with renal impairment.

Age, Gender, Race, Body Mass Index

Specific clinical studies have not been conducted to assess the effect of age, gender, race, or body mass index on the pharmacokinetics of metreleptin in patients with lipodystrophy.

5.3 Preclinical safety data

Non-clinical data based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity reveal no risks additional to those attributed to an excess of the expected pharmacodynamic responses, such as loss of appetite and body weight.

Two-year carcinogenicity studies in rodents have not been conducted. Metreleptin exhibits no genotoxic potential and no proliferative or preneoplastic lesions were observed in mice or dogs following treatment up to 6 months.

Reproductive toxicity studies conducted in mice have revealed no adverse effects on mating, fertility or embryo-foetal development up to the maximum tested dose, approximately, 15-fold the maximum recommended clinical dose, based on body surface area of a 60 kg patient.

In a pre- and postnatal development study in mice, metreleptin caused prolonged gestation and dystocia at all tested doses, starting at, approximately, a dose identical to the maximum recommended clinical dose, based on body surface area of a 60 kg patient. Prolonged gestation resulted in the death of some females during parturition and lower survival of offspring within the immediate postnatal period. These findings are considered to be related indirectly to metreleptin pharmacology, resulting in nutritional deprivation of treated animals, and also possibly, due to an inhibitory effect on spontaneous and oxytocin-induced contractions, as has been observed in strips of human myometrium exposed to leptin. Decreased maternal body weight was observed from gestation throughout lactation at all doses and resulted in reduced weight of offspring at birth, which persisted into adulthood. However, no developmental abnormalities were observed and reproductive performance of the first or second generations was not affected at any dose.

Reproductive toxicity studies have not included toxicokinetics analysis. However, separate studies revealed that exposure of the mouse foetus to metreleptin was low (< 1%) after subcutaneous administration of metreleptin to pregnant mice. The AUC exposure of pregnant mice was approximately 2 to 3 times greater than observed in non-pregnant mice after 10 mg/kg subcutaneous administration of metreleptin. A 4 to 5-fold increase in the $t_{1/2}$ values was also observed in pregnant mice compared to non-pregnant mice. The greater metreleptin exposure and longer $t_{1/2}$ observed in the pregnant animals may be related to a reduced elimination capacity by binding to soluble leptin receptor found at higher levels in pregnant mice.

No studies with direct administration of metreleptin to juvenile animals have been conducted. However, in published studies, leptin treatment of euleptinaemic prepubertal female mice has led to an earlier onset of puberty.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine
Sucrose
Polysorbate 20
Glutamic acid
Sodium Hydroxide (for pH adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products, except those mentioned in section 6.6.

6.3 Shelf life

3 years.

Following reconstitution with water for injections, the medicinal product must be used immediately and cannot be stored for future use.

6.4 Special precautions for storage

Store in a refrigerator (2 °C–8 °C). Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Myalepta 3 mg powder for solution for injection
Type I glass vial (3 mL) with a chlorobutyl rubber stopper and an aluminium seal/red plastic flip-off cap.

Myalepta 5.8 mg powder for solution for injection
Type I glass vial (3 mL) with a chlorobutyl rubber stopper and an aluminium seal/blue plastic flip-off cap.

Myalepta 11.3 mg powder for solution for injection
Type I glass vial (5 mL) with a bromobutyl rubber stopper and an aluminium seal/white plastic flip-off cap.

Pack sizes of 1 or 30 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The patient will receive a carton containing 1 or 30 vials of Myalepta, depending on the pack size, which should be stored in a refrigerator until the day of use.

The patient will also receive separately the solvent for reconstitution (i.e. water for injection), the syringes/needles for reconstitution, the syringes/needles for administration, the cleansing alcohol swabs, and a sharps disposal container.

Instructions for reconstitution

1. Remove the vial from the refrigerator and allow the vial to warm for 10 minutes to reach room temperature (20 °C–25 °C) prior to reconstitution.
2. Visually inspect the vial containing the medicinal product. The cake of lyophilised powder should be intact and white in colour.
3. Myalepta 3 mg powder for solution for injection
   Using a 1 mL syringe with a 21-gauge or smaller diameter needle, withdraw 0.6 mL of water for injection. Do not reconstitute with other diluents.

   Myalepta 5.8 mg powder for solution for injection
   Using a 3 mL syringe with a 21-gauge or smaller diameter needle, withdraw 1.1 mL of water for injection. Do not reconstitute with other diluents.

   Myalepta 11.3 mg powder for solution for injection
   Using a 3 mL syringe with a 21-gauge or smaller diameter needle, withdraw 2.2 mL of water for injection. Do not reconstitute with other diluents.

4. Insert the needle into the vial containing the lyophilized powder, through the centre of the stopper and direct the stream of solvent to the wall of the vial to avoid excessive foaming.
5. Remove the needle and syringe from the vial and **gently swirl** the contents to reconstitute, until the liquid is clear. **Do not shake or vigorously agitate**. The reconstituted solution will take less than 5 minutes to become clear. When properly mixed, the Myalepta reconstituted solution should be clear, colourless, and free of clumps or dry powder, bubbles or foam. Do not use the solution if discoloured or cloudy, or if particulate matter remains.
6. After reconstitution, each mL contains 5 mg of metreleptin.
7. For instructions on administration, see section 4.2.

Disposal

Myalepta reconstituted with water for injection is for single use only and should be administered immediately. Unused reconstituted solution cannot be stored for later use. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Amryt Pharmaceuticals DAC
45 Mespil Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

Myalepta 3 mg powder for solution for injection
EU/1/18/1276/003
EU/1/18/1276/004

Myalepta 5.8 mg powder for solution for injection
EU/1/18/1276/005
EU/1/18/1276/006

Myalepta 11.3 mg powder for solution for injection
EU/1/18/1276/001
EU/1/18/1276/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 July 2018

10. DATE OF REVISION OF THE TEXT

11/2020

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.