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RARE DISEASE
New medicinal product
February 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

MYALEPTA (metreleptin), recombinant human leptin analogue

High clinical benefit as an adjunct to diet, in congenital or acquired generalised lipodystrophy, with leptin deficiency, in patients over 2 years of age and minor clinical improvement in the management of their disease.

High clinical benefit as an adjunct to diet in familial or acquired partial lipodystrophy, with leptin deficiency, in patients over 12 years of age for whom standard treatments were unable to achieve adequate metabolic control, but without demonstrated clinical advantage in their management.

Main points

- MYALEPTA has been granted a marketing authorisation as an adjunct to diet, as replacement therapy for treating complications associated with leptin deficiency in patients suffering from lipodystrophy (LD): with generalised congenital LD (Berardinelli-Seip syndrome) or acquired LD (Lawrence syndrome) confirmed in patients over the age of 2 years; with familial or acquired partial LD (Barraquer-Simons syndrome) confirmed in patients over the age of 12 years in whom standard treatments failed to achieve adequate metabolic control.
- The efficacy and safety data come from uncontrolled studies. The efficacy of leptin supplementation on the progression of glucose and lipid parameters observed in the pivotal study is difficult to quantify, due in particular to modifications of concomitant glycaemia and lipid lowering drugs and to missing data.
- In the group of patients suffering from generalised lipodystrophy (GL) and whose endogenous leptin levels are negligible, the observed reductions in HbA1c and triglyceride levels at 12 months were clinically relevant. The clinical relevance of the results observed in the group of patients suffering from partial lipodystrophy (PL) is debatable. The long-term progression of patient management under metreleptin is yet to be assessed.
- Serum concentrations, allowing to define the leptin deficiency and to discuss the indication of replacement therapy, have not been specified.

Therapeutic strategy

- There are currently no treatments allowing reconstitution of adipose tissue and correcting lipoatrophy, a major symptom of lipodystrophy. Patient management is complex and should ideally be performed by a multidisciplinary team. It focuses primarily on preventing and treating metabolic disturbances, associated complications (particularly cardiovascular) and the pathological modifications of adipose tissue distribution.
- **Role of the medicinal product in the therapeutic strategy**
  MYALEPTA's indication will be documented by an initial leptinaemia assay, by diagnostic and progressive features and by the presence of associated comorbidities.
  MYALEPTA represents an option for treating metabolic complications in patients with leptin deficiency suffering from generalised lipodystrophy. In patients with leptin deficiency and suffering from partial lipodystrophy, MYALEPTA represents a treatment option pending product reassessment, particularly based on the results of the study requested by the EMA.
  The effects of metreleptin treatment on disease progression and/or mortality rates in lipodystrophy patients have not as yet been established.

Clinical data

- One open-label, non-comparative study assessed the effect of metreleptin on HbA1c and triglyceride levels after 12 months of treatment in patients with a clinical diagnosis of lipodystrophy and at least one of the following 3 anomalies: type 2 diabetes, fasting hyperinsulinaemia > 30 µU/ml or fasting triglycerides > 2.26 mmol/l. Upon inclusion, patients had low leptin levels. The study included 107 patients: 66 patients (mean age 18 years) had GL (68% congenital GL); 41 patients (mean age 34 years) had PL (85% familial PL). Upon inclusion, 80% of GL patients group and 90% of PL patients group were given an anti-diabetic agent; 52% of GL patients group and 83% of PL patients group were given a lipid lowering agent.
  The mean variation in HbA1c levels at 12 months of treatment was of -2.2%, CI95% [-2.7; -1.6] in the GL group and of -0.6% CI95% [-1.0; -0.2] in the PL group. The mean relative variation in triglyceride levels at 12 months was of -32.1% [-51.0; -13.2] in the GL group and of -20.8% [-37.1; -4.6] in the PL group (after excluding one patient for outlier value at one year). In patients with GL, these results remain statistically significant in the population of patients for whom the dosages of concomitant glycaemia and lipid lowering drugs were not increased during the study.
- Some adverse events were reported: hypersensitivity reactions, hypoglycaemia, tumours (in particular T-cell lymphoma), acute pancreatitis, injection site reactions, autoimmune disorders and severe infections.
  Metreleptin was found to be immunogenic. Investigations are in progress to determine whether there is a causal relationship between Nab antibody formation and the occurrence of severe infections and whether these antibodies can impact treatment efficacy by neutralising the metreleptin injected.

Special prescription requirements

- Medicinal product subject to hospital prescription
- Initial prescription and renewal reserved for specialists in paediatrics, or in endocrinology, diabetes and nutrition

Considering the specificity of lipodystrophy cases and the therapeutic strategy in these diseases, the guidelines below should be followed:
- the indication must be validated and regularly reassessed during multidisciplinary review meetings by the PRISIS Rare Diseases Reference Centre,
- the medicinal product must be prescribed at least once a year by the Reference Centre, or by one of the PRISIS Rare Diseases Expert Centres,
- a serum leptin assay must be performed before treatment initiation,
- it must be possible to screen for anti-metreleptin antibodies (neutralising and non-neutralising), according to prescriber recommendations.

Benefit of the medicinal product

- The actual clinical benefit* of MYALEPTA is high in its indications.
- In partial lipodystrophy, maintaining the actual clinical benefit is subject to reassessment of MYALEPTA, in particular based on the results of the clinical study requested by EMA, considering in particular the concomitant glycaemia and lipid lowering drug saving data (final report expected in 2022).
- MYALEPTA provides a minor clinical added value** (CAV IV) in the management of patients suffering from generalised lipodystrophy.
- MYALEPTA provides no clinical added value** (CAV V) in the management of patients suffering from partial lipodystrophy.
- Approved for retail pharmacy and hospital reimbursement.

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This document was drafted on the basis of the Transparency Committee opinion dated 27 February 2019 (CT-17457) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) corresponds to the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV level from I, major, to IV, minor. A level V CAV (equivalent to "no clinical added value") denotes a "lack of clinical improvement".