PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr MYALEPTA™

Metreleptin for injection

Powder for solution, 3 mg/ vial, 5.8 mg/ vial and 11.3 mg/ vial, Subcutaneous injection

Recombinant human leptin analog

ATC code: A16AA07

Manufacturer:

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A, 43122 Parma, Italy

Date of Initial Authorization:
JAN 17, 2024

Imported by:

Medison Pharma Canada Inc.
One Dundas Street West, Suite 2500
Toronto, Ontario
Canada, M5G 1Z3

Date of Revision:

AUG 2, 2024

Submission Control Number: 287676

RECENT MAJOR LABEL CHANGES

Not Applicable.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

MYALEPTA (metreleptin for injection) 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 (PL) or acquired PL (Barraquer-Simons syndrome), in adults and children 12 years of age and above with persistent significant metabolic disease for whom standard treatments have failed to achieve adequate metabolic control.

1.1 Pediatrics

The safety and efficacy of Myalepta 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 in children with generalised LD < 6 years of age (n=5; range: 1-4 years). Very limited data are available in children with partial LD <18 years of age (n=5; range: 15-17 years).

Myalepta lyophilized powder when reconstituted with the diluent Bacteriostatic Water for Injection (benzyl alcohol preserved) is not indicated in patients under 3 years of age or in patients with a known sensitivity to benzyl alcohol (see 7 WARNINGS AND PRECAUTIONS).

1.2 Geriatrics

Clinical trials of Myalepta did not include sufficient numbers of patients aged 65 and older (n=1) to determine whether they respond differently from younger patients.

2 CONTRAINDICATIONS

- Myalepta is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Myalepta is contraindicated in patients with general obesity not associated with confirmed generalised leptin deficiency or confirmed partial lipodystrophy.
- Myalepta is contraindicated in patients with HIV-related lipodystrophy

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Anti-metreleptin antibodies with neutralizing activity have been identified in patients treated with Myalepta. The consequences are not well characterized but could include inhibition of endogenous leptin action and loss of Myalepta efficacy. Worsening metabolic control and/or severe infection have been reported. Test for anti-metreleptin antibodies with neutralizing activity in patients with severe infections or loss of efficacy during Myalepta treatment. Contact Chiesi (medinfo@amrytpharma.com) for neutralizing antibody testing (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS).
- T-cell lymphoma has been reported in patients with acquired generalised lipodystrophy, both treated and not treated with Myalepta. Carefully consider the benefits and risks of treatment with Myalepta in patients with significant hematologic abnormalities and/or acquired lipodystrophy (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Treatment should be initiated and monitored by a healthcare professional experienced in the diagnosis and management of metabolic disorders associated with lipodystrophy.
- Dosage adjustments, including possible large reductions, of insulin or insulin secretagogue (e.g., sulfonylurea) may be necessary in some patients to minimize the risk of hypoglycemia. Closely monitor blood glucose in patients on concomitant insulin therapy, especially those on high doses, or insulin secretagogue (e.g., sulfonylurea) when treating with Myalepta (see 7 WARNINGS AND PRECAUTIONS).
- Limit the use of Bacteriostatic Water for Injection (BWFI) to patients 3 years of age and older. (see 7 WARNINGS AND PRECAUTIONS).
- 7WARNINGS AND PRECAUTIONSWhen discontinuing Myalepta, 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 7 WARNINGS AND PRECAUTIONS).

4.2 Recommended Dose and Dosage Adjustment

The recommended daily dose of Myalepta 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.

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

Table 1 Myalepta 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)

Dosage Adjustment

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 by the recommended dose adjustment levels 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% haemoglobin A1c (HbA1c) reduction and/or 25% reduction in insulin requirements; and/or
- 15% reduction in triglycerides.

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.

Myalepta dose increases in adults and children based on incomplete clinical response can be considered after a minimum of 6 months following initiation of treatment.

Reductions in HbA1c and triglycerides 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 triglycerides 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.

The once daily dose of Myalepta can be increased by increments as shown in Table 1 to a maximum

daily dose.

Table 2 Starting 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

Special Populations

Pediatrics: The safety and efficacy of Myalepta 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 in children with generalised LD < 6 years of age (n=5; range: 1-4 years). Very limited data are available in children with partial LD <18 years of age (n=5; range: 15-17 years). Myalepta lyophilized powder when reconstituted with the diluent BWFI (benzyl alcohol preserved) should not be administered in patients under 3 years of age.

Geriatrics (≥65 years old): Clinical trials of Myalepta did not include sufficient numbers of patients aged 65 and older (n=1) to determine whether they respond differently from younger patients.

Renal impairment: Myalepta has not been studied in patients with impaired renal function.

Hepatic impairment: Myalepta has not been studied in patients with impaired hepatic function.

4.3 Reconstitution

Instruct patients to follow the directions below for reconstitution of the lyophilized powder. Patients should also be directed to the Educational Materials at (https://www.medisonpharma.com/product-monographs/):

a) Remove the vial containing the Myalepta lyophilized powder from the refrigerator and allow the vial to warm to room temperature (20°C to 25°C) prior to reconstitution.
b) Visually inspect the vial containing Myalepta. The cake of lyophilized powder should be intact and white in colour.
c) Myalepta 3 mg powder for solution for injection – for single use

Using a 1 mL syringe with a 21 gauge or smaller diameter needle, withdraw 0.6 mL of preservative-free sterile water for injection (SWFI) only. Do not reconstitute with other diluents.

Myalepta 5.8 mg powder for solution for injection – for single use
Using a 3 mL syringe with a 21 gauge or smaller diameter needle, withdraw 1.1 mL of preservative-free sterile water for injection (SWFI) only. Do not reconstitute with other diluents.

Myalepta 3 mg and 5.8 mg should be used immediately, and any remaining reconstituted solution should be discarded.

Myalepta 11.3 mg powder for solution for injection – For multi-use
Using a 3 mL syringe with a 21 gauge or smaller diameter needle, withdraw 2.2 mL of bacteriostatic water for injection (BWFI).

BWFI diluent contains 0.9% benzyl alcohol as a preservative.

Myalepta 11.3 mg reconstituted with BWFI should be used within 3 days of reconstitution when stored at 2°C to 8 °C and protected from light.

In patients under 3 years of age or with known hypersensitivity to benzyl alcohol, Myalepta 3 mg, 5.8 mg, and 11.3 mg vials must be reconstituted with SWFI (see 7 WARNINGS AND PRECAUTIONS).

Myalepta which has been reconstituted with SWFI must be used immediately and any unused portion discarded. Use of other reconstitution diluents should be avoided.

d) Inject the SWFI or BWFI into the vial containing the lyophilized powder of Myalepta, slowly injecting down the side of the vial. It is normal for some bubbles to form.
e) Remove the needle and syringe from the vial and **gently swirl** the contents to reconstitute. **Do not shake or vigorously agitate**. When properly mixed, the Myalepta reconstituted solution should be clear and free of clumps or dry powder, bubbles or foam. Do not use the solution if discoloured or cloudy, or if particulate matter remains.
f) After reconstitution each mL contains 5mg of Myalepta.
g) Regarding the compatibility of Myalepta reconstituted solution with other solutions:
    - Do not mix with, or transfer into, the contents of another vial of Myalepta.
    - Do not add other medications, including insulin. Use a separate syringe for insulin injections.

Table 3 Required syringe for Myalepta reconstitution with SWFI or BWFI

Syringe	Needle gauge and length
Myalepta 3 mg powder for solution for injection	
1.0 mL	21 gauge 40 mm needle
Myalepta 5.8 mg powder for solution for injection	
3.0 mL	21 gauge 40 mm needle
Myalepta 11.3 mg powder for solution for injection	
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
3.0 mL OR 2 x 1.0 mL*	30 gauge 13 mm needle	For doses of: > 5 mg – 10 mg / > 1.0 mL volume daily

*Doses exceeding 1mL can be administered as two injections using two 1.0 mL syringes.

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

Weight of child	Dose of Myalepta	Actual amount of solution*	Rounded amount of solution	'Unit' measurement volume in 0.3 mL syringe to inject
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 Total daily volume to be injected is total dose in mg divided by 5. 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 divided by 5, in this case it is 1.2 mg/5 = 0.24 mL which equals 24 units on the 0.3 mL insulin syringe. The maximum daily dose in males and females is 0.13 mg/kg or 0.026 mL/kg injection volume.
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 divided by 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.

4.4 Administration

Myalepta should be administered once daily at the same time every day. Myalepta can be administered any time of day without regard to the timing of meals.

Healthcare practitioners should instruct patients and caregivers on the proper subcutaneous injection technique with care 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. Never administer Myalepta intravenously or intramuscularly.

Instruct patients to follow the recommended injection technique:

a) Using a syringe with a needle appropriate for subcutaneous injection (see Table 4), withdraw the prescribed dose of Myalepta reconstituted solution.
b) Remove any large air pockets or large bubbles from the filled syringe prior to administration. Some small bubbles may remain in the syringe.
c) Administer Myalepta into the subcutaneous tissue of the abdomen, thigh or upper arm. Advise patients to use a different injection site each day when injecting in the same region. After choosing an injection site, pinch the skin and at a 45-degree angle, inject the Myalepta reconstituted solution subcutaneously. Avoid intramuscular injection, especially in patients with minimal subcutaneous adipose tissue.
d) Doses exceeding 1 mL can be administered as two injections (the total daily dose divided equally) to minimize potential injection-site discomfort due to injection volume. When dividing doses due to volume, doses can be administered one after the other.
e) In pediatric patients, small volumes for administration can result in medication errors when measured incorrectly. Smaller syringe sizes may be more appropriate for pediatric patients weighing less than or equal to 25 kg. Ensure the proper size syringe is selected.
f) When small doses/volumes are prescribed (e.g. children under 3 years of age where BWFI cannot be used), the vials will remain almost completely filled with product after withdrawal of the required dose. Remaining reconstituted product with WFI should be discarded after use.

Do not mix Myalepta with insulin. Use a separate syringe for each medication. If Myalepta and insulin are administered at the same time of day, they may be injected in the same body area using two different injection sites.

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

4.5 Missed Dose

Instruct patients that if a dose is missed, administer the dose as soon as noticed, and resume the normal dosing schedule the next day. A double dose should not be administered to make up for a missed dose.

5 OVERDOSAGE

In one post marketing case, an infant was exposed to a 10-fold overdose of Myalepta 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 (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS).

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 7 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous injection	3mg/ vial, 5.8 mg/ vial and 11.3 mg/ vial powder for solution for injection	Glutamic acid, glycine, polysorbate 20, sodium hydroxide, sucrose

The cake of lyophilised powder should be intact and white in colour.

Myalepta 3 mg/ vial 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/ vial 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/ vial 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.

7 WARNINGS AND PRECAUTIONS

General

Benzyl alcohol toxicity

Myalepta contains benzyl alcohol when reconstituted with BWFI. Myalepta contains no preservative when reconstituted with sterile Water for Injection (SWFI). The preservative benzyl alcohol has been associated with serious adverse events and death in pediatric patients, particularly in neonates and premature infants.

Medication Dosing Errors

In pediatric patients, small volumes for administration can result in medication errors. In a post marketing case, an infant was exposed to a 10-fold overdose of Myalepta 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.

Carcinogenesis and Mutagenesis

T cell lymphoma

Three cases of T-cell lymphoma have been reported in the Myalepta lipodystrophy clinical studies; all three patients had acquired generalised lipodystrophy. Two of these patients were diagnosed with

peripheral T-cell lymphoma while receiving Myalepta. Both had immunodeficiency and significant hematologic abnormalities including severe bone marrow abnormalities before the start of Myalepta treatment. A separate case of anaplastic large cell lymphoma was reported in a patient receiving Myalepta who did not have hematological abnormalities before treatment.

Lymphoproliferative disorders, including lymphomas, have been reported in patients with acquired generalised lipodystrophy not treated with Myalepta. A causal relationship between Myalepta treatment and the development and/or progression of lymphoma has not been established. Acquired lipodystrophies are associated with autoimmune disorders, and autoimmune disorders are associated with an increased risk of malignancies including lymphomas.

The benefits and risks of Myalepta treatment should be carefully considered in patients with acquired lipodystrophy and/or those with significant hematologic abnormalities (including leukopenia, neutropenia, bone marrow abnormalities, lymphoma, and/or lymphadenopathy), (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX and 8 ADVERSE REACTIONS).

Driving and Operating Machinery

Exercise caution when driving or operating a vehicle or potentially dangerous machinery. Myalepta has minor influence on the ability to drive and use machines due to fatigue and dizziness. (see 8 ADVERSE REACTIONS).

Endocrine and Metabolism

Hypoglycaemia with concomitant use of insulin and other antidiabetic medication

There is a risk of hypoglycaemia in patients treated with Myalepta who are on antidiabetic medications, in particular but not limited to insulin or insulin secretagogues (e.g. sulphonylureas). Large dose reductions of baseline insulin requirements may be needed in the first 2 weeks of treatment. Dose adjustments of other antidiabetic medications may also be needed 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. Hypoglycemia management should be reviewed and reinforced when initiating Myalepta therapy (see 8 ADVERSE REACTIONS).

Hepatic/Biliary/Pancreatic

Acute pancreatitis

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).

If a patient develops pancreatitis whilst being treated with MYALEPTA, it is advised that Myalepta be continued uninterrupted, as stopping treatment abruptly may exacerbate the condition. When discontinuing Myalepta, tapering of the dose over a two week period is recommended in conjunction with a low fat diet, see 4.2 Recommended Dose and Dosage Adjustment. 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 8 ADVERSE REACTIONS).

Immune

Hypersensitivity reactions

There have been reports of generalised hypersensitivity (e.g. anaphylaxis, urticaria or generalised rash) in patients using metreleptin. 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.

Antidrug Antibodies

In clinical trials, antidrug antibodies (ADA) to Myalepta occurred in 86% of a subset of evaluable patients in the GL and PL subgroup (48/56 patients). Neutralizing activity has been observed in 95% of patients in an extended subset (78/82 patients; see 8.2 Clinical Trial Adverse Reactions).

Serious and/or severe infections that were temporally associated with neutralizing antibodies against Myalepta occurred in 6 GL patients, and 2 PL patients in the PL subgroup. LD patients with a blocking activity against Myalepta and concurrent infections responded to standard of care treatment. In patients with serious and severe infections, continuation of Myalepta should be at the discretion of the prescriber. An association between the development of a blocking activity against Myalepta and serious and severe infections cannot be excluded.

Anti-metreleptin antibodies with neutralizing activity could inhibit endogenous leptin action and/or result in loss of Myalepta efficacy.

Test for anti-metreleptin antibodies with neutralizing activity in patients with severe infections or loss of efficacy during Myalepta treatment. Contact Chiesi (medinfo@amrytpharma.com) for neutralizing antibody testing (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX).

Autoimmune Diseases

Autoimmune disorder progression / flares, including severe autoimmune hepatitis, have been observed in some patients treated with Myalepta. Leptin plays a role in immune system homeostasis. Acquired lipodystrophies are associated with autoimmune disorders including autoimmune hepatitis and membranoproliferative glomerulonephritis. Cases of progression of autoimmune hepatitis and membranoproliferative glomerulonephritis (associated with massive proteinuria and renal failure) were observed in some patients with acquired generalised lipodystrophy treated with Myalepta. A causal relationship between Myalepta treatment and the development and/or 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.

Reproductive Health: Female and Male Potential

- **Fertility**

Unplanned pregnancies may occur due to effects on luteinizing hormone (LH).

7.1 Special Populations

7.1.1 Pregnant Women

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. In two pre- and postnatal development studies conducted in mice,

administration of metreleptin caused prolonged gestation and dystocia resulting in maternal death during parturition and lower survival of offspring in the immediate postnatal period at doses starting approximately at the maximum recommended clinical dose (see 16 NON-CLINICAL TOXICOLOGY).

7.1.2 Breast-feeding

It is unknown whether metreleptin or its metabolites are excreted in human milk; however, endogenous leptin is present in human milk. There are no available data on the effects of metreleptin on the breastfed infant or the effects on milk production.

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.

7.1.3 Pediatrics

The safety and efficacy of Myalepta 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 in children with generalised LD < 6 years of age (n=5; range: 1-4 years). Very limited data are available in children with partial LD <18 years of age (n=5; range: 15-17 years).

Myalepta lyophilized powder when reconstituted with the diluent BWFI (benzyl alcohol preserved) should not be administered in patients under 3 years of age.

7.1.4 Geriatrics

Clinical trials of Myalepta did not include sufficient numbers of patients aged 65 and older (n=1) to determine whether they respond differently from younger patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most commonly reported adverse events were weight decreased (17%), hypoglycaemia (14%), and fatigue (7%) (see 4.1 Dosing Considerations, 7 WARNINGS AND PRECAUTIONS and 8.2 Clinical Trial Adverse Reactions).

In the clinical trials (study NIH 991265/20010769 and study FHA101), serious AEs reported in >1 GL patient were abdominal pain and pancreatitis (4 patients each, 5%); and pneumonia, sepsis, liver disorder (worsening underlying liver disease), cardiac failure and liver function test increased (2 patients each, 3%). The most common SAEs in the PL subgroup were abdominal pain (3 patients, 8%) and cellulitis (2 patients, 5%). Autoimmune diseases with cases of progression of autoimmune hepatitis and membranoproliferative glomerulonephritis (associated with massive proteinuria and renal failure) were observed in some patients with acquired generalised lipodystrophy treated with Myalepta (See 7 WARNINGS AND PRECAUTIONS).

Overall, 7 (6%) of the patients withdrew due to a treatment-emergent adverse event, including 6 (8%) of 75 patients with GL and 1 (3%) of 38 patients in the PL subgroup. The treatment-emergent adverse events leading to discontinuation in GL (reported in 1 patient each) were: diabetes mellitus inadequate

control and blood triglycerides increased, renal failure, peripheral T-cell lymphoma unspecified, chronic hepatic failure, cardiac arrest, adenocarcinoma and in the PL subgroup the treatment-emergent adverse event leading to discontinuation was hypoxic-ischemic encephalopathy. Five (4%) of the patients died during the studies, including 4 out of the 6 patients with GL who withdrew due to a treatment-emergent adverse event (renal failure, chronic hepatic failure, cardiac arrest and adenocarcinoma) and the 1 patient in the PL subgroup (hypoxic-ischemic encephalopathy).

Adverse drug reactions identified in the post-market setting are described below in 8.5 Liver function

In Study NIH 991265/2001769, elevations of ALT or AST to a level above 5.0 x ULN were noted in 4 patients with GL. Three of these four patients had AEs reported in association with these elevations: hepatic enzyme increased, progression of underlying liver disease (liver disorder) and hypoalbuminemia, and ALT increased. All of these patients had hepatic disease at baseline, including autoimmune hepatitis, hepatic fibrosis, non-alcoholic steatohepatitis (NASH), hepatic steatosis, or hepatomegaly.

During Study FHA101, AEs of liver function test increased were reported in 2 patients in the GL group (in one of them AST was elevated to a level 5.0-20.0 x ULN) and 1 patient in the PL subgroup (elevation of both ALT and AST to a level 1.0-3.0 x ULN).

Proteinuria

In the NIH 991265/2001769 study, proteinuria was reported as an AE (1 of them SAE) in 5 patients in the GL group, all of whom had high protein excretion rates at baseline. There were no AEs of proteinuria in the PL subgroup.

Urinalysis data was not captured for patients in the FHA101 study.

Post-Market Adverse Reactions.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 ≥ 6.5%.

A total of 113 patients (aged 1 year to 68 years) with generalised and partial LD received Myalepta during clinical studies. The duration of follow-up ranged from 79 days to 14 years, including 75 patients with GL and 38 patients in the PL subgroup.

The treatment-emergent adverse events identified in patients treated with Myalepta (frequencies ≥ 5%) are presented in Table 8.

Table 8 Treatment-emergent adverse events reported in clinical trials (studies NIH 991265/20010769, FHA101) (frequencies ≥ 5%)

System Organ Class	MedDRA Preferred Term	Generalised Lipodystrophy (N=75) n(%)	Partial Lipodystrophy (N=38) n(%)	Overall (N=113) n(%)
Gastrointestinal disorders	Abdominal pain	13 (17.3%)	7 (18.4%)	20 (17.7%)
	Constipation	4 (5.3%)	3 (7.9%)	7 (6.2%)
	Nausea	7 (9.3%)	7 (18.4%)	14 (12.4%)
	Vomiting	3 (4.0%)	4 (10.5%)	7 (6.2%)
General disorders and administration site conditions	Fatigue	6 (8.0%)	4 (10.5%)	10 (8.8%)
Infections and infestations	Ear infection	8 (10.7%)	0 (0.0%)	8 (7.1%)
	Sinusitis	2 (2.7%)	4 (10.5%)	6 (5.3%)
	Upper respiratory tract infection	7 (9.3%)	4 (10.5%)	11 (9.7%)
	Urinary tract infection	4 (5.3%)	4 (10.5%)	8 (7.1%)
Investigations	Weight decreased	18 (24.0%)	2 (5.3%)	20 (17.7%)
Metabolism and nutrition disorders	Decreased appetite	8 (10.7%)	1 (2.6%)	9 (8.0%)
	Hypoglycaemia	12 (16.0%)	9 (23.7%)	21 (18.6%)
Musculoskeletal and connective tissue disorders	Arthralgia	7 (9.3%)	3 (7.9%)	10 (8.8%)
	Back pain	5 (6.7%)	3 (7.9%)	8 (7.1%)
	Pain in extremity	4 (5.3%)	2 (5.3%)	6 (5.3%)
Nervous system disorders	Headache	9 (12.0%)	1 (2.6%)	10 (8.8%)
Psychiatric disorders	Anxiety	6 (8.0%)	2 (5.3%)	8 (7.1%)
Respiratory, thoracic and mediastinal disorders	Cough	4 (5.3%)	2 (5.3%)	6 (5.3%)
Skin and subcutaneous tissue disorders	Alopecia	3 (4.0%)	3 (7.9%)	6 (5.3%)
Vascular disorders	Hypertension	5 (6.7%)	1 (2.6%)	6 (5.3%)

System organ classes and preferred terms are coded using the MedDRA dictionary (Version 19.0)

Acute pancreatitis

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 (See 7 WARNINGS AND PRECAUTIONS).

Hypoglycaemia

Myalepta may decrease insulin resistance in diabetic patients, resulting in hypoglycaemia in patients with LD and co-existing diabetes. Hypoglycaemia was reported in 12 (16%) of the 75 GL patients. Among the 38 patients in the PL subgroup, 9 (24%) experienced hypoglycaemia on study, w All reports were mild to moderate in severity, and none led to treatment withdrawal.

There was no pattern of onset; hypoglycemia events occurred at varying times relative to treatment start from the first week to 2 to 10 years after treatment start. Generally, the events were managed by food intake, and 4 patients were reported to have a modification in their antidiabetic medication as action for the hypoglycaemia.

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 (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX and 7 WARNINGS AND PRECAUTIONS).

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. The immunogenicity assays utilized in clinical trials lacked sensitivity, resulting in potential underestimation of the number of samples positive for anti-metreleptin antibodies with neutralizing activity. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to metreleptin with the incidence of antibodies to other products may be misleading.

Data for binding ADAs was available for 56 (50%) of the 113 patients in the GL and PL subgroups combined. Among these 56 patients, 48 (86%) were positive for ADAs and 8 (14%) were negative. Blocking (neutralizing) activity was observed in 95% of an extended set of patients (78 out of 82 patients). The incompleteness of the current immunogenicity database precludes understanding of the magnitude and persistence of the observed ADA responses.

Peak ADA titer data were available for a subset of 31 patients with GL and 12 patients in the PL subgroup. Across these 43 patients, peak titres were ≤125 for the majority of patients (23, 53%); peak titres were 625 or 3125 for 15 patients (35%) and ≥15,625 for 5 patients (12%).

Serious and/or severe infections that were temporally associated with blocking (neutralising) activity against metreleptin occurred in 6 GL patients and in 2 patients in the PL subgroup. 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, 2 episodes of serious and severe cellulitis in 2 patients, one of them together with serious and severe pharyngitis due to severe

streptococcal infection, the other developed to serious and severe osteomyelitis, and 1 episode of non-serious severe ear infection in 1 patient. LD patients with a blocking activity against metreleptin and concurrent infections responded to standard of care treatment (see 7 WARNINGS AND PRECAUTIONS).

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.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Across two completed clinical studies (NIH 991265/20010769 and FHA101), there were 53 paediatric patients (5 in the subgroup of partial LD patients and 48 with generalised LD) enrolled and exposed to Myalepta. Very limited data are available in children with generalised LD < 6 years of age (n=5; range: 1-4 years). Very limited data are available in children with partial LD <18 years of age (n=5; range: 15-17 years). Overall, the observed safety and tolerability profile of Myalepta appears similar in children and adults.

In generalised LD patients, the overall incidence of adverse reactions appears 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.

8.3 Less Common Clinical Trial Adverse Reactions

Table 9 Treatment related adverse reactions that were reported in clinical trials (studies NIH 991265/20010769, FHA101) with a frequency below 5%

System Organ Class	MedDRA Preferred Term	Generalised Lipodystrophy (N=75) n (%)	Partial Lipodystrophy (N=38) n (%)	Overall (N=113) n (%)
Blood and lymphatic system disorders	Iron deficiency anaemia	1 (1.3%)	0 (0.0%)	1 (0.9%)
Cardiac disorders	Tachycardia	1 (1.3%)	0 (0.0%)	1 (0.9%)
Gastrointestinal disorders	Abdominal pain	1 (1.3%)	1 (2.6%)	2 (1.8%)
	Anal incontinence	1 (1.3%)	0 (0.0%)	1 (0.9%)
	Dyspepsia	1 (1.3%)	0 (0.0%)	1 (0.9%)
	Nausea	2 (2.7%)	2 (5.3%)	4 (3.5%)
	Vomiting	1 (1.3%)	0 (0.0%)	1 (0.9%)

System Organ Class	MedDRA Preferred Term	Generalised Lipodystrophy (N=75) n (%)	Partial Lipodystrophy (N=38) n (%)	Overall (N=113) n (%)
General disorders and administration site conditions	Chest pain	1 (1.3%)	0 (0.0%)	1 (0.9%)
	Injection site bruising	1 (1.3%)	1 (2.6%)	2 (1.8%)
	Injection site erythema	2 (2.7%)	0 (0.0%)	2 (1.8%)
	Injection site induration	1 (1.3%)	0 (0.0%)	1 (0.9%)
	Injection site inflammation	1 (1.3%)	0 (0.0%)	1 (0.9%)
	Injection site pain	0 (0.0%)	1 (2.6%)	1 (0.9%)
	Injection site reaction	2 (2.7%)	2 (5.3%)	4 (3.5%)
	Injection site urticaria	1 (1.3%)	1 (2.6%)	2 (1.8%)
Investigations	Liver function test increased	1 (1.3%)	0 (0.0%)	1 (0.9%)
	Neutralising antibodies	4 (5.3%)	0 (0.0%)	4 (3.5%)
Metabolism and nutrition disorders	Decreased appetite	4 (5.3%)	0 (0.0%)	4 (3.5%)
Musculoskeletal and connective tissue disorders	Arthralgia	0 (0.0%)	1 (2.6%)	1 (0.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Anaplastic large-cell lymphoma	1 (1.3%)	0 (0.0%)	1 (0.9%)
Nervous system disorders	Disturbance in attention	0 (0.0%)	1 (2.6%)	1 (0.9%)
	Dizziness	0 (0.0%)	1 (2.6%)	1 (0.9%)
	Headache	1 (1.3%)	1 (2.6%)	2 (1.8%)
Renal and urinary disorders	Urinary incontinence	1 (1.3%)	0 (0.0%)	1 (0.9%)
Reproductive system and breast disorders	Menorrhagia	2 (2.7%)	0 (0.0%)	2 (1.8%)
	Vaginal haemorrhage	1 (1.3%)	0 (0.0%)	1 (0.9%)
Respiratory, thoracic and mediastinal disorders	Respiratory distress	1 (1.3%)	0 (0.0%)	1 (0.9%)
Skin and subcutaneous tissue disorders	Alopecia	2 (2.7%)	2 (5.3%)	4 (3.5%)
	Night sweats	0 (0.0%)	1 (2.6%)	1 (0.9%)
Vascular disorders	Hypertension	1 (1.3%)	0 (0.0%)	1 (0.9%)

System organ classes and preferred terms are coded using the MedDRA dictionary (Version 19.0)

Table 10 Serious or severe treatment-emergent adverse events that were reported in clinical trials with a frequency less than 5% (2 to 5 patients)

System Organ Class	MedDRA Preferred Term	Generalised Lipodystrophy (N=75) n(%)	Partial Lipodystrophy (N=38) n(%)	Overall (N=113) n(%)
Cardiac disorders	Cardiac failure	2 (2.7%)	0 (0.0%)	2 (1.8%)
Gastrointestinal disorders	Lower gastrointestinal haemorrhage	1 (1.3%)	1 (2.6%)	2 (1.8%)
	Nausea	2 (2.7%)	0 (0.0%)	2 (1.8%)
	Pancreatitis	4 (5.3%)	1 (2.6%)	5 (4.4%)
	Vomiting	2 (2.7%)	0 (0.0%)	2 (1.8%)
Hepatobiliary disorders	Liver disorder	2 (2.7%)	0 (0.0%)	2 (1.8%)
Infections and infestations	Cellulitis	0 (0.0%)	2 (5.3%)	2 (1.8%)
	Pneumonia	3 (4.0%)	0 (0.0%)	3 (2.7%)
	Sepsis	2 (2.7%)	0 (0.0%)	2 (1.8%)
Investigations	Liver function test increased	2 (2.7%)	0 (0.0%)	2 (1.8%)
	Neutralising antibodies	4 (5.3%)	0 (0.0%)	4 (3.5%)
Musculoskeletal and connective tissue disorders	Back pain	1 (1.3%)	2 (5.3%)	3 (2.7%)
	Pain in extremity	3 (4.0%)	0 (0.0%)	3 (2.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Peripheral T-cell lymphoma unspecified	2 (2.7%)	0 (0.0%)	2 (1.8%)
Psychiatric disorders	Suicidal ideation	1 (1.3%)	1 (2.6%)	2 (1.8%)
Renal and urinary disorders	End stage renal disease	1 (1.3%)	1 (2.6%)	2 (1.8%)
	Proteinuria	2 (2.7%)	0 (0.0%)	2 (1.8%)
Respiratory, thoracic and mediastinal disorders	Dyspnoea	2 (2.7%)	0 (0.0%)	2 (1.8%)

System organ classes and preferred terms are coded using the MedDRA dictionary (Version 19.0)

8.5 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Liver function

In Study NIH 991265/2001769, elevations of ALT or AST to a level above 5.0 x ULN were noted in 4 patients with GL. Three of these four patients had AEs reported in association with these elevations:

hepatic enzyme increased, progression of underlying liver disease (liver disorder) and hypoalbuminemia, and ALT increased. All of these patients had hepatic disease at baseline, including autoimmune hepatitis, hepatic fibrosis, non-alcoholic steatohepatitis (NASH), hepatic steatosis, or hepatomegaly.

During Study FHA101, AEs of liver function test increased were reported in 2 patients in the GL group (in one of them AST was elevated to a level 5.0-20.0 x ULN) and 1 patient in the PL subgroup (elevation of both ALT and AST to a level 1.0-3.0 x ULN).

Proteinuria

In the NIH 991265/2001769 study, proteinuria was reported as an AE (1 of them SAE) in 5 patients in the GL group, all of whom had high protein excretion rates at baseline. There were no AEs of proteinuria in the PL subgroup.

Urinalysis data was not captured for patients in the FHA101 study.

8.6 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval use of Myalepta. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Incorrect dose administered, accidental overdose
- Injection site reaction, including inflammation and hyperpigmentation.

Medication Dosing Error

In one post marketing case, an infant was exposed to a 10-fold overdose of MYALEPTA 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 (see 7 WARNINGS AND PRECAUTIONS).

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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.

9.3 Drug-Behavioural Interactions

Interactions with behaviours have not been established.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Metreleptin mimics the physiological effects of leptin by binding to and activating the human leptin receptor (ObR), 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.

10.2 Pharmacodynamics

No formal pharmacodynamic studies have been performed with metreleptin.

10.3 Pharmacokinetics

There are very limited data on the pharmacokinetics of metreleptin following subcutaneous (SC) administration in patients with lipodystrophy, and the impact of disease etiology (generalised or partial LD) on metreleptin PK is unknown. The metreleptin assay measures both endogenous leptin as well as exogenously administered metreleptin.

Table 11 Pooled Summary of Metreleptin Pharmacokinetic Parameters in four adult partial lipodystrophy patients and one pediatric generalised lipodystrophy patient 16 years of age.

	C_{max} (ng/mL/kg)	T_{max} (h)	AUC_{0-10} (ng•h/mL/kg)
Baseline adjusted and dose normalised mean (SD)	9.02 (5.555)	4.00 (2.0, 6.0)	58.55 (32.564)

C_{max}: Observed peak serum metreleptin concentration
T_{max}: Time of peak serum metreleptin concentration (C_{max}), expressed as median (range)
AUC_{0-10}: Area under the concentration versus time curve from time 0 to 10 hours

Absorption

Metreleptin exposure increased in an approximately dose-proportional fashion following SC administration of single doses ranging from 0.01 to 0.3 mg/kg in healthy subjects. The mean metreleptin T_{max} was 4.0 to 4.8 hours in healthy subjects. The median T_{max} of metreleptin was 4 hours (range: 2 to 8 hours; N=5) following single-dose administration of metreleptin in lipodystrophy patients (Table 11).

Distribution

Observed apparent volume of distribution during the terminal phase (V_z/F) following SC bolus dosing in healthy subjects ranged from 803.8 mL/kg, to 444.4 mL/kg, at doses ranging from 0.01 to 0.3 mg/kg, respectively.

Metabolism

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. The half-life of metreleptin in LD patients is unknown. A higher metreleptin exposure is observed with higher ADA levels.

Special Populations and Conditions

- **Pediatrics**

  Pharmacokinetic data were collected for 1 pediatric patient 16 years of age with generalised lipodystrophy. Metreleptin exposure and ADA levels increased from baseline to 3 months.

  Very limited data are available in children with generalised LD < 6 years of age (n=5; range: 1-4 years)). Very limited data are available in children with partial LD <18 years of age (n=5; range: 15-17 years). Health Canada has not authorized an indication for use in general LD patients < 2 years of age and for partial LD patients < 12 years of age.

- **Age, Sex, Race, Body Mass Index** Specific clinical studies have not been conducted to assess the effect of age, sex, race, or body mass index on the pharmacokinetics of metreleptin in patients with lipodystrophy.
- **Hepatic Insufficiency** No formal pharmacokinetic studies were conducted in patients with hepatic impairment.
- **Renal Insufficiency** No formal pharmacokinetic studies were conducted in patients with renal impairment.

11 STORAGE, STABILITY AND DISPOSAL

- Myalepta should be stored in the refrigerator at 2°C to 8°C and protected from light until preparing for use. Keep Myalepta vials in the carton when not in use.
- Myalepta should not be used past the expiration date.
- Do not freeze Myalepta.
- Do not use if the white lyophilized cake is discoloured.

- Use with BWFI: when 11.3 mg Myalepta is reconstituted with BWFI, the vial can be used for multiple doses within 3 days when stored in the refrigerator at 2°C to 8°C and protected from light.
- Use with SWFI: when Myalepta is reconstituted with SWFI, the vial can be used for a single dose only and should be administered immediately. Unused reconstituted solution cannot be saved for later use and should be discarded.
- After reconstitution, the vials should not be frozen (below 0°C) or shaken vigorously. If the reconstituted product is inadvertently frozen, it should be thrown away.
- Keep out of the reach of children.

12 SPECIAL HANDLING INSTRUCTIONS

Not Applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Metreleptin

Chemical name: recombinant methionyl-human leptin

Molecular formula and molecular mass: $C_{714}H_{1167}N_{191}O_{221}S_6$
molecular weight of approximately 16.15 kDa

Structural formula: Metreleptin is a 147 amino acid polypeptide with one disulphide bond between Cys-97 and Cys-147.

Physicochemical properties: Metreleptin is an acidic protein with a pI of 6.2. Its extinction coefficient is 0.97 mL mg-1 cm-1 at 280 nm. The solubility of metreleptin at pH 4 is in excess of 70 mg/mL, declining to about 2 mg/mL at neutral pH. Metreleptin self-associates to form soluble oligomers in aqueous solution. This reversible self-association is concentration-, temperature- and time-dependent.

14 CLINICAL TRIALS

14.1 Trial design and study demographics

Table 12 Summary of patient demographics for clinical trials in congenital or acquired generalised LD or familial or acquired partial LD

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age	Sex
NIH 991265/ 20010769	Open label, single arm study	Metreleptin subcutaneous injection weight-based dosing Up to 14 years	107 (66 GL and 41 PL). Of 41 PL patients, 31 were included in the PL Subgroup*	GL: 15 years PL Subgroup*: 38 years	GL: 77% F, 23% M PL Subgroup*: 97% F, 3% M

* PL subgroup = patients with baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L.

The efficacy of treatment with metreleptin was evaluated in an open-label, single-arm study, Study NIH 991265/20010769. The pilot study (991265) was a short-term dose-escalation study (up to 8 months) and the long-term study (20010769) allowed for the rollover of patients from the pilot study, as well as for direct enrolment of new patients. Male and female patients with congenital or acquired generalised LD or familial or acquired partial LD were enrolled if they had at least one of the following 3 metabolic abnormalities:

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

Concomitant antihyperglycemic and lipid-altering medication dosage regimens were not held constant during the study; for example, some patients treated with insulin had their dosage increased and others had large reductions or discontinuation of insulin.

Generalised Lipodystrophy (GL)

A total of 66 GL patients were enrolled and treated, including 45 patients with congenital GL (CGL) and 21 patients with acquired GL (AGL). 77% of the patients were females. 47% of the patients were Caucasian, 3% were Hispanic, 24% were Black. The median age at baseline was 15 years (range: 1 to 68 years); 45 (68%) of the patients were pediatric (<18 years of age) patients. Median fasting leptin concentration at baseline was 1.0 ng/mL (range: 0.3-3.3 ng/mL) in males and 1.1 ng/mL in females.

Median overall duration of treatment was 49.9 months (range: 3.4 to 166.0 months). Myalepta 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 patients weighing over 40kg (48 patients) in the first year of treatment 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.

Partial Lipodystrophy (PL)

A total of 41 PL patients were enrolled, of which 31 patients were included in the PL subgroup (PL patients with baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L) and were analyzed in a post-hoc analysis. The PL Subgroup included 27 patients with familial partial PL (FPLD) and 4 patients with acquired PL (APL). 30 (97%) of the patients in the PL Subgroup were females. The PL Subgroup included 84% Caucasian patients, 7% Hispanic patients and no Black patients. The median age at baseline was 38 years (range: 15 to 64 years); 5 (16%) of the patients were pediatric (<18 years of age) patients. Median fasting leptin concentration at baseline was 5.9 ng/mL (range 1.6-16.9 ng/mL) in the PL subgroup (the 1 male patient had fasting leptin concentration of 5.4 ng/mL at baseline).

Median overall duration of treatment was 29.3 months (range: 6.7 to 167.7 months). Myalepta was administered subcutaneously either once daily or twice daily (in two equal doses). All 31 patients in the PL subgroup weighed over 40kg. The weighted average daily dose in the first year of treatment was 7.0 mg and 8.4 mg over the study period.

14.2 Study Results

The efficacy of metreleptin was measured using the following co-primary efficacy endpoints:

- Absolute change from baseline in HbA1c at Month 12, and
- Relative change from baseline in fasting serum triglycerides (TGs) at Month 12

The descriptive findings for generalised and partial lipodystrophy are shown in Table 12 and Table 13, respectively.

Table 13 Results for the primary outcome in an open-label, single-arm study (NIH 991265/20010769) in patients with generalised lipodystrophy

Parameter		Baseline	Month 12	Change from baseline at month 12
HbA1c (%)	N Mean (SD) [95% CI]	62 8.6 (2.33) [8.0, 9.2]	59 6.4 (1.68) [6.0, 6.9]	59 -2.2 (2.15) [-2.7, -1.6]
Triglycerides (mmol/L)	N Median (Q1, Q3) Mean (SD) [95% CI]	61 4.6 (2.5, 13.8) 14.7 (25.66) [8.1, 21.2]	58 2.3 (1.5, 3.5) 4.5 (6.10) [2.9, 6.1]	57 -53.3 (-77.0, -0.2) -32.1% (71.28%) [-51.0%, -13.2%]

Abbreviations: CI = confidence interval; HbA1c = haemoglobin A1c; SD = standard deviation
Notes:
a Ns presented in table body are the number of patients with changes from baseline analysed for that parameter.

Table 14 Results for the primary outcome in an open-label, single-arm study (NIH 991265/20010769) in patients with partial lipodystrophy with baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L

Parameter		Baseline	Month 12	Change from baseline at month 12
HbA1c (%)	N Mean (SD) [95% CI]	29 8.8 (1.91) [8.1, 9.5]	27 8.0 (1.83) [7.2, 8.7]	27 -0.9 (1.23) [-1.4, -0.4]
Triglycerides (mmol/L)	N Median (Q1, Q3) Mean (SD) [95% CI]	29 5.7 (2.9, 14.0) 15.7 (26.42) [5.6, 25.7]	27 3.4 (2.0, 5.6) 6.0 (8.41) [2.7, 9.4]	27 -37.9% (-54.2, -17.3) -37.4% (30.81%) [-49.6%, -25.2%]

Abbreviations: CI = confidence interval; HbA1c = haemoglobin A1c; SD = standard deviation
Notes:
a Ns presented in table body are the number of patients with changes from baseline analysed for that parameter.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Two pivotal repeat-dose toxicity studies were conducted in mice and dogs. Consistent findings between the two species included exaggerated pharmacodynamic effects that caused reductions in body weight, food consumption, and atrophy of adipose tissue.

Metreleptin (0, 0.3, 1, 3, 10, 30 mg/kg) was administered subcutaneous once daily for 3 or 6 months (including 28-day recovery assessment after 6-month treatment) to mice, the no observed adverse effect level (NOAEL) was determined to be 1 mg/kg/day. No adverse effects were observed at doses ranging between (0.12 and 0.24-fold the maximum recommended clinical dose, based on body surface area of a 20- and 60-kg patient, respectively). The principal toxic effects noted at higher doses were decreased thymus weight and spleen weight, centrilobular hepatocyte degeneration, lymphocytolysis in lymphoid tissues and gastric mucosal erosion. Abscess of the preputial glands with skin ulceration and osteosarcoma were each observed in one low-dose mouse, while lymphosarcoma was observed in one high-dose mouse; the relationship of these findings to test article is unknown.

Metreleptin (0.05, 0.15, 0.5, 1.5, 5 mg/kg) was administered subcutaneous once daily to dogs for 1, 3 or 6 months, a NOAEL could not be established due to adverse effects observed at all doses. The lowest observed adverse effect level (LOAEL) was approximately equal to the maximum recommended clinical dose, based on body surface area of a 20- and 60-kg patient, respectively. The findings included hemorrhage and inflammation in the GI tract, gingival tissues, conjunctiva of the eye, urinary bladder; perivasculitis in adipose tissue, liver and kidney; hyperplasia of the lymph nodes; and thyroid hypertrophy/hyperplasia.

Carcinogenicity: Carcinogenicity studies have not been conducted with metreleptin.

Genotoxicity: *In vitro,* metreleptin was demonstrated to be non-mutagenic when tested in the bacterial reverse mutation (AMES) assay and did not induce chromosome aberrations in human peripheral blood lymphocytes. Two separate hypoxanthine-guanine phosphorybosyl transferase (HGPRT) forward gene mutation assays undertaken using Chinese Hamster Ovary (CHO) cells were also judged to be negative. During i*n vivo* studies*,* clastogenicity was investigated in a mammalian erythrocyte micronucleus assay in CD-1 male mice using single i.v. doses of 0, 10, 30 and 100 mg/kg. No increases in micronucleated polychromatic erythrocytes were observed in the test animals at 24 and 48 hours after dosing.

Reproductive and Developmental Toxicology: A fertility study, an embryofetal development study, and two pre- and postnatal development studies were conducted in mice with metreleptin. A normal requirement, an embryofetal development study conducted in a second species (such as rabbits), was not available for metreleptin. Based on the reproductive toxicity studies that were conducted, no adverse effects on mating, fertility or embryo foetal development were observed at doses ranging between 4 and 7-fold the maximum recommended clinical dose, based on body surface area of a 20- and 60-kg patient, respectively.

Two pre- and postnatal development studies were conducted in mice. In the first study, metreleptin (3, 10, 30 mg/kg) was administered subcutaneous once daily to mated female mice from gestational day (GD) 6 to lactation day 20 (LD). In the second study, Metreleptin 10 mg/kg was administered subcutaneous once daily to mated female mice for different treatment durations (GD 6-15, GD 15-18, or GD 6-18). A NOAEL could not be determined for either study because metreleptin caused prolonged gestation and dystocia at all tested doses. The LOAEL was approximately equal 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 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 t1/2 values was also observed in pregnant mice compared to non pregnant mice. The greater metreleptin exposure and longer t1/2 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.

Juvenile Toxicity: No studies with direct administration of metreleptin to juvenile animals have been conducted.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

MYALEPTA

Metreleptin for injection

Read this carefully before you start taking **Myalepta** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Myalepta**.

Serious Warnings and Precautions

- Risk for loss of naturally-occurring (endogenous) leptin activity or loss of Myalepta efficacy due to neutralizing antibodies. Antibodies are made in the blood of people who use Myalepta that may reduce how well the leptin in your body (endogenous) works or how well Myalepta works. Side effects may include:
    - infection
    - problems with blood sugar, including diabetes
    - an increase in the amount of fat in your blood (triglycerides)

  If you experience these effects while taking Myalepta you should talk to your healthcare provider about contacting the manufacturer for neutralizing antibody testing (contact: medinfo@amrytpharma.com).
- Risk of lymphoma (a type of blood cancer) in people with generalized lipodystrophy whether or not they are using Myalepta. You may be at higher risk of getting a lymphoma when using Myalepta.

What is Myalepta used for?

Myalepta is used to treat the complications of not having enough leptin in patients with lipodystrophy. It is used in adults, adolescents and children 2 years or over:

- who have generalised lipodystrophy (the whole of your body does not have enough fatty tissue)

It is used, when there is ongoing metabolic disease and other treatments have been ineffective, in adults, and adolescents 12 years or over:

- who have partial lipodystrophy which is inherited (also called congenital or familial lipodystrophy)
- or partial lipodystrophy has been caused by your body's response to something such as a viral illness (also called acquired lipodystrophy).

How does Myalepta work?

Natural leptin is produced by fatty tissue and has many functions in the body including:

- controlling how hungry you feel and your energy levels
- helping the insulin in your body manage sugar levels.

Myalepta works by copying the effects of leptin. This improves the ability of the body to control energy levels.

What are the ingredients in Myalepta?

Medicinal ingredients: metreleptin

Non-medicinal ingredients: Glutamic acid, glycine, polysorbate 20, sodium hydroxide, sucrose

Myalepta comes in the following dosage forms:

Powder for solution, 3 mg/ vial, 5.8 mg/ vial and 11.3 mg/ vial

Do not use Myalepta if you:

- are allergic to any ingredients in this drug
- have general obesity that is not caused by generalised or partial lipodystrophy
- Have HIV-related lipodystrophy

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Myalepta. Talk about any health conditions or problems you may have, including if you:

- you are pregnant
- you have ever had problems with your blood (such as a low blood count)
- you have ever had inflammation of an organ called the pancreas ('pancreatitis')
- you have or ever have had problems with your immune system (autoimmune disease including autoimmune-related liver problems)
- you have ever had a type of cancer called lymphoma

Other warnings you should know about:

Lymphoma

- People with lipodystrophy can get a type of blood cancer called lymphoma, whether or not they are using Myalepta.
- However, you may be at higher risk of getting a lymphoma when using the medicinal product.
- Your doctor will decide if you should use Myalepta and will monitor you during treatment.

Serious and severe infections

- While being treated with Myalepta, your body produces antibodies that may increase the risk of developing serious or severe infections. Tell your doctor straight-away if you develop a high temperature, accompanied by increasing tiredness.

Low blood sugar with insulin or other antidiabetic medicines

- If you are using a medicine such as insulin or other medicines to treat diabetes, your doctor will closely monitor your blood sugar. Your doctor will change your dose of insulin or other medicines if needed.
- This is to prevent your blood sugar from getting too low ('hypo-glycaemia'). Signs of low blood sugar include shaking, sweating, rapid heartbeat, change in vision, hunger, headache and change in mood.

Autoimmune Disease

- People who have or have had problems with their immune system (autoimmune disease, including autoimmune-related liver problems) may have worsening of their symptoms with

Myalepta. Talk to your healthcare provider about what symptoms you should watch for that would warrant further testing.

Allergic reactions

- While being treated with Myalepta, you may get an allergic reaction. Tell your doctor straight-away if you have any symptoms of an allergic reaction.

Fertility

- Myalepta might increase fertility in women with lipodystrophy.

Pregnancy and breast-feeding

- If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.
- You should not use Myalepta if you are pregnant or might become pregnant. This is because it is not known how Myalepta will affect your unborn baby.
- Women who could get pregnant should use effective contraception, including non-hormonal methods such as condoms, while using Myalepta.
- Talk to your doctor if you are breast-feeding. You and your doctor will decide whether or not to continue breast-feeding while using this medicine.
- It is not known if Myalepta will pass into breast milk.

Driving and using machines

- Myalepta has minor influence on the ability to drive and use machines. You might feel dizzy or tired when using this medicine. If this happens, do not drive or use any tools or machines. Talk to your doctor if you are not sure.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Myalepta:

- statins for reducing cholesterol (such as atorvastatin)
- blood pressure medicines called ‘calcium channel blockers’
- theophylline used in lung problems such as asthma
- blood-thinning medicines (such as warfarin or phenprocoumon)
- medicines for epilepsy or fits (such as phenytoin)
- medicines which suppress the immune system (such as cyclosporine)
- medicines for sleep or anxiety called ‘benzodiazepines’

How to take Myalepta:

- Myalepta is an injection once a day under the skin (‘subcutaneous injection’). This medicine is for use in children aged 2 years and above, adolescents and adults with generalised lipodystrophy; it is also for use in children aged 12 years and above, adolescents and adults with partial lipodystrophy.
- While using this medicine, you or your child will be monitored by your doctor, who will decide the dose you or your child should use.
- See INSTRUCTIONS FOR USE for full administration instructions.

Your doctor may decide that you inject yourself. Your doctor, nurse or pharmacist will show you how to prepare and inject this medicine.

- Do not try to prepare the medicine or inject yourself if you have not been trained.

Usual dose:

How much to inject

Your dose of Myalepta may change over time depending on how this medicine works for you. The Myalepta powder is dissolved by mixing it with water for injections to make the solution for injecting. Sterile water for injection should be used in infants less than 3 years of age, or in adults with a known hypersensitivity to benzyl alcohol. Bacteriostatic water for injection should be used for older children and adults. Read the INSTRUCTIONS FOR USE for how to make the solution before injecting.

Your doctor will have prescribed the correct dose for you, based on the following:

- If you weigh 40 kg or less:
  - A starting dose is 0.06 mg (0.012 mL of solution) for each kilogram of body weight.
- If you are male and weigh more than 40 kg:
  - A starting dose is 2.5 mg (0.5 mL of solution).
- If you are female and weigh more than 40 kg:
  - A starting dose is 5 mg (1 mL of solution).

Your doctor or pharmacist will tell you how much of the solution to inject. If you are not sure how much of the solution to inject, talk to your doctor or pharmacist before injecting.

The syringe you need to use to inject this medicine depends on the dose prescribed for you.

- See the INSTRUCTIONS FOR USE to find out which syringe to use.

To know how much medicine to inject (in mL), you divide your dose (in mg) by 5.

- For example, if you have been prescribed a 5 mg dose of Myalepta, 5 mg divided by 5 gives you 1 mL which is the amount you need to inject of the solution, using a 1 mL syringe.

If your dose is 1.50 mg (0.30 mL of solution) or less, you will need to use a 0.3 mL syringe.

- The 0.3 mL syringe will show the injection amount in ‘Unit’ instead of ‘mL’. See the INSTRUCTIONS FOR USE for more information on reading and using the different syringes.
- To know how much solution to inject (in Units), divide your dose (in mg) by 5, and then multiply it by 100.

If you need to inject 1 mL or more of Myalepta solution, your doctor might tell you to give the dose as two separate injections. This can help make the injections more comfortable.

- You must use a clean syringe and needle for both injections.

If you are not sure how much of the solution to inject, talk to your doctor or pharmacist before injecting.

Overdose:

In one case, an infant received a 10-fold overdose of Myalepta for 8 months. This led to large weight loss causing vitamin deficiency, low iron (anaemia) and malnutrition. The infant got better when the dose was changed.

If you think you, or a person you are caring for, have taken too much Myalepta, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to inject a dose, inject it as soon as you remember. Then have your normal dose the next day.

Do not use a double dose to make up for a forgotten dose.

If you have injected less Myalepta than you should, talk to your doctor straight away. Your doctor will monitor you for side effects.

What are possible side effects from using Myalepta?

These are not all the possible side effects you may have when taking Myalepta. If you experience any side effects not listed here, tell your healthcare professional.

- loss of interest in food
- headache
- hair loss
- feeling tired
- weight loss
- joint pain
- back pain
- arm or leg pain
- cough
- constipation
- abdominal pain
- stuffy or runny nose
- vomiting
- ear pain
- a faster than normal heart rate
- chest infection

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNKNOWN			
Low Blood Sugar: dizzy, sleepy or confused, clumsy, feeling mor		X	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
hungry than normal, feeling irritable or nervous			
Inflamed pancreas (pancreatitis): sudden severe pain in your stomach, feeling sick, diarrhoea		X	
Allergic reaction: breathing problems, swelling and redness of the skin, hives, swelling of your face, lips tongue or throat, stomach pain, fainting or feeling dizzy, very fast heartbeat		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Myalepta should be stored in the refrigerator at 2°C to 8°C and protected from light until preparing for use. Keep Myalepta vials in the carton when not in use.

Do not freeze Myalepta.

Do not use this medicine if the solution is not clear, is coloured or has bits or lumps in it.

Use with BWFI: when 11.3 mg Myalepta is reconstituted with BWFI, the vial can be used for multiple doses within 3 days when stored in the refrigerator at 2°C to 8°C and protected from light. The BWFI diluent contains 0.9% benzyl alcohol as a preservative.

Use with SWFI: when Myalepta is reconstituted with SWFI, the vial can be used for a single dose should be administered immediately. Unused reconstituted solution cannot be saved for later use and should

be discarded.

After reconstitution, the vials should not be frozen (below 0°C) or shaken vigorously. If the reconstituted product is inadvertently frozen, it should be thrown away.

Keep out of reach and sight of children.

If you want more information about Myalepta:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.amrytpharma.com, or by calling 1-800-696-1341 or emailing medinfo@amrytpharma.com.

This leaflet was prepared by Chiesi Farmaceutici S.p.A.

Last Revised TBD

INSTRUCTIONS FOR USE

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

MYALEPTA

Metreleptin for injection

Read this carefully before you start taking Myalepta and each time you get a refill. Before you begin self-administering this medicine at home, your doctor, nurse or pharmacist will train you how to prepare and inject Myalepta. Contact them if you are unclear about anything or if you need more information or help. Take your time to carefully prepare and inject your medicine, which when including the period of the vial warming up after being taken out of the fridge, can be approximately 20 minutes in total.

Make sure you have all the supplies listed below BEFORE using Myalepta.

You can get these supplies with a prescription from your healthcare provider, from a retail or hospital pharmacy, or the specialty pharmacy that distributes Myalepta.

- a vial with liquid for mixing Myalepta
    - Sterile water for injection should be used in infants less than 3 years of age, or in adults with a known hypersensitivity to benzyl alcohol
    - Bacteriostatic water for injection should be used for older children and adults
- a 3 mL syringe with a longer needle for mixing Myalepta
- a vial with Myalepta powder
    - 3 mg and 5.8 mg vial are for single use reconstituted with SWFI. Should be used immediately and any remaining reconstituted solution should be discarded.
    - 11.3 mg vial is for multi use reconstituted with BWFI. Should be used within 3 days of reconstitution when stored at 2°C to 8°C and protected from light.
- a syringe for injecting the Myalepta medicine under your skin – this syringe has a much shorter needle.
    - The size of this second syringe will be chosen by your doctor or pharmacist for your dose of Myalepta.
        - If your dose is 1.25 mg or less - you will use a 0.3 mL syringe.
        - If your dose is more than 1.25 mg up to 5 mg - you will use a 1 m syringe.
        - If your dose is more than 5 mg - you will use a 3.0 mL syringe.
- 2 alcohol wipes
- 1 sharps container for throwing away used needles and syringes. See "**Disposing of used needles and syringes**" at the end of these instructions.
- Stickers to note discard date for mixed medicine

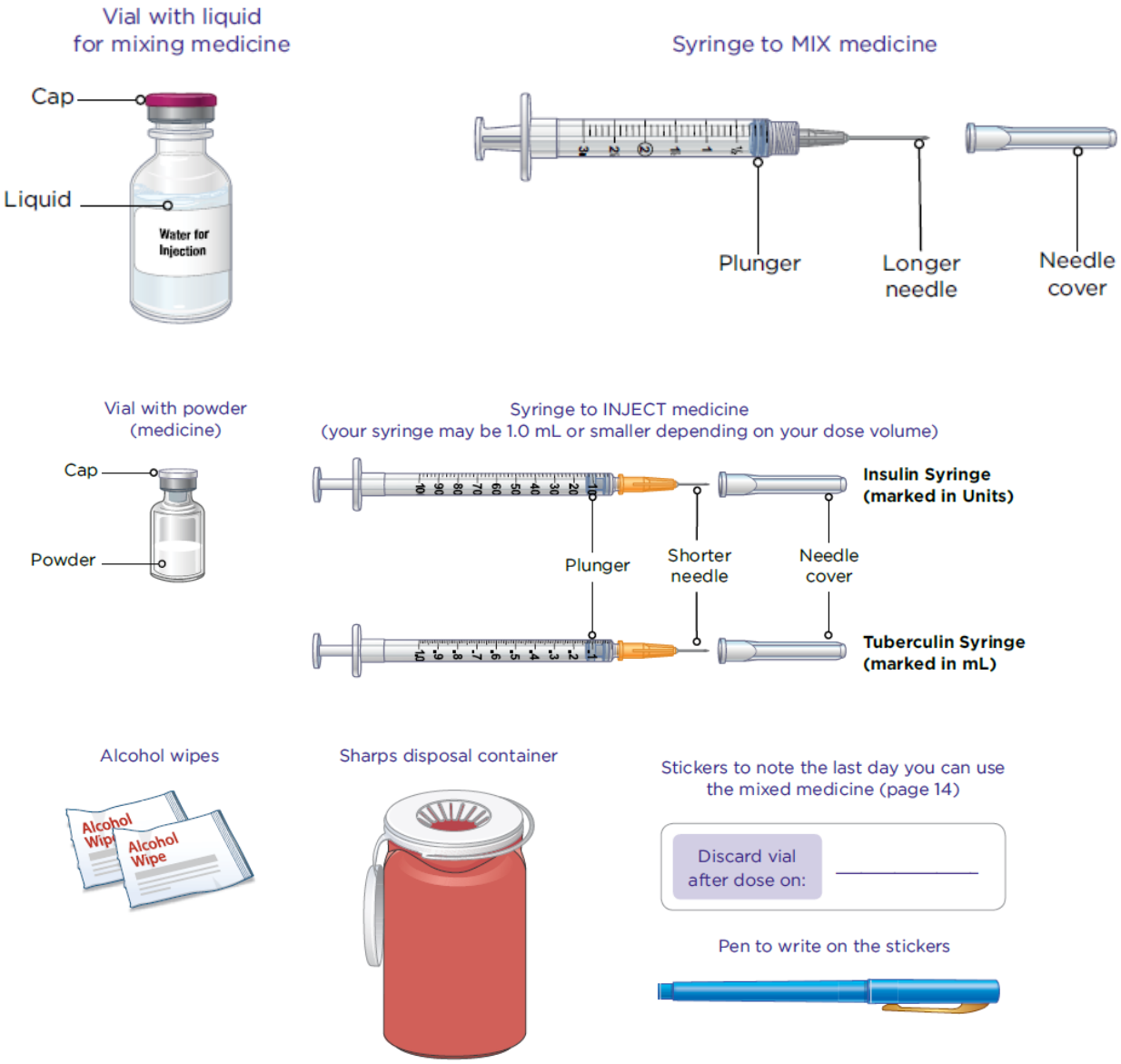


Figure A

How to read your syringes:

0.3 mL syringe (Figure B)

- The 0.3 mL syringe shows the injection amount in 'U' instead of 'mL'
- 1 U is the same as 0.01 mL. See section 3, "How much to inject" for more information.
- Each 0.05 mL is shown as a number with a big line. This is the same as 5 U.
- Each 0.005 mL is shown as a smaller line between the big lines. This is the same as 0.5 U.

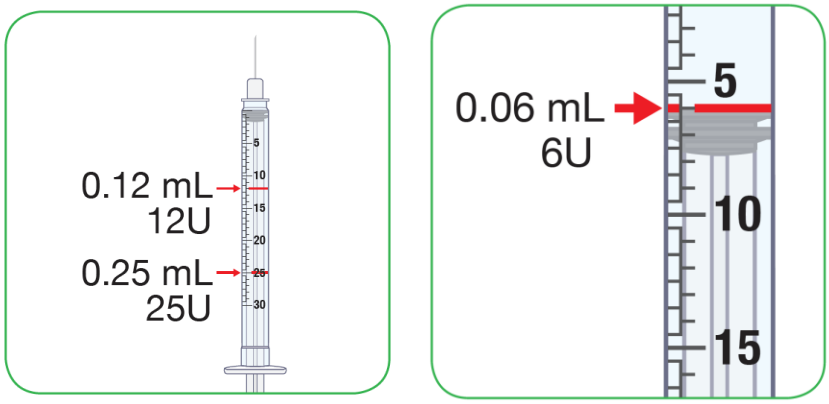


Figure B

1 mL syringe (Figure C)

- Each 0.1 mL is shown as a number with a big line.
- Each 0.05 mL is shown as a medium size line.
- Each 0.01 mL is shown as a smaller line.

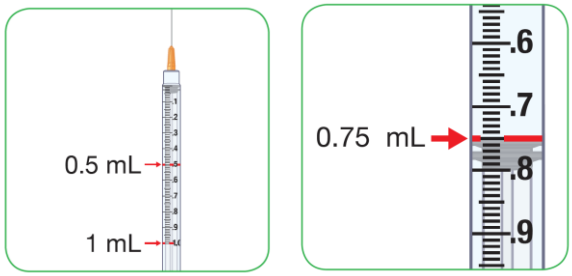


Figure C

3.0 mL syringe (Figure D)

- Each 0.5 mL is shown as a number next to a big line.
- Each 0.1 mL is shown as a smaller line between the big lines.

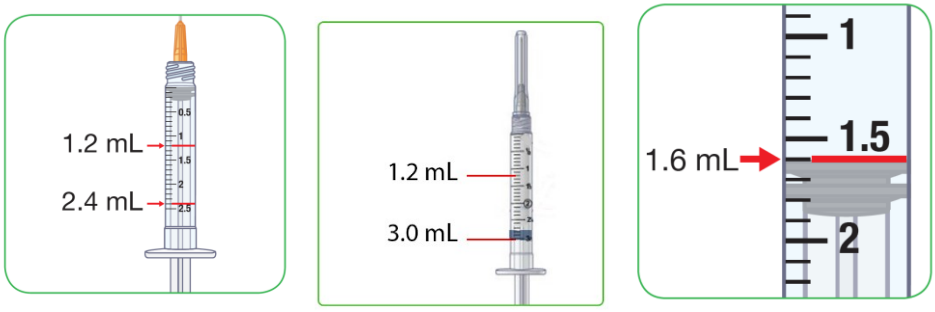


Figure D

The 3 mL syringe has a longer needle (see Figure B).

The 3 mL syringe is the syringe you will use to mix Myalepta. Always fill the 3 mL syringe with 2.2 mL of liquid. **Do not** inject yourself with the 3 mL syringe.

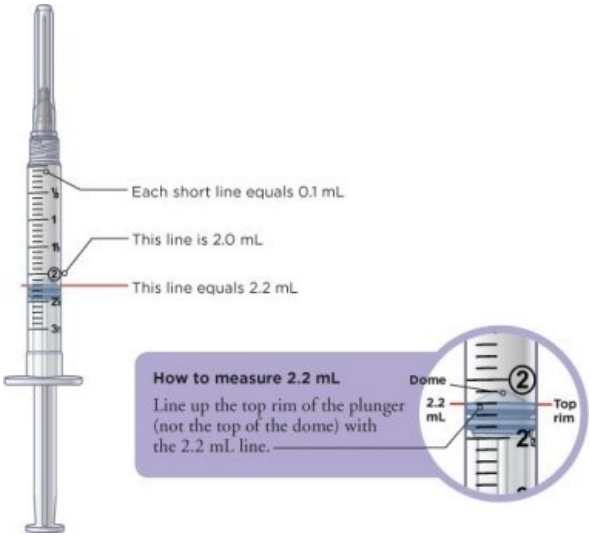


Figure E

The injection syringes have a shorter needle (see Figures B-D).

- The size of this injection syringe will be chosen by your doctor or pharmacist for your dose of Myalepta.
    - If your dose is 1.25 mg or less - you will use a 0.3 mL syringe.
    - If your dose is more than 1.25 mg up to 5 mg - you will use a 1 mL syringe.
    - If your dose is more than 5 mg - you will use a 3.0 mL syringe.

STEP 1: Getting Started

Your dose of Myalepta may change over time, depending on how Myalepta works for you. So it is important to keep track of your dose. On the line below, write down your dose in mL and the date. Be sure to keep this up-to-date if your dose changes:

_____ mL
Dose you will take each day

_____
Date

Take 1 Myalepta vial out of the refrigerator 10 minutes before you plan to inject to allow it to reach room temperature.

Set 1 vial with the liquid you will need to mix Myalepta on your work surface.

Check the powder in the Myalepta vial. It should be white. **Do not** use Myalepta if the powder is discolored. Throw it away and get a new one.

Check the expiration date printed on the Myalepta vial. **Do not** use Myalepta past the expiration date printed on the vial **(see Figure F)**.

Figure F

For this step, you will need:

Vial with liquid for mixing a dose of Myalepta	Vial with powder (Myalepta)	Alcohol wipes
		

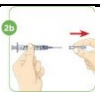
			
Wash your hands with soap and water.	Remove 2 alcohol wipes from their wrappers. Please the wipes on their wrappers to keep them clean.	Use your thumb to remove the caps from the vials	Clean the tops of the vials with one of the alcohol wipes.

STEP 2: Filling the 3 mL syringe (used to mix Myalepta) with 2.2 mL of liquid

For this step, you will need:

A 3 mL syringe (with longer needle) used to mix Myalepta	Vial with liquid (from Step 1)	Sharps disposal container
		

2a	Take the 3 mL syringe out of the plastic wrapper. Always use a new syringe.

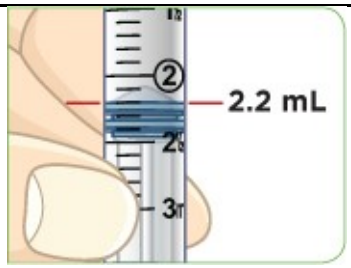


Pull the needle cover straight off. **Do not** twist the needle when removing the cover.

Put the needle cover in the sharps disposal container.

Pull down the plunger to fill the syringe with air.

You **must first** fill the syringe with air and put that air into the vial to make it easier to later fill the syringe with liquid.



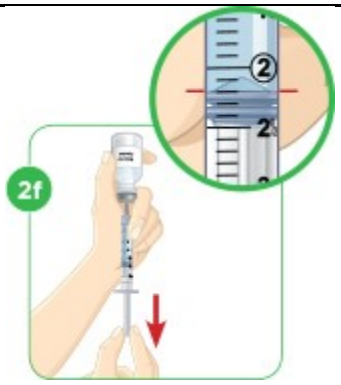
Line up the top rim of the plunger with the black 2.2 mL line.

Set the vial with the liquid on the work surface. Insert the needle into the top of the vial.

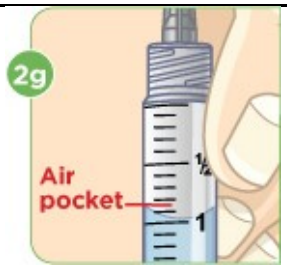
Push the plunger down all the way to fill the vial with air.

With the needle still in the vial, turn the vial and syringe upside down.

Keep the whole needle in the liquid.

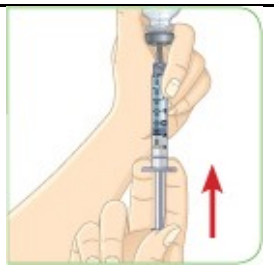


Pull down the plunger until the top rim of the plunger lines up with the black 2.2 mL line.



Check to see if there is an air pocket in the syringe.

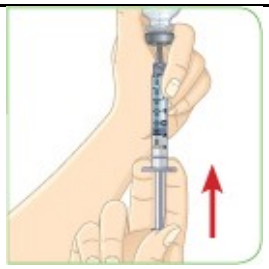
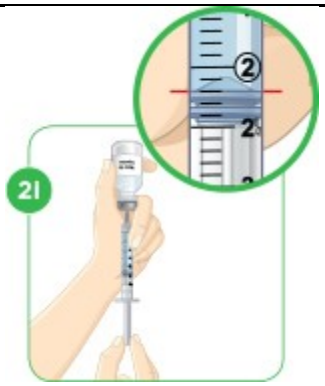
If you see an air pocket, tap the side of the syringe to move the air pocket to the top of the syringe.



Push the plunger up to remove the air pocket.

You must remove the air pocket to be able to fill the syringe with 2.2 mL of liquid.

Tip: You will always fill the 3 mL syringe with 2.2 mL of liquid.

			
Check to see if there are large air bubbles in the syringe. If you see large air bubbles in the syringe, tap the syringe to move the air bubbles to the top. If there are a few small bubbles left, that is okay.	Push the plunger up to remove as many large air bubbles as you can.	Pull down the plunger so the top rim of the plunger lines up with the black 2.2 mL line. Keep the whole needle in the liquid.	Remove the needle from the vial. Be careful not to move the plunger. Keep the syringe in your hand. **Do not** set it down. For instructions on how to discard the used vial of liquid, read the carton that contained those vials.

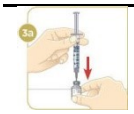
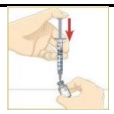
STEP 3: Preparing Myalepta

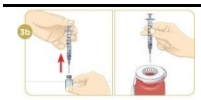
Note: If you already mixed your Myalepta before today, go to "Using a vial of mixed Myalepta" at the end of this step.

Option 1: Mixing a new vial of Myalepta:

For this step, you will need:

The 3 mL syringe filled with 2.2 mL of liquid (from Step 2) 	Vial with powder (from Step 1) 	Sharps disposal container 

			
Set the vial with the Myalepta powder on the work surface. Insert the needle straight down into the center of the vial.	Then tilt the vial so that the tip of the needle is pointing toward the inside wall of the vial.	With your thumb, slowly push the plunger down all the way. The liquid should go down the inside wall of the vial.	**Make sure you add the liquid slowly so that bubbles do not form in the vial.** No liquid should be left in the syringe.

		
While keeping the plunger all the way down, take the needle out of the vial. Throw away the syringe with the needle still attached into your sharps disposal container. **Do not** recap the needle. Recapping the needle can lead to a needlestick injury.	To mix the powder and liquid, **move the vial gently in a circle** (swirl) until the liquid is clear. **Do not** shake the vial.	When the medicine is mixed well, the liquid should be clear. You should not see any clumps, powder, bubbles, or foam.

Tip: If your vial of Myalepta is not mixed well, go back to Step 3c.
Note: Go to Step 4 if you just mixed a new vial of Myalepta.

Option 2: Using a vial of mixed Myalepta:

Note: For **newborns or infants** using Myalepta, **throw away any unused mixed Myalepta right away**. Do not store it for reuse.

For this step, you will need:

Vial of mixed Myalepta	Alcohol wipes
	

Choose a **clean, flat work surface** large enough to let you prepare the medicine.

Take 1 vial of mixed Myalepta out of the refrigerator.

Only Myalepta mixed with bacteriostatic water for injection can be stored for reuse.

You must use the vial within 2 days after the day the medicine was mixed.

Set the vial of mixed Myalepta on the work surface for 10 to 15 minutes so that it comes to room temperature.

Wash your hands with soap and water.

Remove 2 alcohol wipes from their wrappers.

Place the wipes on their wrappers to keep them clean.

Clean the top of the vial with the alcohol wipe.

Check that the Myalepta is mixed well and is clear. You should not see any clumps, powder, bubbles, or foam.

If you see clumps, powder, bubbles, or foam, throw away the vial in the sharps disposal container.

Important: Do not mix any liquid or mixed medicine from another vial with the vial you just cleaned.

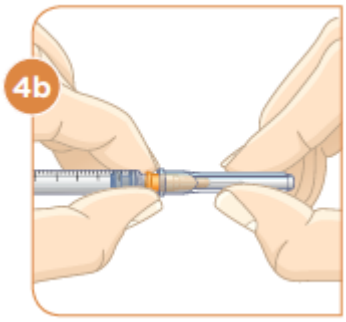
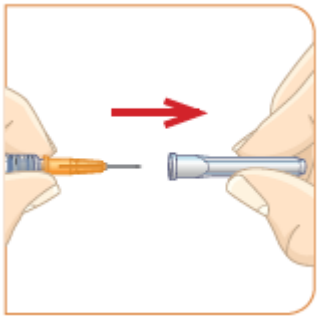
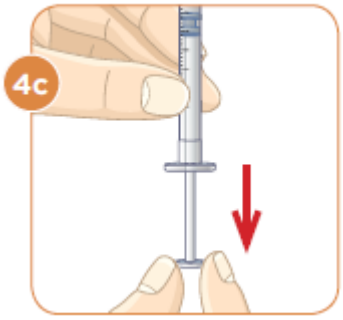
STEP 4: Filling the syringe used for injecting Myalepta

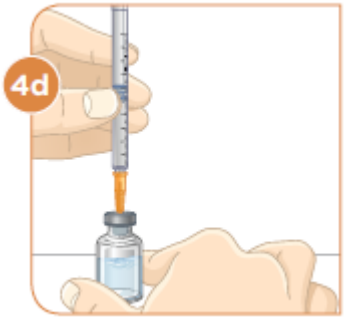
Ensure the proper size syringe is selected.

For this step, you will need:

A syringe (with shorter needle) used to inject Myalepta (see Figure B-D)	Vial of mixed Myalepta (from Step 3) 	Sharps disposal container 

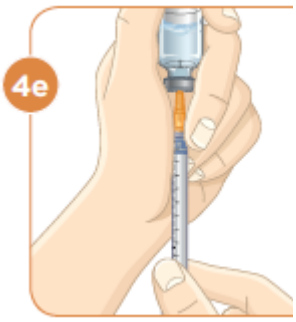
4a Remove the injection syringe from the plastic wrapper. Always use a new syringe.

		
Firmly grip the needle base.	Pull the needle cover straight off. Throw away the needle cover in the sharps disposal container.	Pull down the plunger until the top rim of the plunger lines up with the black line of the dose prescribed by your healthcare provider. You **must first** fill the syringe with air and put that air into the vial to make it easier to later fill the syringe with liquid.



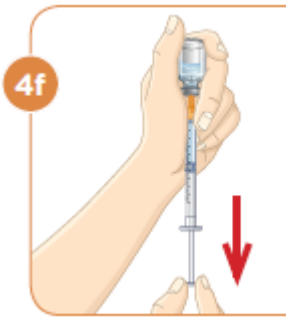
Hold the vial with the mixed Myalepta. Insert the needle into the top of the Myalepta vial.

Push the plunger down all the way, to fill the vial with air.

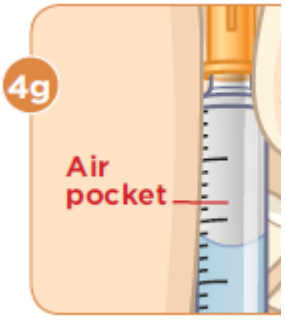


With the needle still in the vial, turn the vial and syringe upside down.

Keep the whole needle in the liquid. It is okay if the plunger moves down.

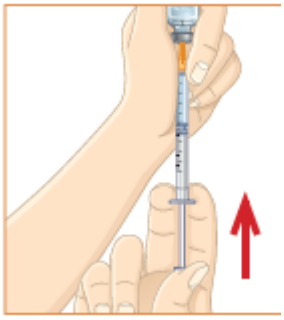


Pull down the plunger until the top rim of the plunger lines up with the black line of the dose prescribed by your healthcare provider.



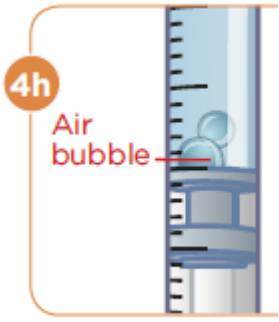
Check to see if there is an air pocket in the syringe.

If you see an air pocket, tap the side of the syringe to move the air pocket to the top of the syringe.



Push the plunger up to remove the air pocket.

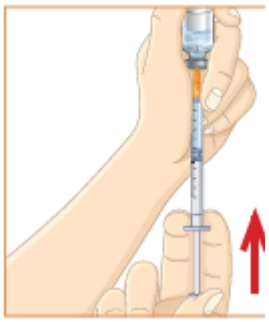
You must remove the air pocket to be able to fill the syringe with a full dose of Myalepta.



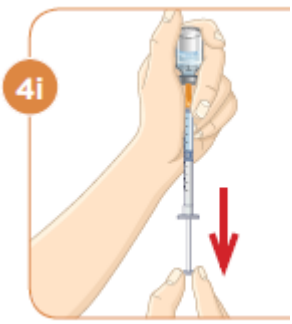
Check to see if there are large air bubbles in the syringe.

If you see large air bubbles in the syringe, tap the side of the syringe to move the air bubbles to the top.

If there are a few small bubbles left, that is okay.



Push the plunger up to remove as many large air bubbles as you can.



Pull down the plunger again until the top rim of the plunger lines up with the black line of the dose prescribed by your healthcare provider.

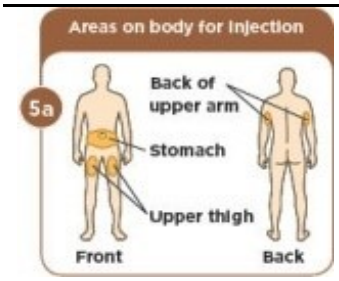
Remove the needle from the vial.

Set the vial down. **Do not** set the syringe down.

STEP 5: Injecting Myalepta

For this step, you will need:

Syringe filled with your Myalepta dose (from Step 4)	Alcohol wipe (from Step 1)	Sharps disposal container for used syringes and needles
		



Choose an injection site that you will use to inject your Myalepta.

The recommended injection sites are an area of your body that has the most fat, such as the stomach (abdomen), thigh, or the back of your upper arm.

You can use the same area of the body for each injection. But be sure to choose a

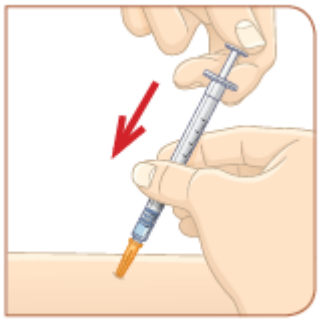
Use an alcohol wipe to clean the injection site.

Let the alcohol dry before you move on to 5c.

Pinch the skin with one hand.

With the other hand, hold the syringe like a pencil.

Insert the needle into the skin at an angle.
Do not insert the needle straight up and down.



Let go of the skin.

Use your thumb to push the plunger down until it stops.

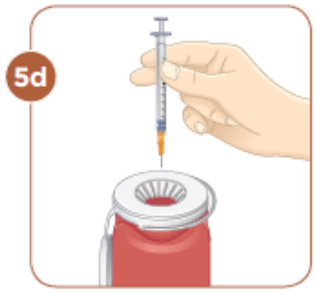
Take the needle out of your skin.

different injection site in that area.

If you inject other medicines you should choose a different site from where you inject Myalepta. **Do not** inject Myalepta in the same site as your other medicines.

Important:

Inject Myalepta under the skin (subcutaneous). **Do not** inject Myalepta into a muscle or vein.



Throw away the used syringe with the needle still attached in your sharps disposal container. See "**Disposing of used needles and syringes**" at the end of this document.

Do not recap the needle. Recapping the needle can lead to a needlestick injury.

Important:

Unused Myalepta mixed with sterile water for injection (for infants less than 3 years of age, or adults with a known hypersensitivity to benzyl alcohol), **must be thrown away.**
Do not store it for reuse.

Myalepta mixed with bacteriostatic water for injection can be stored for reuse.

Store the vial of mixed Myalepta in the refrigerator as soon as you are done.

Looking at a calendar, count 2 days after the day you mixed the Myalepta.

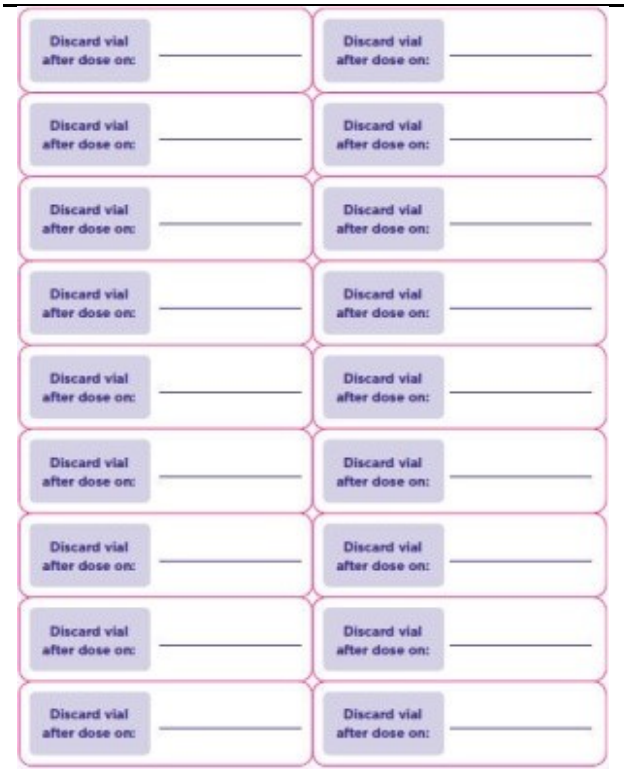
Write that date on the stickers found to the right.

Place the sticker on the vial of mixed Myalepta.

For example, if you mixed Myalepta on Monday, January 2, you would throw it away **after your dose** on Wednesday, January 4.

Important:

Stickers to Note the Last Day You Can Use Myalepta When Mixed with Bacteriostatic Water for Injection



STEP 6: Disposing of used needles and syringes:

Put your used needles and syringes in a sharps disposal container right away after use. **Do not** throw away (dispose of) loose needles and syringes in your household trash.

If you want more information about Myalepta:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.amrytpharma.com, or by calling 1-800-696-1341.

This Instructions For Use was prepared by Chiesi Farmaceutici S.p.A.

Last Revised: