CLINICAL PRIORITIES ADVISORY GROUP
06 and 07 November 2018

Agenda Item No	04.7
National Programme	Internal Medicine
Clinical Reference Group	Specialised Endocrinology
URN	170095P

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

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend the relative priority

Proposition
This proposal is for routine commissioning of metreleptin for patients with 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. Affected individuals develop abnormal behaviour around eating, such as 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.

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 an: Evidence Review; Clinical Panel Report
2.	The Head of Acute Programmes confirms the proposal is supported by an: Impact Assessment; Stakeholder Engagement Report; Consultation Report; Equality Impact and Assessment Report; Clinical Policy 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.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality Impact and Assessment Report

The Benefits of the Proposition		
No	*Metric*	*Summary from evidence review*
1.	Survival	Not measured
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 /	Not measured

	supporting independence	
10.	Safety	Not measured
11.	Delivery of intervention	Not measured

Other health metrics determined by the evidence review		
No	Metric	Summary from evidence review
1.	Weight-loss	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 Body Mass Index (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. One patient had a reduction in BMI, from a baseline of 39.6 kg/m2 before treatment at age 5 years, to 22.6 kg/m2 at age 9 years. 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 Turkish, German or Austrian in origin, limiting generalisability to the UK population.
2.	Bone Mineral Density	There is controversy around how obesity may influence Bone Mineral Density (BMD) (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	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 low density lipoprotein (LDL) cholesterol and triglycerides are seen as undesirable, whilst high density lipoprotein (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	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	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	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	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, Neutral 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.
8.	Reproductive Function	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 Rare Disease Advisory Group
RDAG supported the proposal for a Clinical Commissioning Policy Proposition for metreleptin for congenital leptin deficiency on the basis that it covered those seven patients who were the commissioning responsibility of NHS England. The other 13 patients being treated ([redacted] from Scotland and the majority of the others from outside the EU) were not the commissioning responsibility of NHS England.

Pharmaceutical considerations
This policy recommends metreleptin for the treatment of congenital leptin deficiency. This is an off label use of the drug. It is excluded from tariff.

Considerations from review by National Programme of Care Board
The NPoC Board noted this proposal is for a defined group of patients with congenital leptin deficiency who were not considered within the licensed indication or by the NICE HTA. The NPOC Board agreed some further actions should be taken to reach out to families affected by this condition. Aside from this point the proposal received the full support of the National Programme of Care Board Meeting 27th September 2018.