30 July 2018
EMA/462162/2018
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Myalepta (metreleptin)
Sponsor: Aegerion Pharmaceuticals B.V.

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Introductory comment:

The approved therapeutic indication *"Myalepta is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients:*

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

falls within the scope of the four designated orphan conditions familial partial lipodystrophy (FPLD), Barraquer-Simons Syndrome (acquired partial lipodystrophy (APL)), Lawrence syndrome (acquired generalized lipodystrophy (AGL)), and Berardinelli-Seip syndrome (congenital generalised lipodystrophy (CGL)) and are covered in this one document.

2. Metreleptin for treatment of familial partial lipodystrophy EU/3/12/1022 (EMA/OD033/12)

2.1. Product and administrative information

Product	
Active substance	Metreleptin
International Non-Proprietary Name	Metreleptin
Orphan indication	Treatment of familial partial lipodystrophy
Pharmaceutical form	Powder for solution for injection
Route of administration	Subcutaneous use
Pharmaco-therapeutic group (ATC Code)	Other alimentary tract and metabolism products, amino acids and derivatives (A16AA07)
Sponsor's details:	Aegerion Pharmaceuticals B.V. Atrium Building, 8th Floor Strawinskylaan 3127 1077 ZX Amsterdam The Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Aptiv Solutions (UK) Limited
COMP opinion date	13 June 2012
EC decision date	17 July 2012
EC registration number	EU/3/12/1022
Post-designation procedural history	
Transfer of sponsorship	Transfer from Aptiv Solutions (UK) Limited to Bristol-Myers Squibb / AstraZeneca EEIG– EC decision of 13 February 2014 Transfer from Bristol-Myers Squibb / AstraZeneca EEIG to AstraZeneca AB- EC decision of 8 April 2014 Transfer from AstraZeneca AB to Aegerion Pharmaceuticals Limited – EC decision of 25 March 2015 Transfer from Aegerion Pharmaceuticals Limited to Aegerion Pharmaceuticals B.V. – EC decision of 30 November 2017
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	B. Van der Schueren / A. Gyurasics
Applicant	Aegerion Pharmaceuticals B.V.
Application submission date	21 December 2016
Procedure start date	19 January 2017
Procedure number	EMEA/H/C/004218
Invented name	Myalepta

Therapeutic indication	Myalepta is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients: • with confirmed congenital generalised LD (Berardinelli-Seip syndrome) or acquired generalised LD (Lawrence syndrome) in adults and children 2 years of age and above • with confirmed familial partial LD or acquired partial LD (Barraquer-Simons syndrome), in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control. Further information on Myalepta can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/Find medicine/Human medicines/European public assessment reports.
CHMP opinion date	31 May 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	K. Westermark / V. Tillmann
Sponsor's report submission date	16 December 2016
COMP discussion	22-24 May 2018
COMP opinion date	5 June 2018

2.2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2012 was based on the following grounds:

- familial partial lipodystrophy (hereinafter referred to as "the condition") was estimated to be affecting approximately 0.2 in 10,000 people in the European Union (EU), at the time the application was made; the sponsor has done an extensive literature search and has obtained written statements from several European experts to support the prevalence calculation;
- the condition is chronically debilitating due to diabetes mellitus and other metabolic abnormalities which usually develop in adulthood, with women affected more severely than men. Marked hypertriglyceridemia can lead to acute pancreatitis, and fatty liver can develop in some patients. Coronary artery disease and other types of atherosclerotic vascular disease are more prevalent in women. Acanthosis nigricans is relatively uncommon. Most affected women are able to reproduce normally, but some develop hirsutism and menstrual irregularities, suggestive of polycystic ovary syndrome. Some patients develop mild to moderate myopathy, cardiomyopathy, and conduction system abnormalities;
- there is, at present, no satisfactory treatment that has been authorised in the EU for patients affected by the condition.

2.3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The sponsor is proposing that familial partial lipodystrophy continues to be recognised as a distinct medical entity and still suitable as an orphan condition.

Familial partial lipodystrophy (FPLD) is a group of usually autosomal dominant disorders characterized by loss of fat affecting the limbs, buttocks, and hips. Regional excess fat accumulation is frequent, varies by subtype, and may result in a Cushingoid appearance. Fat distribution is typically normal in early childhood, with loss of fat occurring around puberty.

Muscular hypertrophy is common. Metabolic complications are common in adulthood, with increased risk of coronary heart disease and occasionally early cardiomyopathy.

It is part of a broader group of disorders called the lipodystrophy syndromes. These are a heterogeneous group of rare disorders that have in common selective deficiency of adipose tissue in the absence of nutritional deprivation or catabolic state. Lipodystrophies are categorized based on aetiology (genetic or acquired) and distribution of lost adipose tissue, affecting the entire body (generalized) or only regions (partial). This yields four major categories: congenital generalized lipodystrophy (CGL), familial partial lipodystrophy (FPLD), acquired generalized lipodystrophy (AGL), and acquired partial lipodystrophy (APL).

The proposed condition continues to be a distinct medical entity as described in the original orphan designation.

The approved therapeutic indication *"Myalepta is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients:*

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

falls within the scope of the designated orphan indication Familial Partial Lipodystrophy.

Intention to diagnose, prevent or treat

Based on the CHMP assessment, the intention to treat the condition has been justified.

Chronically debilitating and/or life-threatening nature

This condition is frequently associated with hormonal and metabolic derangements resulting in severe comorbidities that depend on the subtype, extent of fat loss, age, and gender. Many complications of lipodystrophy are secondary to deficient adipose mass, resulting in ectopic lipid storage in the liver, muscle, and other organs and causing insulin resistance. Insulin resistance leads to diabetes,

hypertriglyceridemia, polycystic ovarian syndrome (PCOS), and nonalcoholic fatty liver disease (NAFLD)

Major causes of mortality include heart disease (cardiomyopathy, heart failure, myocardial infarction, arrhythmia, liver disease (liver failure, gastrointestinal haemorrhage, hepatocellular carcinoma), kidney failure, acute pancreatitis, and sepsis.

Number of people affected or at risk

The sponsor has conducted an updated literature search to establish the prevalence of the condition. This has been submitted as an annex to the general report. It consists of 13 new publications of case reports specifically from different European countries within the European Union (reports ranging from 2012-2016) and provides a more current understanding of the prevalence of the condition since the original designation in 2012 (published in Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2017:10 375–383). From this new data the sponsor proposes a revised prevalence calculation of 0.027 in 10,000 (rounded of to 0.03 in 10,000) a revision downwards from 0.2 in 10,000 in 2012.

The COMP accepted the revised prevalence estimate proposed by the sponsor as the submitted calculation was based on recent data from more reliable sources than the original prevalence calculation.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

There are currently no authorised medicines for this condition in Europe. A recent publication, *The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline J Clin Endocrinol Metab, December 2016, 101(12):4500–4511,* offers guidance on how to manage and treat the condition.

Current therapies prevent or ameliorate the comorbidities of lipodystrophy syndromes. There is no cure for lipodystrophy and no treatment that can regrow adipose tissue. The cornerstone of therapy for metabolic complications of lipodystrophy is diet.

Significant benefit

Not applicable.

2.4. COMP position adopted on 5 June 2018

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product;
- the prevalence of familial partial lipodystrophy (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.03 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to diabetes mellitus and other metabolic abnormalities which usually develop in adulthood, with women affected more severely than men. Marked hypertriglyceridemia can lead to acute pancreatitis, and fatty liver can develop in some patients. Coronary artery disease and other types of atherosclerotic vascular disease are more prevalent in women. *Acanthosis nigricans* is relatively uncommon. Most affected women are able to reproduce normally, but some develop hirsutism and menstrual irregularities, suggestive of polycystic ovary syndrome. Some patients develop mild to moderate myopathy, cardiomyopathy, and conduction system abnormalities;
- there is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Myalepta, metreleptin, EU/3/12/1022 for treatment of familial partial lipodystrophy is not removed from the Community Register of Orphan Medicinal Products.

3. Metreleptin for Treatment of Barraquer-Simons syndrome EU/3/12/1023 (EMA/OD034/12)

3.1. Product and administrative information

Product	
Active substance	Metreleptin
International Non-Proprietary Name	Metreleptin
Orphan indication	Treatment of Barraquer-Simons syndrome
Pharmaceutical form	Powder for solution for injection
Route of administration	Subcutaneous use
Pharmaco-therapeutic group (ATC Code)	Other alimentary tract and metabolism products, amino acids and derivatives (A16AA07)
Sponsor's details:	Aegerion Pharmaceuticals B.V. Atrium Building, 8th Floor Strawinskylaan 3127 1077 ZX Amsterdam The Netherlands
Orphan medicinal product designation procedural history	
Sponsor	Aptiv Solutions (UK) Limited
COMP opinion date	13 June 2012
EC decision date	17 July 2012
EC registration number	EU/3/12/1023
Post-designation procedural history	
Transfer of sponsorship	Transfer from Aptiv Solutions (UK) Limited to Bristol-Myers Squibb / AstraZeneca EEIG– EC decision of 13 February 2014 Transfer from Bristol-Myers Squibb / AstraZeneca EEIG to AstraZeneca AB- EC decision of 8 April 2014 Transfer from AstraZeneca AB to Aegerion Pharmaceuticals Limited – EC decision of 25 March 2015 Transfer from Aegerion Pharmaceuticals Limited to Aegerion Pharmaceuticals B.V. – EC decision of 30 November 2017
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Rapporteur / co-Rapporteur	B. Van der Schueren / A. Gyurasics
Applicant	Aegerion Pharmaceuticals B.V.
Application submission date	21 December 2016
Procedure start date	19 January 2017
Procedure number	EMEA/H/C/004218
Invented name	Myalepta

Therapeutic indication	Myalepta is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients: • with confirmed congenital generalised LD (Berardinelli-Seip syndrome) or acquired generalised LD (Lawrence syndrome) in adults and children 2 years of age and above • with confirmed familial partial LD or acquired partial LD (Barraquer-Simons syndrome), in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control. Further information on Myalepta can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/Find medicine/Human medicines/European public assessment reports.
CHMP opinion date	31 May 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	K. Westermark / V. Tillmann
Sponsor's report submission date	16 December 2016
COMP discussion	22-24 May 2018
COMP opinion	5 June 2018

3.2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2012 was based on the following grounds:

- Barraquer-Simons syndrome (hereinafter referred to as "the condition") was estimated to be affecting approximately 0.1 in 10,000 people in the European Union (EU), at the time the application was made. This is based on articles available in the public domain as well as expert statements;
- the condition is chronically debilitating due to the consequences of uncontrolled diabetes mellitus, hypertriglyceridemia, and steatohepatitis (e.g. risk of accelerated micro- and macrovascular complication, liver cirrhosis). The severity of metabolic abnormalities can lead to acute complications that can be debilitating such as painful eruptive xanthomas and life-threatening due to repeating bouts of acute pancreatitis;
- there is, at present, no satisfactory treatment that has been authorised in the EU for patients affected by the condition.

3.3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The sponsor is proposing that Barraquer-Simons syndrome continues to be a distinct medical entity and still suitable as an orphan condition..

Barraquer-Simons syndrome has been recently renamed acquired partial lipodystrophy (APL) APL is more frequent in females (females:males, 4:1) and usually begins in childhood or adolescence. Loss of fat follows a cranio-caudal trend, progressively affecting the face, neck, shoulders, arms, and trunk. Fat accumulation can appear in the hips, buttocks, and legs. APL is associated with autoimmune diseases, especially membranoproliferative glomerulonephritis (MPGN) in approximately 20% of patients. Most patients have low serum complement 3 (C3) levels, and some have presence of C3 nephritic factor. Metabolic complications are uncommon.

APL is part of a broader group of disorders called the lipodystrophy syndromes. These are a heterogeneous group of rare disorders that have in common selective deficiency of adipose tissue in the absence of nutritional deprivation or catabolic state. Lipodystrophies are categorized based on aetiology (genetic or acquired) and distribution of lost adipose tissue, affecting the entire body (generalized) or only regions (partial). This yields four major categories: congenital generalized lipodystrophy (CGL), familial partial lipodystrophy (FPLD), acquired generalized lipodystrophy (AGL), and acquired partial lipodystrophy (APL).

The proposed condition continues to be a distinct medical entity as described in the original orphan designation.

The approved therapeutic indication: *“Myalepta is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients:*

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

falls within the scope of the designated orphan indication “treatment of Barraquer Simmons syndrome or acquired partial lipodystrophy”.

Intention to diagnose, prevent or treat

Based on the final CHMP Day assessment, the intention to treat the condition has been justified.

Chronically debilitating and/or life-threatening nature

This condition is associated with hormonal and metabolic derangements resulting in severe comorbidities that depend on extent of fat loss, age, and gender. Many complications of lipodystrophy

are secondary to deficient adipose mass, resulting in ectopic lipid storage in the liver, muscle, and other organs and causing insulin resistance. Insulin resistance leads to diabetes, hypertriglyceridemia, polycystic ovarian syndrome (PCOS), and non-alcoholic fatty liver disease (NAFLD). Acquired partial lipodystrophy is the mildest form of lipodystrophic syndrome.

Major causes of mortality include heart disease (cardiomyopathy, heart failure, myocardial infarction, arrhythmia, liver disease (liver failure, gastrointestinal haemorrhage, hepatocellular carcinoma), kidney failure, acute pancreatitis, and sepsis.

Number of people affected or at risk

The sponsor has conducted an updated literature search to establish the prevalence of the condition. This has been submitted as an annex to the general report. It consists of 6 new publications of case reports specifically from different European countries within the European Union and provides a more current understanding of the prevalence of the condition since the original designation in 2012. (published in Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2017:10 375–383). From this new data the sponsor proposes a revised prevalence calculation of 0.0024 in 10,000 a revision downwards from 0.1 in 10,000 in 2012.

The COMP accepted the revised prevalence estimate proposed by the sponsor as the submitted calculation was based on recent data from more reliable sources than the original prevalence calculation.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

There are currently no authorised medicines for this condition in Europe. A recent publication, The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline J Clin Endocrinol Metab, December 2016, 101(12):4500–4511, offers guidance on how to manage and treat the condition.

Current therapies prevent or ameliorate the comorbidities of lipodystrophy syndromes. There is no cure for lipodystrophy and no treatment that can regrow adipose tissue. The cornerstone of therapy for metabolic complications of lipodystrophy is diet.

Significant benefit

Not applicable.

3.4. COMP position adopted on 5 June 2018

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product;
- the prevalence of Barraquer-Simons syndrome (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.002 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to the consequences of uncontrolled diabetes mellitus, hypertriglyceridemia, and steatohepatitis (e.g. risk of accelerated micro- and macrovascular complication, liver cirrhosis). The severity of metabolic abnormalities can lead to acute complications that can be debilitating such as painful eruptive xanthomas and life-threatening due to repeating bouts of acute pancreatitis;
- there is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Myalepta, metreleptin, EU/3/12/1023 for treatment of Barraquer-Simons syndrome is not removed from the Community Register of Orphan Medicinal Products.

4. Metreleptin for Treatment of Lawrence syndrome EU/3/12/1024 (EMA/OD035/12)

4.1. Product and administrative information

Product	
Active substance	Metreleptin
International Non-Proprietary Name	Metreleptin
Orphan indication	Treatment of Lawrence syndrome
Pharmaceutical form	Powder for solution for injection
Route of administration	Subcutaneous use
Pharmaco-therapeutic group (ATC Code)	Other alimentary tract and metabolism products, amino acids and derivatives (A16AA07)
Sponsor's details:	Aegerion Pharmaceuticals B.V. Atrium Building, 8th Floor Strawinskylaan 3127 1077 ZX Amsterdam The Netherlands
Orphan medicinal product designation procedural history	
Sponsor	Aptiv Solutions (UK) Limited
COMP opinion date	13 June 2012
EC decision date	17 July 2012
EC registration number	EU/3/12/1024
Post-designation procedural history	
Transfer of sponsorship	Transfer from Aptiv Solutions (UK) Limited to Bristol-Myers Squibb / AstraZeneca EEIG– EC decision of 13 February 2014 Transfer from Bristol-Myers Squibb / AstraZeneca EEIG to AstraZeneca AB- EC decision of 8 April 2014 Transfer from AstraZeneca AB to Aegerion Pharmaceuticals Limited – EC decision of 25 March 2015 Transfer from Aegerion Pharmaceuticals Limited to Aegerion Pharmaceuticals B.V. – EC decision of 30 November 2017
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	B. Van der Schueren / A. Gyurasics
Applicant	Aegerion Pharmaceuticals B.V.
Application submission date	21 December 2016
Procedure start date	19 January 2017
Procedure number	EMEA/H/C/004218
Invented name	Myalepta

Therapeutic indication	Myalepta is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients: • with confirmed congenital generalised LD (Berardinelli-Seip syndrome) or acquired generalised LD (Lawrence syndrome) in adults and children 2 years of age and above • with confirmed familial partial LD or acquired partial LD (Barraquer-Simons syndrome), in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control. Further information on Myalepta can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/Find medicine/Human medicines/European public assessment reports.
CHMP opinion date	31 May 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	K. Westermark / V. Tillmann
Sponsor's report submission date	16 December 2016
COMP discussion	22-24 May 2018
COMP opinion	5 June 2018

4.2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2012 was based on the following grounds:

- Lawrence syndrome (hereinafter referred to as "the condition") was estimated to be affecting 0.1 in 10,000 people in the European Union (EU), at the time the application was made; the sponsor has based this on articles available in the public domain as well as expert statements;
- the condition is chronically debilitating due to type II diabetes mellitus, and/or severe hypertriglyceridaemia. It is primarily the severe and often life-threatening metabolic consequences of Lawrence syndrome that contribute to significant morbidity and mortality. Severe hypertriglyceridemia is independently associated with cardiovascular risk, particularly coronary artery disease, and predisposes patients to serious conditions such as acute pancreatitis, which can be life-threatening, especially when the underlying predisposing factor cannot be corrected. Hepatic steatosis and steatohepatitis are the most common causes of cirrhosis. There is also a high incidence of proteinuric nephropathies;
- there is, at present, no satisfactory treatment that has been authorised in the EU for patients affected by the condition.

4.3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The sponsor is proposing that Lawrence syndrome continues to be a distinct medical entity which is still suitable as an orphan condition.

Lawrence syndrome has been recently renamed acquired generalized lipodystrophy (AGL).

AGL is more common in females (females:males, 3:1) and appears usually before adolescence (but may develop at any time in life) with progressive loss of fat affecting the whole body including palms and soles. Some fat accumulation can appear in the face, neck, or axillae. Metabolic complications are frequent and may be severe. AGL is often associated with autoimmune diseases.

AGL is part of a broader group of disorders called the lipodystrophy syndromes. These are a heterogeneous group of rare disorders that have in common selective deficiency of adipose tissue in the absence of nutritional deprivation or catabolic state. Lipodystrophies are categorized based on aetiology (genetic or acquired) and distribution of lost adipose tissue, affecting the entire body (generalized) or only regions (partial). This yields four major categories: congenital generalized lipodystrophy (CGL), familial partial lipodystrophy (FPLD), acquired generalized lipodystrophy (AGL), and acquired partial lipodystrophy (APL).

The proposed condition continues to be a distinct medical entity as described in the original orphan designation.

The approved therapeutic indication "*Myalepta is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients:*

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

falls within the scope of the designated orphan indication "treatment of Lawrence syndrome or acquired generalised lipodystrophy"

Intention to diagnose, prevent or treat

Based on the final CHMP assessment, the intention to treat the condition has been justified.

Chronically debilitating and/or life-threatening nature

This condition is associated with hormonal and metabolic derangements resulting in severe comorbidities that depend on extent of fat loss, age, and gender. Many complications of lipodystrophy are secondary to deficient adipose mass, resulting in ectopic lipid storage in the liver, muscle, and

other organs and causing insulin resistance. Insulin resistance leads to diabetes, hypertriglyceridemia, polycystic ovarian syndrome (PCOS), and non-alcoholic fatty liver disease (NAFLD). Acquired generalised lipodystrophy is associated with metabolic complications which are frequent and may be severe as well as autoimmune diseases.

Major causes of mortality include heart disease (cardiomyopathy, heart failure, myocardial infarction, arrhythmia, liver disease (liver failure, gastrointestinal haemorrhage, hepatocellular carcinoma), kidney failure, acute pancreatitis, and sepsis.

Number of people affected or at risk

The sponsor has conducted an updated literature search regarding establishing the prevalence of the condition. This has been submitted as an annex to the general report. It consists of 2 new publications of case reports specifically from different European countries within the European Union and provides a more current understanding of the prevalence of the condition compared to the original designation in 2012 (published in Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2017:10 375–383). From this new data the sponsor proposes a revised prevalence calculation of 0.001 in 10,000 a revision downwards from 0.1 in 10,000 in 2012.

The COMP accepted the revised prevalence estimate proposed by the sponsor as the submitted calculation was based on recent data from more reliable sources than the original prevalence calculation.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

There are currently no authorised medicines for this condition in Europe. A recent publication, The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline J Clin Endocrinol Metab, December 2016, 101(12):4500–4511, offers guidance on how to manage and treat the condition.

Current therapies prevent or ameliorate the comorbidities of lipodystrophy syndromes. There is no cure for lipodystrophy and no treatment that can regrow adipose tissue. The cornerstone of therapy for metabolic complications of lipodystrophy is diet.

Significant benefit

Not applicable.

4.4. COMP position adopted on 5 June 2018

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product;
- the prevalence of Lawrence syndrome (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.001 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to type II diabetes mellitus, and/or severe hypertriglyceridaemia. It is primarily the severe and often life-threatening metabolic consequences of Lawrence syndrome that contribute to significant morbidity and mortality. Severe hypertriglyceridemia is independently associated with cardiovascular risk, particularly coronary artery disease, and predisposes patients to serious conditions such as acute pancreatitis, which can be life-threatening, especially when the underlying predisposing factor cannot be corrected. Hepatic steatosis and steatohepatitis are the most common causes of cirrhosis. There is also a high incidence of proteinuric nephropathies;
- there is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Myalepta, metreleptin, EU/3/12/1024 for treatment of Lawrence syndrome is not removed from the Community Register of Orphan Medicinal Products.

5. Metreleptin for treatment of Berardinelli-Seip syndrome EU/3/12/1025 (EMA/OD036/12)

5.1. Product and administrative information

Product	
Active substance	Metreleptin
International Non-Proprietary Name	Metreleptin
Orphan indication	Treatment of Berardinelli-Seip syndrome
Pharmaceutical form	Powder for solution for injection
Route of administration	Subcutaneous use
Pharmaco-therapeutic group (ATC Code)	Other alimentary tract and metabolism products, amino acids and derivatives (A16AA07)
Sponsor's details:	Aegerion Pharmaceuticals B.V. Atrium Building, 8th Floor Strawinskylaan 3127 1077 ZX Amsterdam The Netherlands
Orphan medicinal product designation procedural history	
Sponsor	Aptiv Solutions (UK) Limited
COMP opinion date	13 June 2012
EC decision date	17 July 2012
EC registration number	EU/3/12/1025
Post-designation procedural history	
Transfer of sponsorship	Transfer from Aptiv Solutions (UK) Limited to Bristol-Myers Squibb / AstraZeneca EEIG– EC decision of 13 February 2014 Transfer from Bristol-Myers Squibb / AstraZeneca EEIG to AstraZeneca AB- EC decision of 8 April 2014 Transfer from AstraZeneca AB to Aegerion Pharmaceuticals Limited – EC decision of 25 March 2015 Transfer from Aegerion Pharmaceuticals Limited to Aegerion Pharmaceuticals B.V. – EC decision of 30 November 2017
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	B. Van der Schueren / A. Gyurasics
Applicant	Aegerion Pharmaceuticals B.V.
Application submission date	21 December 2016
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Procedure number	EMEA/H/C/004218
Invented name	Myalepta

Therapeutic indication	Myalepta is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients: • with confirmed congenital generalised LD (Berardinelli-Seip syndrome) or acquired generalised LD (Lawrence syndrome) in adults and children 2 years of age and above • with confirmed familial partial LD or acquired partial LD (Barraquer-Simons syndrome), in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control. Further information on Myalepta can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/Find medicine/Human medicines/European public assessment reports.
CHMP opinion date	31 May 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	K. Westermark / V. Tillmann
Sponsor's report submission date	16 December 2016
COMP discussion	22-24 May 2018
COMP opinion	5 June 2018

5.2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2012 was based on the following grounds:

- Berardinelli-Seip syndrome (hereinafter referred to as "the condition") was estimated to be affecting approximately 0.05 in 10,000 persons in the European Union (EU), at the time the application was made. This is based on published articles available in the public domain as well as expert statements;
- the condition is chronically debilitating due to diabetes mellitus and its long-term complications. Patients develop recurrent episodes of acute pancreatitis from extreme hypertriglyceridemia; end stage liver disease resulting from progressive cirrhosis secondary to hepatic steatosis and/or steatohepatitis; end-stage renal disease due to chronic kidney diseases related to diabetes or associated with the syndrome; cardiomyopathy, and accelerated atherosclerotic vascular disease. These patients die generally at a young age typically from cardiovascular, renal, or hepatic causes;
- there is, at present, no satisfactory treatment that has been authorised in the EU for patients affected by the condition.

5.3. Review of criteria for orphan designation at the time of marketing authorisation.

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The sponsor is proposing that Berardinelli-Seip syndrome continues to be a distinct medical entity and still suitable as an orphan condition.

Berardinelli-Seip syndrome has been recently renamed congenital generalized lipodystrophy (CGL). CGL is an autosomal recessive disorder characterized by near-complete lack of fat starting at birth or infancy, prominent muscles, phlebomegaly, acanthosis nigricans, hepatomegaly, umbilical prominence, and voracious appetite in childhood. Multiple genetic causes have been identified, each with unique clinical features. Metabolic complications are frequent and may be severe. Cardiomyopathy or rhythm disturbances may occur.

CGL part of a broader group of disorders called the lipodystrophy syndromes. These are a heterogeneous group of rare disorders that have in common selective deficiency of adipose tissue in the absence of nutritional deprivation or catabolic state. Lipodystrophies are categorized based on aetiology (genetic or acquired) and distribution of lost adipose tissue, affecting the entire body (generalized) or only regions (partial). This yields four major categories: congenital generalized lipodystrophy (CGL), familial partial lipodystrophy (FPLD), acquired generalized lipodystrophy (AGL), and acquired partial lipodystrophy (APL).

The proposed condition continues to be a distinct medical entity as described in the original orphan designation.

The approved therapeutic indication: *"Myalepta is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients:*

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

falls within the scope of the designated orphan indication "treatment of Berardinelli-Seip syndrome or congenital generalized lipodystrophy".

Intention to diagnose, prevent or treat

Based on the final CHMP assessment, the intention to treat the condition has been justified.

Chronically debilitating and/or life-threatening nature

This condition is associated with hormonal and metabolic derangements resulting in severe comorbidities that depend on extent of fat loss, age, and gender. Many complications of lipodystrophy are secondary to deficient adipose mass, resulting in ectopic lipid storage in the liver, muscle, and

other organs and causing insulin resistance. Insulin resistance leads to diabetes, hypertriglyceridemia, polycystic ovarian syndrome (PCOS), and non-alcoholic fatty liver disease (NAFLD)

Major causes of mortality include heart disease (cardiomyopathy, heart failure, myocardial infarction, arrhythmia, liver disease (liver failure, gastrointestinal haemorrhage, hepatocellular carcinoma), kidney failure, acute pancreatitis, and sepsis.

Number of people affected or at risk

The sponsor has conducted an updated literature search to establish the prevalence of the condition. This has been submitted as an annex to the general report. It consists of 14 new publications of case reports specifically from different European countries within the European Union and provides a more current understanding of the prevalence of the condition compared to the original designation in 2012 (published in Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2017:10 375–383). From this new data the sponsor proposes a revised prevalence calculation of 0.01 in 10,000 a revision downwards from 0.05 in 10,000 in 2012.

The COMP accepted the revised prevalence estimate proposed by the sponsor as the submitted calculation was based on recent data from more reliable sources than the original prevalence calculation.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

There are currently no authorised medicines for this condition in Europe. A recent publication, The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline J Clin Endocrinol Metab, December 2016, 101(12):4500–4511, offers guidance on how to manage and treat the condition.

Current therapies prevent or ameliorate the comorbidities of lipodystrophy syndromes. There is no cure for lipodystrophy and no treatment that can regrow adipose tissue. The cornerstone of therapy for metabolic complications of lipodystrophy is diet.

Significant benefit

Not applicable.

5.4. COMP position adopted on 5 June 2018

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product;
- the prevalence of Berardinelli-Seip syndrome (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be 0.03 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to diabetes mellitus and its long-term complications. Patients develop recurrent episodes of acute pancreatitis from extreme hypertriglyceridemia; end stage liver disease resulting from progressive cirrhosis secondary to hepatic steatosis and/or steatohepatitis; end-stage renal disease due to chronic kidney diseases related to diabetes or associated with the syndrome; cardiomyopathy, and accelerated atherosclerotic vascular disease. These patients die generally at a young age typically from cardiovascular, renal, or hepatic causes;
- there is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Myalepta, metreleptin, EU/3/12/1025 for treatment of Berardinelli-Seip syndrome is not removed from the Community Register of Orphan Medicinal Products.