Clinical Commissioning Policy Proposition: Metreleptin for congenital leptin deficiency [all ages]

Prepared by NHS England Specialised Services Clinical Reference Group for Endocrinology

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Executive Summary

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About congenital leptin deficiency

Leptin is a hormone which regulates appetite and body weight. Leptin also plays an important role in controlling blood sugar, immune control and hormone secretion. When the fat cells of the body are full, leptin is produced and signals the brain to stop eating. People with the extremely rare condition of congenital leptin deficiency are unable to make leptin and so are in a continual state of extreme hunger. This sensation of extreme hunger is overpowering. Affected individuals develop abnormal behaviour around eating, such as hiding food, secretiveness about eating and fighting over food. The condition is also associated with increased risk of infections due to impaired defence against infection; associated hormone abnormalities leads to absence of puberty. Complications of extreme obesity occur, including diabetes, sleep apnoea and bone problems.

High mortality in childhood and adolescence occurs in untreated individuals with the condition.

About current treatments

No treatment is available which modifies the disease. Supportive care can be given but the sensation of hunger overpowers any attempt at dietary control. Without treatment, very few patients survive to adulthood.

About the new treatment

Metreleptin is an artificial form of leptin. It replaces the hormone which is missing. Patients who have congenital leptin deficiency return to normal weight when treated with metreleptin. Treatment with metreleptin leads to either improvement or resolution of many of the comorbidities associated with obesity caused by congenital leptin deficiency.

Metreleptin for treating lipodystrophy. A licensing application has been submitted in the EU for metreleptin to be used to treat complications of leptin deficiency in patients with a different medical condition which also results in a lack of leptin called congenital or acquired generalised lipodystrophy and in a subset of patients with partial lipodystrophy. Marketing authorisation is expected by the end of August 2018.

What we have decided

NHS England has carefully reviewed the evidence for treating congenital leptin deficiency with metreleptin. We have concluded that there is enough evidence to consider making the treatment available.

1. Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal of metreleptin treatment for patients with congenital leptin deficiency.

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether metreleptin treatment for patients with congenital leptin deficiency will be routinely commissioned will be made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

2. Proposed Intervention and Clinical Indication

Leptin is a hormone derived from adipose tissue which plays an important role in the suppression of appetite and inthe regulation of body weight. In normal individuals, serum leptin levels are positively correlated with the mass of adipose tissue. In individuals with congenital leptin deficiency (first described by Montague et al in 1997), the appetite moderating role of leptin is compromised, leading to hyperphagia (over-eating) and severe early-onset obesity. The sensation of extreme hunger is overpowering for affected individuals. Such individuals develop abnormal behaviour around eating, such as hiding food, secretiveness about eating and fighting over food. Whereas most obese individuals exhibit high levels of serum leptin, those with congenital leptin deficiency have undetectable levels.

The condition is also associated with increased risk of infections due to impaired T-cell mediated immunity, hyperinsulinaemia, hypothalamic hypothyroidism and hypogonadotropic hypogonadism leading to failure to go into puberty (von Schnurbein et al 2012). In addition to these, complications commonly seen in obese individuals are frequently observed, such as type 2 diabetes, sleep apnoea and bone and joint problems. High mortality in childhood and adolescence is observed amongst untreated individuals with the condition.

Metreleptin is a synthetic, recombinant analogue of leptin. Successful treatment leads to significant weight loss (Paz Filho 2011) and reversal of certain comorbidities (Paz Filho 2010, Paz Filho 2008, von Schnurbein 2013, Wabisch 2015). There is no alternative treatment currently available and conventional weight loss interventions are ineffective, with bariatric surgery being contraindicated due to

the high level of risk and likely ineffectiveness amongst this patient group.

The treatment is generally administered subcutaneously, once or twice daily and continues for the lifetime of the patient. Dosage may vary depending on age, weight, gender and clinical response. The starting dose in children is calculated to achieve 10% of the predicted normal peak serum leptin concentration (0.028 milligrams per kilogram of lean body mass daily in a reported case). In adults the dose is titrated to achieve normal leptin concentrations (2.8 – 5.3 mg daily in reported cases).

Metreleptin for congenital leptin deficiency has been in clinical use in the UK for over 15 years in an extended compassionate use programme. Expert clinical advice is that it has proved effective with an excellent safety profile. Patients who have been treated usually return to a normal body weight and go through puberty at an appropriate developmental stage.

3. Definitions

Body Mass Index (BMI) – a standard measure of obesity defined as (weight in kilograms) divided by ([height in metres] squared). A BMI of over 50 indicates severe obesity.

Hyperphagia – excessive eating behaviour

Leptin – a hormone whose primary function is to regulate appetite and body weight.

Metreleptin – a synthetic version of leptin.

Z score – is measure of obesity used in children (for whom BMI is not appropriate). Fewer than 1% of children will have z score of greater than 3, so this indicates severe obesity.

4. Aims and Objectives

This policy proposition considered: the use of metreleptin in the treatment of congenital leptin deficiency.

The objectives were to review peer-reviewed evidence, published in the past 10 years, for metreleptin in the treatment of congenital leptin deficiency.

5. Epidemiology and Needs Assessment

Congenital leptin deficiency is extremely rare with only twenty people diagnosed worldwide and reported in the published literature since the condition was first recognised and described in 1997.

There are seven known patients in England with congenital leptin deficiency.

Diagnosis is based on measurement of serum leptin levels, which are undetectable in those with congenital leptin deficiency followed by sequencing of the leptin gene.

6. Evidence Base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of metreleptin in the treatment of congenital leptin deficiency.

The evidence review found seven before-after case studies of metreleptin in individuals with congenital leptin deficiency. The most commonly reported outcomes were various measures of weight reduction, generally reported as either Body Mass Index (BMI) scores or equivalent Z scores where reported for children.

The largest (n=4) study by Paz-Filho et al. (2010) also reported the longest follow-up period of 10 years. However only the effects of treatment withdrawal were observed at this time point.

The majority of studies reported far shorter follow-up periods, approximately two years on average. However this is complicated by the fact that different outcome measures were reported after different periods of follow-up.

All studies included in this review reported significant degrees of weight loss amongst both adult and child participants. Amongst 3 adults of Turkish origin with leptin deficiency, Paz-Filho et al. (2010) found a mean reduction from baseline BMI of 51.2 kg/m2 to 26.9 kg/m2 after 18 months. This represents a change in BMI classification from class 3 obesity to overweight.

Studies by Paz-Filho et al. (2008a), von Schnurbein et al. (2012 & 2013) and Wabitsch et al. (2015a & 2015b) all reported weight loss in children resulting in the equivalent annual reduction in Z score of between 1.03 (Paz-Filho, 2008a) and 2.62 (Wabitsch et al., 2015b).

Several comorbidities and associated proxy measures were reported, including glucose metabolism, lipid metabolism, cognitive development and reproductive function.

Paz-Filho et al. (2010) reported the resolution of type 2 diabetes in a woman with congenital leptin deficiency and the normalisation of blood glucose and insulin levels in three other participants.

Two studies identified the effects of leptin replacement therapy on reproductive function.

Von Schnurbein et al. (2012) identified that treatment with metreleptin lead to fast progression of pubertal development in a teenaged Austrian girl suffering from hypogonadotropic hypogonadism associated with her congenital leptin deficiency.

Paz-Filho et al. (2010) reported the development of regular menstrual periods in two female adults and normalisation of testosterone levels in one adult male. Before treatment, the participants were hypogonadic, however all developed full secondary sexual characteristics and normal sexual function.

Improvements were also noted in the cognitive development of a five year old boy by Paz-Filho (2008a). Measures of cognitive ability indicated that the case's level of ability had increased from baseline measurements placing them in the 4th percentile, this rose to the 14th percentile for verbal scores and the 30th percentile for nonverbal scores after 25 months of treatment (these values being considered within the normal range).

The studies included are of variable quality and suffer a number of limitations. These include extremely small sample sizes, lack of controls, lack of methodological information, unclear or inconsistent reporting of outcomes, lack of information on treatment adherence and lack of patient safety information.

No studies reported quality of life outcome measures or cost-effectiveness.

No comparisons were made to other treatment options or to standard care, meaning that it cannot be certain that changes post receiving treatment were due to metreleptin or due to the natural course of the disease. However this appears unlikely based on the well understood mechanism of leptin on appetite.

Despite the limitations of the evidence base, findings are broadly consistent across different studies. Most of the improvements in outcomes reflect plausible mechanisms of action based on what is known about obesity and/or the effects of leptin.

The published literature on the use of metreleptin to treat congenital leptin deficiency is limited: this is unavoidable due to the rarity of the condition. The available evidence does not preclude its use but is too limited to make blanket recommendations. Earlier reports demonstrate that leptin administration corrects the obesity, endocrine and immune abnormalities associated with congenital leptin deficiency

There is evidence of medium quality which indicates that metreleptin is effective in the treatment of congenital leptin deficiency.

Treatment with metreleptin uniformly leads to clinically meaningful reductions in BMI amongst all study participants. Where investigated further, most of this weight-loss was due to reductions in fat mass. Treatment with metreleptin lead to either improvement or resolution of many of the comorbidities associated with obesity

caused by congenital leptin deficiency.

Where tested, the withdrawal of metreleptin treatment led to the regaining of weight in participants.

In addition to the reduction in excess weight, many of the associated comorbidities such as type 2 diabetes, delayed puberty, non-alcoholic fatty liver disease, high blood pressure and high cholesterol also appear to be positively affected in the small number of participants reported.

The evidence base is sparse with only 20 patients reported in the world literature, and consists of exclusively before-after design. Longest follow up according to the constraints of the Evidence Review is less than 5 years.

Findings for the main outcomes of interest are generally consistent across studies.

The first patient treated in the UK was reported in a publication in 1999 (Farooqi et al 1999). Leptin administration resulted in substantial loss of adiposity and normalisation of metabolic and endocrine features. Further patients treated in the UK have also shown loss of weight and the expected response to treatment with no adverse effects attributable to leptin therapy.

7. Proposed Criteria for Commissioning

Therapy with metreleptin is proposed for patients with a confirmed diagnosis of congenital leptin deficiency.

Criteria for starting treatment

- Undetectable levels of leptin and homozygous mutation in the leptin gene AND measureable leptin with homozygous mutation in the leptin gene (ideally supported by studies of biological activity).

Stopping criteria

Failure of leptin therapy as indicated by:

- Reduction in body mass index of; in adults less than 5 kg/m^2 after one year of therapy; in children a Z score persistently greater than 3 after one year of therapy.

8. Proposed Patient Pathway

Children with untreated congenital leptin deficiency are likely to present to local paediatric or obesity services, because of the behavioural disturbance associated with uncontrolled appetite or because of severe obesity. The proposed pathway is from local paediatric or obesity services to an expert centre with experience in the diagnosis and treatment of genetic disorders of obesity.

Adult patients will present to local obesity services. (Most will be patients with untreated disease moving to England from other countries.) Such patients will be referred from local obesity services to an expert centre with experience in the diagnosis and treatment of genetic disorders of obesity.

This pathway is well established since metreleptin has been available on compassionate supply for over 15 years.

9. Proposed Governance Arrangements

It is proposed that this therapy is only available at centres which have experience in the diagnosis and treatment of congenital leptin deficiency.

As metreleptin is unlicensed in the treatment of congenital leptin deficiency, any provider organisation treating patients with this intervention will be required to provide assurance that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

10. Proposed Mechanism for Funding

The funding and commissioning will be managed through the relevant local NHS England Specialised Commissioning Team.

11. Proposed Audit Requirements

Outcomes will be measured as follows in all patients:

Weight

Body Mass Index or z score as appropriate

Quality of life

12. Documents that have Informed this Policy Proposition

No relevant documents exist.

13. Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned.

14. References

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