MYALEPTA®▼

(metreleptin powder for solution for injection)

IMPORTANT RISK MINIMISATION INFORMATION: HEALTHCARE PROFESSIONAL GUIDE

This brochure should be read in conjunction with the Summary of Product Characteristics.[1]

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

Suspected adverse reactions and adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk or search for MHRA Yellow Card in the Google Play or Apple App Store.

Suspected adverse reactions and adverse events should also be reported to Aegerion by e-mail to **Medinfo.emea@aegerion.com** or by telephoning the free phone number **00800 23437466**.

myalepta® metreleptin

Aegerion® Pharmaceuticals
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- **Treatment should be initiated and monitored by a healthcare professional experienced in the diagnosis and management of metabolic disorders.**
- In the UK, there is a single National Specialist Service for people with lipodystrophy at Addenbrooke's Hospital in Cambridge and patients should be referred to this service for treatment initiation and monitoring.
- **For further information on the Specialist Service, please contact: 01223 768455**

Introduction

This educational material has been developed as part of the risk minimisation measures for Myalepta. It is designed for healthcare professionals including the Specialist Prescriber and other Healthcare Professionals (HCPs) at the Specialist Service, Generalists, Nurses, Pharmacists, and GPs.

Most side effects of Myalepta are manageable. However, it is important that patients are carefully monitored during treatment and trained on injection techniques to minimise consequences arising from non-compliance or medication errors. Please refer to the Specialist Service for further information.

This brochure should be read in conjunction with the Summary of Product Characteristics.[1] Specialist Prescribers should also refer to the Specialist Prescriber Guide (Dose and Prescribing Information: Specialist Prescriber Guide).

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 (metreleptin) 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 patients:[1]

- With confirmed congenital generalised lipodystrophy (Berardinelli-Seip syndrome) or acquired generalised lipodystrophy (Lawrence syndrome) in adults and children 2 years of age and above
- With confirmed familial partial lipodystrophy or acquired partial lipodystrophy (Barraquer-Simons syndrome), in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control

Specific Risks Associated with Myalepta

There are four main areas of risk which the risk minimisation measures are designed to address. They are:

- Hypoglycaemia with concomitant use of insulin and other anti-diabetics
- Acute pancreatitis associated with abrupt discontinuation of Myalepta
- Unplanned pregnancy due to improvement of hormonal dysfunction with Myalepta
- Medication errors

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

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

- **Blood glucose should be monitored closely, especially at the start of treatment and following any dose changes. Patients/carers should be reminded to closely monitor blood glucose levels.**
    - **HCPs at the Specialist Service should advise the patient on the frequency of blood monitoring**
- **Patients/carers should be instructed to talk to the HCPs at the Specialist Service 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**
- **HCPs at the Specialist Service should be informed if patients report repeated or severe signs of hypoglycaemia.**

Further information

- 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 50% or more of baseline insulin requirements may be needed in the first two weeks of treatment. Once insulin requirements have stabilised, dose adjustments of other anti-diabetic therapies may also be needed in some patients to minimise the risk of hypoglycaemia.[1]
- Hypoglycaemia deemed to be related to Myalepta treatment occurred in 14% of patients studied.[1] Post marketing, four cases of hypoglycaemia were reported until July 2016.[6]
- In clinical studies, hypoglycaemia has been managed with food/drink intake and by modifying the dose of anti-diabetic medicinal products. In case of hypoglycaemic events of a non-severe nature, food intake management may be considered as an alternative to dose adjustment of anti-diabetics according to the treating physician's opinion.[1]
- Using different 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/carers should be instructed to avoid abrupt discontinuation with Myalepta and should be encouraged to be compliant with daily treatment.**
- **The Specialist Prescriber at the Specialist Service should be consulted if Myalepta treatment needs to be stopped.**
    - If Myalepta treatment is to be stopped or modified, the Specialist Prescriber must manage this. The specialist prescriber may steadily taper down the dose of Myalepta over a two-week period in conjunction with a low-fat diet and adjustment of other lipid-lowering medicinal products as needed.[1] Triglyceride levels should be monitored as other lipid lowering treatment may be required or modified.[1]
- **Patients/carers should be advised that if the patient misses a dose, the dose should be administered as soon as the omission is noticed and the normal dosing schedule resumed the next day.**
- **Patients/carers should be instructed to talk to the HCPs at the Specialist Service 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 a US study involving 72 lipodystrophy patients, 28% of patients had a medical history of pancreatitis before initiating metreleptin.[8]
- In clinical studies, six patients (four with generalised lipodystrophy and two with partial lipodystrophy), experienced treatment-emergent pancreatitis.[1] All patients had a history of pancreatitis and hypertriglyceridaemia.
- Abrupt interruption and/or non-compliance with Myalepta dosing was suspected to have contributed to the occurrence of pancreatitis in two patients. The mechanism for pancreatitis in these patients was presumed to be return of hypertriglyceridaemia and therefore increased risk of pancreatitis in the setting of discontinuation of effective therapy for hypertriglyceridaemia.

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.**

- **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] **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.
- 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 though there is currently no evidence to suggest a causal relationship with the treatment. Studies in animals have shown some evidence of reproductive toxicity. **Myalepta is not recommended during pregnancy and in women of childbearing potential not using contraception**.
- 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. No pregnancies were reported in the post- marketing period until July 2016.[6]
- Animal studies showed no adverse effects on male or female fertility.[1]

4. Medication errors

- **The first injection of Myalepta should always be supervised by an appropriate HCP at the Specialist Service as it is important to avoid intramuscular injection in patients with minimal subcutaneous adipose tissue.**[1]
- **A HCP at the Specialist Service and the Homecare Nurse should provide patients and carers with training on the reconstitution of the product and proper subcutaneous injection technique.**
- **The Specialist Service** 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.).
- **Specialist Prescribers** should refer to the **Specialist Prescriber guide** for details on dose calculation and prescribing of Myalepta and ancillary items.
- Information and training on the administration of Myalepta will initially be provided to the patient and carer at the **Specialist Service**. **A Homecare Nurse** will then support the patient and/or carer in their initial self-administration of Myalepta at home. A follow-up of injection technique should be performed six-monthly when the patient visits the **Specialist Service**.[1]
- Healthcare professionals may be asked by patients/carers 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 minimise potential injection site discomfort due to injection volume. When dividing doses due to volume, doses can be administered one after the other at different injection sites.
- **It is recommended that patients should use a different injection site each day when injecting Myalepta.**
- **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 the HCP at the Specialist Services or go to a hospital straight away.**

Special precautions for storage, disposal and other handling

- **Myalepta should be stored in a refrigerator until the day of use.**
- **Myalepta reconstituted with water for injection should be used immediately and is for single-use.**
- **Unused reconstituted solution cannot be stored for later use.**
    - When small doses/volumes are prescribed (e.g. in children), the vials will remain almost completely filled with product after drawing up the required dose, however the remaining reconstituted product should always be discarded immediately after use.
- **New syringes must be used each time.**
    - Syringes and all caps, vials, and ampoules should be disposed of straight away in the sharps disposal container provided.

Potentially Serious Adverse Drug Reactions

1. T cell lymphomas

- **Acquired lipodystrophies are associated with autoimmune disorders, and autoimmune disorders are associated with an increased risk of malignancies including lymphomas.**

- **The Specialist Prescriber should be informed if T-cell lymphoma is diagnosed and/or if any haematological abnormalities are diagnosed.**
- **The Specialist Prescriber should carefully consider the benefits and risks of treatment in patients with acquired generalised lipodystrophy and/or in patients with significant haematological abnormalities (including leukopenia, neutropenia, bone marrow abnormalities, lymphoma, and/or lymphadenopathy).**

- 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 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.[1] Post- marketing monitoring indicated that there were no reports of patients developing lymphoma until July 2016.[6] A causal relationship between Myalepta treatment and the development and/or progression of lymphoma has not been established.

2. 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.**

- **The Specialist Prescriber should be consulted if serious or severe infections occur.**
- **In patients with serious and severe infections, discontinuation of metreleptin should be considered by the Specialist Prescriber.**
- **Abrupt discontinuation of Myalepta should be avoided due to the potential risk of acute pancreatitis.**

Further information

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

3. Hypersensitivity reactions

- **Myalepta, like any therapeutic protein, has the potential to cause hypersensitivity reactions.**

- **Patients /carers should prepare and administer the first dose of the medicinal product under the supervision of the Homecare Nurse who will visit the patients at their home.**
- **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
    - Severe pain in the abdomen
    - Very fast heartbeat

Further information

- Post marketing, 24 cases of hypersensitivity have been reported until July 2016.[6] There were reports of anaphylactic reactions, rash and severe urticaria and asthma.[6]

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