NHS Commissioning Board

Clinical Commissioning Policy: Mecasermin for treatment of growth failure

April 2013

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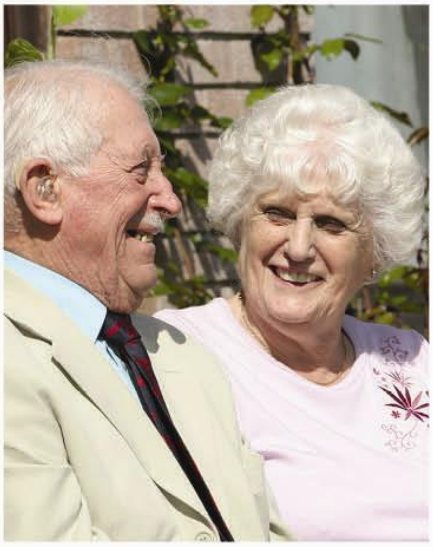

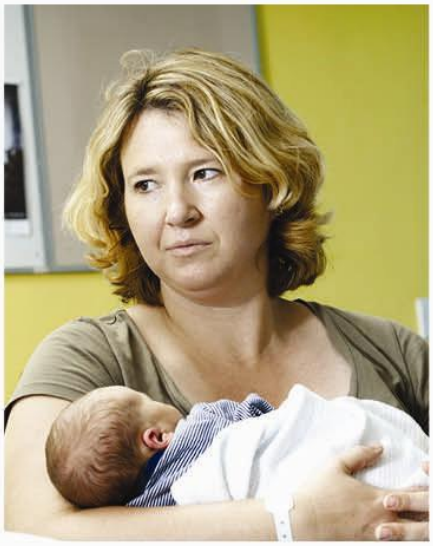

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NHS Commissioning Board

Clinical Commissioning Policy: Mecasermin for treatment of growth failure

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Contents

Policy Statement

The NHS Commissioning Board (NHS CB) will commission mecasermin for children and adolescents with growth failure due to severe primary insulin-like growth factor-1 deficiency (SPIGFD) in accordance with the criteria outlined in this document.

In creating this policy the NHS CB has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

The NHS CB has a duty to have regard to the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012.The NHS CB is committed to ensuring equality of access and non-discrimination, irrespective of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex (gender) or sexual orientation. In carrying out its functions, the NHS CB will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which they are responsible, including policy development, review and implementation.

Plain Language Summary

Primary insulin-like growth factor-1 deficiency (IGFD) or Laron syndrome is a genetic disorder. People with this disorder are not growth hormone deficient, and therefore, cannot be expected to respond adequately to growth hormone treatment. IGFD is caused by a lack of growth hormone receptors that work normally. Primary IGFD is a serious and chronically debilitating condition which if untreated can result in obesity, hyperlipidaemia (high levels of lipids in the blood), insulin resistance (normal amounts of insulin are inadequate to produce a normal insulin response), muscle weakness and osteoporosis (bone disease).

Mecasermin is a drug that works by replacing IGF-1 to mediate the effects of growth hormone, thereby promoting the growth of bones and supporting the growth of tissues. It is licensed for the long-term treatment of growth failure in children and adolescents with severe primary insulin-like growth factor-1 deficiency.

Despite a relatively high cost, the NHS Commissioning Board accepts mecasermin for use in England because of the long-term benefits of the treatment and the lack of treatment alternatives for the condition.

Information on the outcome of treatments for these patients will be collected and considered when this policy is reviewed.

1. Introduction

Growth hormone insensitivity syndrome (GHIS) encompasses a variety of genetic and acquired conditions in which the action of growth hormone (GH) is absent or attenuated. One form of primary GHIS, Primary insulin-like growth factor-1 deficiency (IGFD) or Laron syndrome, is an autosomal recessive disorder caused by a deficiency of functional growth hormone receptors (GHR). Affected individuals have growth failure, physical characteristics of GH deficiency, and low serum concentrations of insulin-like growth factor-1 (IGF-1) despite normal or increased serum GH concentrations.[1] Severe primary insulin-like growth factor-1 deficiency (SPIGFD) includes patients with mutations in the GHR, post-GHR signalling pathway, and IGF-1 gene defects; they are not growth hormone deficient, and therefore, they cannot be expected to respond adequately to exogenous growth hormone treatment.[2] This disorder is distinct from secondary IGFD, which is caused by abnormalities in the GH/IGF-1 axis such as GH deficiency. Primary IGFD is a serious and chronically debilitating condition which if untreated can result in obesity, hyperlipidaemia, insulin resistance, muscle weakness and osteoporosis.[1]

Mecasermin is a recombinant DNA-derived human insulin-like growth factor-1 (rhIGF-1) produced in Escherichia coli. IGF-1 mediates effects of growth hormone, promoting growth in bones and through its insulin-like action supports growth of tissues.[2] It is licensed for the long-term treatment of growth failure in children and adolescents with severe primary insulin-like growth factor-1 deficiency (SPIGFD)[3] SPIGFD is defined by:

- Height standard deviation score ≤ -3.0 and
- Basal insulin-like growth factor-I (IGF-1) levels below the 2.5th percentile for age and gender and
- Growth hormone sufficiency
- Exclusion of secondary forms of IGF-1 deficiency (IGFD), such as malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti- inflammatory steroids.

Mecasermin has been designated an orphan medicinal product for the treatment of primary IGFD. The calculated prevalence of this condition is less than 2 per 10,000 EU population.[1]

2. Definitions

Mecasermin is a recombinant DNA-derived human insulin-like growth factor-1 (rhIGF-1) produced in Escherichia coli. IGF-1 mediates effects of growth hormone, promoting growth in bones and through its insulin-like action supports growth of tissues.

3. Aim and objectives

The aim of this policy is to describe the indications that the NHS Commissioning Board will approve the use of mecasermin in children and adolescents.

4. Criteria for commissioning

Mecasermin is licensed for the long-term treatment of growth failure in children and adolescents with severe primary insulin-like growth factor-1 deficiency (SPIGFD).[3] SPIGFD is defined by:

- Height standard deviation score ≤ -3.0 and
- Basal insulin-like growth factor-I (IGF-1) levels below the 2.5th percentile for age and gender and
- Growth hormone sufficiency
- Exclusion of secondary forms of IGF-1 deficiency (IGFD), such as malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids.

Severe primary IGFD includes patients with mutations in the GH receptor (GHR), post-GHR signaling pathway, and IGF-1 gene defects; they are not GH deficient, and therefore, they cannot be expected to respond adequately to exogenous GH treatment. It is recommended to confirm the diagnosis by conducting an IGF-1 generation test.

Mecasermin is not recommended for use in children below age 2 due to a lack of data on safety and efficacy.

5. Patient pathway

Initial referrals may have originated from a variety of clinicians such as Health Visitors, Community Paediatricians or School Health Service Services for example. Most of these referrals would be via GPs to secondary care and then onwards to tertiary care centres**.**

6. Governance arrangements

Treatment should be directed by physicians who are experienced in the diagnosis and management of patients with growth disorders.

7. Epidemiology and needs assessment

The calculated prevalence of SPIGFD condition is less than 2 per 10,000 EU population.[1]

8. Evidence base

The Bedfordshire and Luton Joint Prescribing Committee has undertaken a review of the literature and national policies.[4] This is summarised below:

Clinical Effectiveness

Evidence presented in the company submission to the authorities includes five studies which have been conducted to evaluate the long-term safety and efficacy of mecasermin in 76 children with severe primary insulin-like growth factor-1 deficiency (SPIGFD). Four of the studies have been completed, including one phase II (F0206s) and three phase III (F0375g, F0632g, and F0671g) trials.

The remaining study (1419) is a long-term, open-label, extension study, which is an integrated analysis of all five studies and is ongoing. Only F0375g was randomised, double-blind and placebo- controlled, the other four trials were single-arm uncontrolled.[2]

Study F0632g [2a cited in 2] was the only dose-response study carried out to determine whether a lower dose of mecasermin than had been administered previously (60 micrograms/kg given subcutaneously twice daily) could be efficacious. A total of six naïve-to treatment patients received this dose for one year; however results showed that this lower dose of mecasermin was not sufficient in the treatment of primary IGFD.[2]

Studies F0375g [2a cited in 2], **F0671g** [2a cited in 2] **F0206s** [2b cited in 2], & **1419** [2c cited in 2]
In study 1419, a total of 76 patients were enrolled, 22 of whom had participated in at least one of four the previously completed studies and had transferred from one protocol to another. All results from the previous studies are integrated into this pivotal study, therefore only this study is discussed below (details of the other trials can be accessed from the All Wales Medicines Strategy Group (AWMSG) evaluation.[2] The main primary enrolment criteria and the exclusion criteria were similar for all studies. Participants in these four studies were enrolled in the US and from 21 other countries and had growth failure due to SPIGFD associated with either GHR defects or growth hormone gene-deletion defects, and anti-growth hormone antibodies.[2]

Study 1419. As study 1419 remains ongoing (designed to follow patients to adult heights), only those subjects who completed one year of therapy have been included in the primary efficacy analysis (n=62), whereas all subjects enrolled in the study have been included in the safety analysis (n=76). It should be noted that in the late 1980s rhIGF-1 was manufactured by a number of companies, and until March 2007 there were two formulations of rhIGF-1 in the US. Some of the patients in this integrated analysis have therefore received different rhIGF-1 materials.[2]

Twenty-two children were from previous studies and an additional 53 patients (44 who were naïve-to treatment) were enrolled in this study. On average, the patients were treated for 4.4 years ± 3.1 years, at the time of cut-off, representing a total exposure of 321 patient-years.[2]

In this pivotal study patients were over 2 years old, with SPIGFD whose definition included height standard deviation scores (HSDS) of <-2, a height velocity <50th percentile and an IGF-1 standard deviation (SD) score <-2. Patients had evidence of GH sufficiency, and resistance defined as failure to increase serum IGF-1

Patients received mecasermin 80 to 120mcg/kg sc twice daily; some received reduced initiation doses. Additionally 14 patients received a gonadotropin releasing hormone analogue in an attempt to achieve greater adult height by delaying puberty and prolonging the growth period. Patients were reviewed biannually for the various outcome assessment measures. On average, the patients were treated for 4.4 years ± 3.1 years, at the time of cut-off, representing a total exposure of 321 patient-years. Height velocity was the primary efficacy endpoint. Of the study population, 62 patients had completed at least one year of mecasermin therapy. Of these, 53 (85%) had Laron syndrome-like syndrome phenotype; seven (11%) had growth hormone deletion, and one (2%) had neutralising antibodies to growth hormone. In total 38 (61%) patients were male and 49 (79%) were Caucasian. Most (90%) were pre-pubertal at baseline.

At baseline patients had a chronological age of 6.8±3.8 years, height of 85±15.3cm and bone age of 3.9±2.8 years. The effect of mecasermin on height velocity could be assessed in 59 patients who were naïve to treatment and also had a pre-treatment height velocity measurement. Mean height velocity rose from 2.8 cm/year pre-treatment, to 8.0 cm/year during the first year of treatment ($p<0.0001$). The patient numbers dropped throughout the duration of the study. The mean height velocities reported however for years 2 through 6 (5.8, 5.5, 4.7, 4.7, and 4.8 cm/year, respectively) remained statistically significantly greater than baseline ($p<0.0001$, $p<0.0001$, $p<0.0001$, $p=0.0015$, and $p=0.0009$, respectively). There were positive trends for years seven and eight (mean height velocities were 4.6 cm/year [n=16] and 4.5 cm/year [n=14], respectively); mean change from baseline was not significant. Further analysis of height velocity showed no significant differences between males (n=38) and females (n=24), nor correlation between age and year one height velocity in treatment naïve patients (n=62). Additionally height velocities between the two cohorts (Laron Syndrome (n=53) and GH gene deletion (n=7)) were similar at all times. Near-adult height was evaluated in all patients whose most recent bone age was at least 16 years for males and 14 years for females. Six patients (2 males and 4 females) attained near-adult height and the average increase in adult height was approximately 16±8cm compared to height changes expected in untreated subjects.[1, 2]

Points to note about the studies [1, 2]

Due to ethical considerations there was no control group in the pivotal study and sample sizes for this orphan indication were small. However, efficacy was assessed with respect to pre-treatment growth velocity and supplemented by height velocity SD scores in order to also compare height velocities with height velocities expected for age-matched children in the general population. A similar analysis was carried out for height SD score.[1]

Growth response was similar for all subjects regardless of the severity of disease.[1]

No quality of life data were included in any of the studies.[2]

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) raised concerns on the efficacy and safety results in Study 1419 due to varying rhIGF-I materials used in the patient population and the fact that patients were collected from several studies. Further analysis carried out by the company demonstrated that the efficacy results for the 44 naive-to treatment patient cohort were

Adverse events were generally lower in the 44-patient cohort; suggesting no specific safety issue with the previous rhIGF-I materials.[2]

In an attempt to achieve greater adult height by delaying puberty and prolonging the growth period, 14 children in Study 1419 received Lupron® (a gonadotropin releasing hormone analogue). Height velocity following initiation of Lupron® therapy was expected to be lower in these individuals; however no special adjustments were made for the analyses of height velocity or height standard deviation score.[2]

According to the guidance from CHMP on products containing somatropin, change in height velocity standard deviation score from baseline is the recommended primary efficacy endpoint. However, in study 1419 height velocity was chosen as the primary endpoint because it is considered by the company to be more interpretable as an endpoint than either height velocity standard deviation score or height standard deviation score (an explanation is outlined in the company submission).[2]

The inclusion criteria for the pivotal study included HSDS <-2 for age and gender which differs from the definition of severe primary IGFD for the indication under review. However the actual mean HSDS at baseline was -6.5±1.8 (range; -12.1 to - 2.8) and reflects the licensed indication.[1]

Although the clinical trials included children and adolescents of various ages, expert opinion obtained by the company suggests that in Welsh clinical practice, subjects with SPIGFD will be diagnosed and commence treatment between the ages of 2-4 years.[2]

The company have highlighted in their submission that the licensed indication in the US is broader than in the UK. In addition to patients with Laron-type SPIGFD, mecasermin is also indicated in the US for the treatment of growth failure in children with growth hormone gene deletion who have developed neutralising antibodies to growth hormone.[2]

Additional published study

Following the evaluation of mecasermin by the AWMSG (October 09)[2] and Scottish Medicines Consortium (SMC) (August 09)[1] one additional study has been published involving 136 patients.[4] However, the patients are not strictly comparable to those patients reported in Study 1419, as they generally have a less severe form of the disease[2] and therefore not all patients may strictly fall within the UK licensed indication.

National Guidance: National Institute of Health and Clinical Excellence (NICE)

Not reviewed by NICE and is not in the current work programme. NICE has issued Final Appraisal Determination on somatropin (human growth hormone) for treatment of growth failure in children (NICE technology appraisal guidance 42).

All Wales Medicines Strategy Group (AWMSG)

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Mecasermin (Increlex®) is recommended for use within NHS Wales for the long-term treatment of growth failure in children and adolescents with severe primary insulin-like growth factor-I deficiency Treatment should be initiated and monitored by physicians who are experienced in the diagnosis and management of patients with growth disorders. AWMSG is of the opinion that mecasermin (Increlex®) is not

Additional notes

AWMSG considers that mecasermin (Increlex®) meets the AWMSG criteria for ultra orphan drug status. AWMSG recommends that there should be careful monitoring of the long term effects of mecasermin (Increlex®) treatment and that information should be collated and included in the already-established European Registry.[2]

Scottish Medicines Consortium (SMC)

Mecasermin (Increlex®) is accepted for use within NHS Scotland for the long-term treatment of growth failure in children and adolescents with severe primary insulin- like growth factor-1 deficiency (SPIGFD). Mecasermin significantly improved mean height velocity, mean height velocity standard deviation (SD) score and mean cumulative change in height SD score for at least 6 years. Serious adverse effects including hypoglycaemia and tonsillar hypertrophy are common and long-term safety data are lacking.[1]

Cost Effectiveness

All Wales Medicines Strategy Group (AWMSG)

The company's submission describes a cost utility analysis of mecasermin compared against no treatment in patients aged 2-4 years with SPIGFD. Short-term data from the open-label, non- comparative study 1419 has been used to model predicted height of patients undergoing treatment up to the point of treatment cessation (assumed to be age 14 years in girls, age 16 years in boys). In the base case analysis, the model estimates an incremental cost per quality adjusted life year (QALY) gained of £47,516. However, the gain in utility with increased height assumed in the base case analysis is subject to considerable uncertainty and sensitivity analyses indicate that the model is extremely sensitive to this parameter. An estimate of utility drawn from the literature on short stature in the general population results in an incremental cost effectiveness ratio (ICER) of £95,459 per QALY gained. There is no consideration given to any potential disutility associated with the incidence of treatment-related adverse events or the requirement for twice daily subcutaneous injections over the long term. There are significant uncertainties in the assumed utility values in the economic model, which leads to significant uncertainty in the estimates of cost effectiveness.

Based on various assumptions to assess the budget impact, the company submission reports that the net cost impact of the use of mecasermin would be around £11,000 in 2009, rising to around £70,000 in 2013 in Wales. This is considered to be the likely upper limit of the costs due to the assumption of one incident case per year in Wales, when currently there are not known to be any diagnosed patients in Wales. It is worth reflecting that a five year budget impact analysis based on patients starting treatment at age three years does not capture the ongoing costs of treatment as patients growth. Treatment is expected to continue until near adult height (assumed to be age 16 years in boys and 14 years in girls in the economic model), during which body weight, and hence the dose and costs of mecasermin, would increase substantially.[2]

Scottish Medicines Consortium (SMC)

Although there were residual concerns with the economic case presented by the company (as stated above), SMC considered the submission within the context of its statement on orphan medicines.

The Committee concluded that the life-long benefits of the treatment and the lack of alternative treatment options justified acceptance of the relatively high cost per QALY and substantial level of uncertainty.

The manufacturer estimated the net budget impact including management costs to be £22k in year 1 rising to £139k. The gross drug budget impact was estimated to be £18k in year 1 rising to £127k in year 5. There is currently one patient in Scotland with this condition and the manufacturer assumed there would be an upper limit of ten new patients over the next 5 years, with two new patients being diagnosed each year[1].

9. Rationale behind the policy statement

Primary IGFD is a serious condition caused by a lack of growth hormone receptors that work normally. Affected individuals fail to grow and have abnormally low levels of insulin-like growth factor-1 (IGF-1) when growth hormone levels are normal or increased. If the condition is untreated, it can result in obesity, hyperlipidaemia (high levels of lipids in the blood), insulin resistance (normal amounts of insulin are inadequate to produce a normal insulin response), muscle weakness and osteoporosis (bone disease).

- Mecasermin is a drug that works by replacing IGF-1 to mediate the effects of growth hormone, thereby promoting the growth of bones and supporting the growth of tissues.
- Mecasermin significantly increased growth by at least 5 cm in the first year and height remained significantly greater than baseline levels for years 2 to 6.
- The most common side effects reported with mecasermin were hypoglycaemia (lower than normal levels of sugar in the blood), lipohypertrophy (accumulation of extra fat) at injection sites, headache, snoring and enlarged tonsils.
- Despite a relatively high cost, the NHS Commissioning Board accepts mecasermin for use in England because of the long-term benefits of the treatment and the lack of treatment alternatives for the condition.

10. Mechanism for funding

The NHS Commissioning Board will fund the use of mecasermin (drug costs, patient follow up and monitoring) within its licensed indications. Prior approval is expected for contract monitoring purposes before commencing treatment for new patients.

11. Audit requirements

Annual height measurements to compare to the model of predicted height of patients undergoing treatment up to the point of treatment cessation (assumed to be age 14 years in girls, age 16 years in boys).

Calculation of annual height velocity standard deviation score against baseline.

12. Documents which have informed this policy

See references.

13. Links to other policies

This policy is informed by the generic NHS CB commissioning policies covering experimental treatments and the process by which individual funding requests (IFR) are handled.

14. Date of review

A decision on when to review of this policy will be taken in April 2014

15. Glossary

Terms are explained in the text except for;

- CRG – Clinical Advisory Group
- DNA – Deoxyribonucleic Acid

References

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3. Summary of Product Characteristics INCRELEX® (Mecasermin) 10 mg/mL solution for injection. (Date of revision 17th March 2009) accessed via http://emc.medicines.org.uk/

4. NHS Bedfordshire March 2011 Bedfordshire and Luton Joint Prescribing Committee (JPC) Report. April 2010 to March 2011 accessed via www.bedforshire.nhs.uk

Change Notice for Published Specifications and Products

developed by Clinical Reference Groups (CRG)

Amendment **to the Published Products**

Product Name	Mecasermin for treatment of growth failure
Ref No	E03/P/a
CRG Lead	Paediatric Medicine

Description of changes required

Describe what was stated in original document	Describe new text in the document	Section/Paragraph to which changes apply	Describe why document change required	Changes made by	Date change made
Mecasermin	Mecasermin for treatment of growth failure	Title page and 2nd page	To standardise naming and coding of products	Programme of Care Director for Women and Children	September 2013