PrMYALEPTA™

(metreleptin for injection)

IMPORTANT RISK MINIMIZATION INFORMATION: HEALTHCARE PROFESSIONAL GUIDE

This brochure should be read in conjunction with the Product Monograph.

Prmyalepta™ metreleptin for injection

Questions or concerns: **1-800-696-1341**

Chiesi

Table of contents

Introduction

This educational material has been developed as part of the risk minimization measures for MYALEPTA.

Most side effects of MYALEPTA are manageable. However, it is important that patients are carefully monitored during treatment and trained on injection techniques to minimize consequences arising from non-compliance or medication errors.

This brochure should be read in conjunction with the Product Monograph.

Disease background

Lipodystrophy comprises a heterogeneous group of rare disorders characterised by partial or complete absence of adipose tissue and can either be inherited or acquired.[2] Patients with lipodystrophy often suffer from early-onset metabolic consequences which are caused by lack of adipose tissue and accompanying leptin deficiency.[3,4] Leptin is a key hormone secreted by adipose tissue and exerts a range of metabolic functions.[3,5] The lack of adipose tissue and leptin in patients with lipodystrophy can cause a range of disorders such as hypertriglyceridaemia and ectopic fat accumulation, hyperglycaemia due to insulin resistance, and insatiable hunger due to missing satiety signals.[2,3]

MYALEPTA

MYALEPTA is a leptin-replacement therapy used in combination with diet to treat the consequences of leptin deficiency in patients with lipodystrophy.[1]

Therapeutic Indications

MYALEPTA is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients:

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

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 medinfo@medisonpharma.com or 1-800-696-1341 for neutralizing antibody testing

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

Specific Risks Associated with MYALEPTA

There are nine main areas of risk which the risk minimization measures are designed to address. They are:

- Hypoglycaemia with concomitant use of insulin and other anti-diabetic treatments
- Acute pancreatitis associated with abrupt discontinuation of Myalepta
- Unplanned pregnancy due to improvement of hormonal dysfunction with Myalepta
- Autoimmune disorder progression
- Medication errors
- Lymphoma
- Serious and severe infections secondary to neutralizing antibodies
- Loss of efficacy, potentially due to neutralizing antibodies
- Hypersensitivity (anaphylaxis, urticaria, and generalized rash)
- Benzyl alcohol toxicity

1. Hypoglycaemia with concomitant use of insulin and other anti-diabetic treatments

- **There is a risk of hypoglycaemia in patients treated with MYALEPTA who are on anti-diabetic medicinal products, in particular insulin or insulin secretagogues (e.g. sulphonylureas).[1]**

- **Blood glucose should be monitored closely, especially at the start of treatment and following any dose changes. Patients/caregivers should be reminded to closely monitor blood glucose levels.**
- **Patients/caregivers should be instructed to talk to the HCPs straight away if they notice any of the following signs of low blood sugar:[1]**
    - **Feeling dizzy**
    - **Feeling more sleepy or confused**
    - **Being clumsy and dropping things**
    - **Feeling more hungry than normal**
    - **Sweating more than normal**
    - **Feeling more irritable or more nervous**

Further information

- 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.
- Severe hyperglycaemia and difficult-to-treat diabetes associated with insulin resistance are serious consequences of lipodystrophy and often lead to the prescription of high doses of insulin and other drugs.[2] If MYALEPTA is taken with unchanged doses of insulin, mild, moderate or severe hypoglycaemia may occur due to the increased sensitivity of insulin receptors and an increased metabolic response to insulin.[1,3]
- Large dose reductions of baseline insulin requirements may be needed in the first two weeks of treatment. Dose adjustments of other anti-diabetic medications may also be needed to minimize the risk of hypoglycaemia.[1]
- Hypoglycaemia deemed to be related to MYALEPTA treatment occurred in 19% of patients studied.[1]
- Rotation of injection sites is recommended in patients co-administering insulin (or other subcutaneous medicinal products) and MYALEPTA.[1]

2. Acute pancreatitis associated with abrupt discontinuation of MYALEPTA

- **Non-compliance with, or abrupt discontinuation of MYALEPTA may result in worsening hypertriglyceridaemia and associated pancreatitis, particularly in patients with risk factors for pancreatitis (e.g. history of pancreatitis, severe hypertriglyceridaemia).[1]**

- **Patients/caregivers should be instructed to avoid abrupt discontinuation with MYALEPTA and should be encouraged to be compliant with daily treatment.**
    - When 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.**
- **Patient should be compliant with daily treatment and advised that if they miss their MYALEPTA daily dose, the dose should be administered as soon as the omission is noticed and the normal dosing schedule resumed the next day.**
- **Patients/caregivers should be instructed to talk to the healthcare professional straight away if they notice any signs of pancreatitis,[1] including:**
    - Sudden severe pain in the abdomen
    - Nausea or vomiting
    - Diarrhoea

Further information

- Patients with lipodystrophy are already predisposed to pancreatitis due to the hypertriglyceridaemia associated with the disease.[7]
- In clinical studies, six patients (four with generalised lipodystrophy and two with partial lipodystrophy), experienced treatment-emergent pancreatitis. All patients had a history of pancreatitis and hypertriglyceridaemia.[1]
- Abrupt interruption and/or non-compliance with MYALEPTA dosing was suspected to have contributed to the occurrence of pancreatitis in two patients.
- 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[1].

3. Unplanned pregnancy due to improvement of hormonal dysfunction with MYALEPTA

- MYALEPTA may increase fertility, due to effects on luteinising hormone, with the consequent potential for unplanned pregnancy.[1]

- **Women of childbearing potential should be advised that MYALEPTA may increase fertility and contraceptive methods should be recommended.**
    - This includes women with lipodystrophy who might previously not have considered themselves as being of childbearing potential due to their low fertility.
- **Due to the potential drug interaction of MYALEPTA with hormonal contraceptives, which may make the contraceptives less effective, additional non-hormonal contraception should be considered.**
- **MYALEPTA is not recommended during pregnancy and in women of childbearing potential not using contraception.**
- **Women should be instructed to talk to a doctor if they are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby.**

Further information

- Patients with lipodystrophy may have decreased fertility due to leptin deficiency.[6] Unplanned pregnancies may occur due to restoration of luteinising hormone release.[1]
- Since it cannot be excluded that MYALEPTA may reduce exposure to substrates of CYP3A through enzyme induction, **the efficacy of hormonal contraceptives may be reduced if co-administered with MYALEPTA** Therefore, an additional non-hormonal contraceptive method should be considered during treatment.[1]
- Abortions, stillbirths and preterm deliveries have been reported in women exposed to metreleptin during pregnancy. **MYALEPTA is not recommended during pregnancy and in women of childbearing potential not using contraception**.[1]
- Data on pregnancies are limited as clinical trials only reported six pregnancies with two live births.[6] It is not known whether these pregnancies were planned or unexpected.

4. Autoimmune Diseases

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

5. Medication errors

- **The first injection of MYALEPTA should always be supervised by a healthcare professional as it is important to avoid intramuscular injection in patients with minimal subcutaneous adipose tissue.[1]**
- **A healthcare professional should provide patients and caregivers with training on the reconstitution of the product and proper subcutaneous injection technique.**
- **The healthcare professional** is responsible for the prescription of the correct dose of MYALEPTA as well as the ancillary items to prepare and administer MYALEPTA (syringe, water vials etc.).
- **Healthcare professional** should refer to the **Specialist Prescriber guide** for details on dose calculation and prescribing of MYALEPTA and ancillary items.
- 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.
- Information and training on the administration of MYALEPTA will initially be provided to the patient and caregiver by the **healthcare professional**. **The HCP** will then support the patient and/or carer in their initial self-administration of MYALEPTA at home. Follow-up of injection technique should be performed on a regular basis.
- Healthcare professionals may be asked by patients/caregiver about the method of administration and special precautions for storage, disposal and other handling (see below).

Method of administration

- **The injection should be administered at the same time every day. It can be administered any time of the day without regard to the timing of meals.**
- **The reconstituted solution should be injected into the abdomen, thigh or upper arm tissue.**
    - 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.
- **It is recommended that patients should use a different injection site each day when injecting MYALEPTA in the same region.**
- **It is also recommended that patients should use different injection sites when co-administering insulin (or other subcutaneous medicinal products) and MYALEPTA.**
- **Patients/carers should be advised that if they inject more MYALEPTA than prescribed they should contact their healthcare professional or go to a hospital straight away.**

Special precautions for storage, disposal and other handling

- **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 discolored.**
- **Use with bacteriostatic water for injection (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 sterile water for injection (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.**

6. T-cell lymphomas

- **Cases of T cell lymphoma have been reported while using MYALEPTA in clinical studies. A causal relationship between MYALEPTA and the development and/or progression of lymphoma has not been established.**

- **The Healthcare professional should carefully consider the benefits and risks of treatment in patients with acquired lipodystrophy and/or in patients with significant hematologic abnormalities (including leukopenia, neutropenia, bone marrow abnormalities, lymphoma, and/or lymphadenopathy).[1]**

- Three cases of T-cell lymphoma have been reported while using metreleptin in clinical studies.[1] 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 treatment. A separate case of anaplastic large cell lymphoma was reported in a patient receiving MYALEPTA who did not have hematological abnormalities before treatment.[1] A causal relationship between MYALEPTA treatment and the development and/or progression of lymphoma has not been established.

7. Serious and severe infections secondary to neutralising antibodies

- **An association between the development of neutralising antibodies or blocking activity and loss of efficacy and serious and severe infections cannot be excluded.**

- **Abrupt discontinuation of MYALEPTA should be avoided due to the potential risk of acute pancreatitis.**
- **LD patients with a blocking activity against metreleptin and concurrent infections responded to standard of care treatment**
- **The Healthcare professional should be consulted if serious or severe infections occur.**
- **In patients with serious and severe infections, continuation of metreleptin should be at the discretion of the Healthcare professional.**
- **In cases of severe or serious infection or significant loss of efficacy despite administration of MYALEPTA (as well as considering poor compliance), the Healthcare professional should consider testing patients for neutralising antibodies**

Further information

- 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)

- 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

- Neutralising antibody activity may in theory affect the endogenous leptin levels, if any.[6]

For further information on how to submit samples for neutralising antibody testing, please contact medinfo@medisonpharma.com

As testing individual patient samples can take up to 4 months, and the clinical consequences of developing *in vitro* neutralizing antibodies to metreleptin are still not well understood, any clinical decision regarding whether to continue or stop treatment with metreleptin should be considered in the context of the patient's condition and the overall clinical situation.

8. 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.**

- **Patients/caregivers should prepare and administer the first dose of the medicinal product under the supervision healthcare professional.**
- **Anaphylactic reactions may follow immediately after administration of MYALEPTA.**
    - If an anaphylactic reaction or other serious allergic reaction occurs, administration of MYALEPTA should be permanently discontinued immediately and appropriate therapy initiated.[1]
- **Patients should be instructed to contact their doctor straight away if they notice any signs or symptoms of an allergic reaction including:[1]**
    - Breathing problems
    - Swelling and reddening of the skin
    - Hives
    - Swelling of the face, lips, tongue or throat
    - Stomach pain, nausea and vomiting
    - Fainting or feeling dizzy
    - Very fast heartbeat

Further information

- Post marketing, cases of hypersensitivity have been reported.[6] There were reports of anaphylactic reactions, rash and severe urticaria and asthma.[6]

9. Benzyl Alcohol Toxicity

- **Myalepta contains benzyl alcohol when reconstituted with BWFI. Myalepta contains no preservative when reconstituted with SWFI. The preservative benzyl alcohol has been associated with serious adverse events and death in pediatric patients, particularly in neonates and premature infants.[1]**

- **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.[1]**

For current Product Monograph and Instructions for use scan the QR code

References

1. Chiesi Farmaceutici S.p.A. Myalepta Product Monograph available at https://health-products.canada.ca/dpd-bdpp/
2. Brown RJ, Araujo-Vilar D, Cheung PT, *et al*. The diagnosis and management of lipodystrophy syndromes: a multi-society practice guideline. *J Clin Endocrinol Metab* 2016;101:4500-4511.
3. Rodriguez AJ, Mastronardi CA, Paz-Filho GJ. New advances in the treatment of generalized lipodystrophy: role of metreleptin. *Ther Clin Risk Manag* 2015;11:1391-1400.
4. Gupta N, Asi N, Farah W, *et al*. Clinical features and management of non-HIV related lipodystrophy in children: a systematic review. *J Clin Endocrinol Metab* 2017;102:363-374.
5. Mantzoros CS, Magkos F, Brinkoetter M, *et al*. Leptin in human physiology and pathophysiology. *Am J Physiol Endocrinol Metab* 2011;301:E567-E584.
6. Chiesi Farmaceutici S.p.A. Data on file.
7. Chan JL, Oral EA. Clinical classification and treatment of congenital and acquired lipodystrophy. Endocr Pract 2010;16:310-323.

Date of Preparation 06/2024 MY/CA/01/06-24-EN