CLINICAL PRIORITIES ADVISORY GROUP
Month Year

Agenda Item No	
National Programme	Internal Medicine
Clinical Reference Group	Specialised Endocrinology
URN	1698

Title
Policy Proposition: Metreleptin for Congenital Leptin Deficiency [all ages]

Actions Requested	1. Recommend the adoption of the policy proposition 2. Consider relative prioritisation

Proposition
Routinely commissioned
Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes where necessary an: Evidence Review; Clinical Panel Report
2.	The Head of Acute Programmes/Head of Mental Health Programme confirms the proposal is supported by an: Impact Assessment; Stakeholder Engagement Report; Consultation Report; Equality Impact and Assessment Report; Service Specification Proposition. The relevant National Programme of Care Board has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Operational Delivery Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.
5.	The Director of Nursing (Specialised Commissioning) confirms that the proposed quality indicators have been adequately defined.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report
3.	Evidence Summary including additional advice from the NCD Obesity and Diabetes
4.	Clinical Panel Report
5.	Equality Impact and Assessment Report

The Benefits of the Proposition			
No	*Metric*	*Grade of evidence (where evidence review completed)*	*Summary of benefit (where applicable)*
1.	Survival	Not measured	Where an evidence review has been completed, please include metric of survival (e.g., 30 days benefit, 50 years benefit)
2.	Progression free survival	Not measured	
3.	Mobility	Not measured	
4.	Self-care	Not measured	
5.	Usual activities	Not measured	
6.	Pain	Not measured	
7.	Anxiety / Depression	Not measured	
8.	Replacement of more toxic treatment	Not measured	
9.	Dependency on care giver / supporting independence	Not measured	
10.	Safety	Not measured	
11.	Delivery of intervention	Not measured	

Other health metrics determined by the evidence review *(where evidence review completed)*			
No	Metric	Grade of evidence	Summary from evidence review
1	Weight-loss	Grade A	Weight gain is one of the primary symptoms of congenital leptin deficiency and is associated with complications commonly seen in obese individuals, such as type 2 diabetes, sleep apnoea and advanced bone age. The findings by Paz-Filho et al (2010) report that three adults reduced from a mean BMI of 51.2 kg/m2 to one of 26.9 kg/m2 after 18 months of treatment. This represents a change in classification from class 3 obesity to overweight and compares favourably to the rate of weight-loss seen in bariatric surgery for individuals being treated for normal obesity (Colquitt et al., 2014). However, after ten years the mean BMI value had increased slightly to 29.5 kg/m2. The boy saw a reduction in BMI, from a baseline of 39.6 kg/m2 before treatment at age 5, to 22.6 kg/m2 at age 9. These results suggest that all patients administered metreleptin will see a clinically significant degree of weight loss. However, whether this can be maintained in the long-term is unknown, with some doubt being cast by the increase observed after longer term follow-up. This is not unusual amongst weight-loss interventions in general, where drastic weight-loss is often followed by a degree of regain. All cases reported in the identified papers are either Turkish, German or Austrian in origin, limiting generalisability to the UK population.
2	Bone Mineral Density	Grade A	There is controversy around how obesity may influence Bone Mineral Density (Migliaccio et al., 2010). Low BMD is related to an increased risk of bone fracture. Bone Mineral Density (BMD) was reported by just one study in this review (Paz-Filho

			et al., 2010). Before treatment, one patient had low BMD of 0.924 g/cm2 at the lumbar spine whilst two females had normal BMD measurements at all sites. After 6 years, the male participant's BMD at the lumbar spine increased by 11% to 1.042 g/cm2. The female participants' BMDs remained within normal range, without significant changes. These findings should be interpreted with caution. Findings were reported for a single patient from a single, small, trial. In addition to this, no statistical tests were performed to check the significance of the change. This means that the results may not be applicable to the wider population and could have been caused by chance, bias or confounding.
3	Lipid Metabolism	Grade A	Cholesterol levels are used as an indicator of cardiac and vascular disease risk, particularly in the presence of other conditions such as type 2 diabetes. High levels of LDL cholesterol and triglycerides are seen as undesirable, whilst HDL cholesterol has been shown to lend a protective effect, specifically by reducing accumulation of atherosclerosis on artery walls. Changes in blood lipids were reported by Paz-Filho et al (2010) over an 18 or 24 month time period. Before treatment, all patients had low HDL-cholesterol and normal or high triglycerides. Leptin replacement normalised serum lipid levels, with LDL cholesterol reducing on average (mean) by 31.5 mg/dL after 24 months, triglycerides reducing by 79.0 mg/dL over 18 months and HDL increasing by 19.2 mg/dL over 18 months.
4	Glucose Metabolism	Grade A	Measurements of glucose and insulin provide important information around risk of type 2 diabetes. Type 2 diabetes carries with it significant health impacts for the patient as well as costs to the health system associated with long-term treatment. Reducing the risk of onset of type 2 diabetes is therefore an important outcome, as is resolution of the condition

			in those who have already acquired it. Paz-Filho et al. (2010) reported that type 2 diabetes was resolved in a 49-year-old female participant after normalisation of blood insulin and glucose levels. Blood glucose and insulin levels were normalised in the remaining three participants also. The study by Paz-Filho et al. (2010) only reported on a single case with type 2 diabetes. This means that the causality of resolution of this condition cannot be attributed to metreleptin for certain. However, taking into account the effects of metreleptin on glucose metabolism amongst other reported cases, the effects of treatment on type 2 diabetes appear plausible.
5	Hepatic Lipids	Grade B	Fatty liver disease (also known as hepatic steatosis) is a complication of congenital leptin deficiency, also seen in cases of normal obesity. It is associated with the accumulation of fat in the liver, leading to inflammation and in serious cases cirrhosis. The condition is complicated by its relationship with hyperinsulinemia which leads to hepatic insulin resistance. Von Schnurbein et al. (2013) reported outcomes for a single case with non-alcoholic fatty liver disease. Hepatic lipids were high (49.7%) prior to leptin therapy. Within 3 days after the start of leptin therapy, there was a slight but obvious decrease in hepatic lipids to 46.5%, which continued to 24.0% after 3 months and to 9.4% after 15 months. A value of 3.05% is representative of normal-weight 20-29 year old women (Ulbrich et al., 2015). This study does not report if the observed changes are statistically significant and the study is a single-subject, before-after design without controls. It is uncertain therefore how generalisable the findings are. The follow-up time of the study is limited and whether the changes observed are representative of long-term

			improvements cannot be concluded.
6	Cardiac Risk	Grade B	Blood pressure is a known risk factor for many diseases, such as heart disease, stroke and kidney failure. Paz-Filho et al. (2008a) reported blood pressure normalisation in a child of Turkish background. At baseline the patient's blood pressure was 110/70 mmHg, just above the 90th percentile for their age. After 25 months of treatment, their blood pressure was normalised, at 101/66 mmHg. As with several of the other studies included in this review, this study describes only a single case, making it difficult to generalise to the wider population of congenital leptin deficient individuals. In addition to this the case is from a consanguineous, Turkish background which may not be as common in England as it is in other European countries. The follow-up period was limited to 25 months meaning evaluation of the long-term impact of treatment is not possible.
7	Cognitive Development	Grade B	A connection between leptin and cognitive development is hypothesised due to the links between the hormone and several aspects of neural development, including neuron excitability, synaptic plasticity, neural differentiation, migration of neuronal lineage cells to the cortical plate, and regulation of development of hypothalamic feeding (Paz-Filho et al., 2008a). Paz-Filho et al. (2008a) reported that leptin replacement therapy in a 7 year old Turkish child appeared to be associated with changes in rates of development in several neurocognitive domains. The patient's pre- and post- treatment verbal and nonverbal cluster scores were lower than those for age-matched comparators. Treatment was followed by an upward

			trend in development, with scores generally normalising after two years. Pre-treatment verbal and nonverbal scores were in the 4th percentile. After two years, the patient's verbal scores were in the 14th percentile while his nonverbal scores were in the 30th percentile, both broadly within normal limits for his age. Despite the translation of the test instructions and language based measures, it should be noted that the tests used to measure neurocognitive development in this study may have given biased results due to the patient's cultural background and language. Although this may not affect the internal validity of the study, it presents another issue affecting how generalisable the findings may be. Due to the lack of controls in the study, the patient could only be compared against their own baseline values, it was presumed by the authors that the case's cognitive functioning at pre-treatment evaluation was representative of their cognitive functioning from birth until baseline evaluation. Whilst the authors hypothesis the link between leptin and neuro cognitive development, it is not clear whether there may be other factors contributing towards this, potentially stemming from the known consanguinity within the patient's family.
8	Reproductive Function	Grade B	Leptin is known to play a role in pubertal development and progression, acting as a marker of metabolic status and body weight for the hypothalamus to trigger puberty (El-Eshmawy et al., 2010). It can be profoundly distressing for those experiencing it and has implications for fertility. Paz-Filho et al. (2010) reported that before treatment, three adult participants were hypogonadic. After treatment, menstrual periods became regular in both female adults. The male adult's testosterone and free testosterone levels reached normal values. All adults fully developed

			secondary sexual characteristics and developed normal sexual function. As with all studies included in this review, the small number of cases does make it extremely challenging to generalise to the wider population of those with congenital leptin deficiency. That being said, the effects of leptin upon pubertal development are known in the wider literature and the association between metreleptin treatment and pubertal onset is biologically plausible.

Considerations from review by the Rare Disease Advisory Group
To be completed

Pharmaceutical considerations
A licensing application has been submitted in the EU for metreleptin to be used to treat complications of leptin deficiency in patients with congenital or acquired generalised lipodystrophy and in a subset of patients with partial lipodystrophy. Following marketing authorisation, use for congenital leptin deficiency would be classed as an off-label use of an approved medication. Currently metreleptin is provided free of charge by Aegerion Pharmaceuticals as part of a named patient programme for compassionate use.

Considerations from review by National Programme of Care
POC Board support: 1) The proposal received the full support of the Internal Medicine PoC Board on the <insert date> 2) The proposal received the support of the <insert PoC name> PoC Board on the <insert date>, subject to the following comments <insert comments> 3) The proposal received the support of the <insert PoC name> PoC Board on the <insert date> but CPAG is asked to note that the proposal did not have the full support of the Policy Working Group, who have raised the following concerns: <insert reasons> 4) Other – free text (only for minority of cases not fitting into the above)

SECTION 2 – IMPACT REPORT (Not included in CPAG Papers, section 2 only)

No	Item	N/Cost £K	Level of uncertainty
1.	Number of patients affected in England	Source: IA Report, A1.2	[FOR IN-HOUSE POLICIES, TO BE COMPLETED BY FINANCE LEAD]
2.	Total cost per patient over 5 years	Source: IA Report C2.1 and 2.2, and Model	[FOR IN-HOUSE POLICIES, TO BE COMPLETED BY FINANCE LEAD]
3.	Budget impact year 1	Source: IA Report C3.1 and Model	[FOR IN-HOUSE POLICIES, TO BE COMPLETED BY FINANCE LEAD]
4.	Budget impact year 2	Source: IA Report C3.1 and Model	[FOR IN-HOUSE POLICIES, TO BE COMPLETED BY FINANCE LEAD]
5.	Budget impact year 3	Source: IA Report C3.1 and Model	[FOR IN-HOUSE POLICIES, TO BE COMPLETED BY FINANCE LEAD]
6.	Budget impact year 4	Source: IA Report C3.1 and Model	[FOR IN-HOUSE POLICIES, TO BE COMPLETED BY FINANCE LEAD]
7.	Budget impact year 5	Source: IA Report C3.1 and Model	[FOR IN-HOUSE POLICIES, TO BE COMPLETED BY FINANCE LEAD]
8.	Total number of patients treated over 5 years	Source: IA Report A3.2	[FOR IN-HOUSE POLICIES, TO BE COMPLETED BY FINANCE LEAD]]
9.	Net cost per patient treated over 5 years	(Sum of Budget impact year 1-5) / (Total no. patients treated over 5 years)	[FOR IN-HOUSE POLICIES, TO BE COMPLETED BY FINANCE LEAD]
Key additional information			
[TO BE COMPLETED BY NHS ENGLAND FINANCE (Andy Leary / Justine)			