A.42	Somatropin – hypoglycaemia secondary to growth hormone deficiency – EMLc
Draft recommendation	☐ Recommended ☒ Not recommended Justification: Human growth hormone (GH) stimulates growth and cell regeneration. Somatropin (rhGH) is a recombinant form and used to treat growth hormone deficiency – and resulting hypoglycaemia - in children and adolescents. While neonatal hypoglycaemia is a common condition (the most common metabolic problem in neonates, with an incidence of 5–15% of all births and is common with 30% of at-risk infants[1], hypoglycaemia due to GH deficiency is dependent on GHD epidemiology. The prevalence rate of idiopathic GH deficiency in the USA and UK is between 1 in 3,400 and 4,000. Other estimates give worldwide prevalence of GHD at approximately 1:4,000 to 1:10,000[2]. Letters of support were added to the application from patient and professional societies, joining interested parties form several countries. These letters were sent from societies harbored in Canada, New Zealand, Switzerland, and the USA (Global Pediatric Endocrinology and Diabetes, the International Consortium for Pediatric Endocrinology and Diabetes (ICPE), the Endocrine Society and the MAGIC Foundation. All stress the importance of role of hypoglycemia control in neonates, infants and young children with with GH deficiency. However, the indication lacks evidence of effectiveness and of comparative effectiveness, and three other drugs that may be used for the same indication are present in the EMLc. There is also very little information on safety. Of course, in neonatal and infant population, RCTs are very rare. But some do exist – and even SR with MA - for other alternatives on the list. Also, because of lack of evidence of effectiveness, there is no evidence of cost-effectiveness. One aspect that must be highlighted is the misuse of rhGH for performance enhancement because of its anabolic properties, which may result in unsanctioned off label use in several jurisdictions[3,4].
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Human growth hormone (GH), somatotropin, is a pituitary hormone, a peptide, that stimulates growth and cell regeneration. It acts in stimulation of longitudinal bone structure, increase in mineral bone density, body mass, glomerular filtration, differentiation of pre-adipocytes into adipocytes and development of the immune system. Somatropin (rhGH) is a recombinant form and used to treat growth hormone deficiency – and resulting hypoglycaemia - in children and adolescents. While neonatal hypoglycaemia is a common condition (the most common metabolic problem in neonates, with an incidence of 5–15% of all births and is common with 30% of at-risk infants[1], hypoglycaemia due to GH deficiency is dependent on GHD epidemiology. The prevalence rate of idiopathic GH deficiency in the USA and UK is between 1 in 3,400 and 4,000. Other estimates give worldwide prevalence of GHD at approximately 1:4,000 to 1:10,000[2].

Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☐ Yes ☒ No ☐ Not applicable Comments: The 2021 EMLc does not include GH or rhGH in their main indication (growth stimulant). The application asks for inclusion of rhGH to treat hypoglycaemia secondary to GH deficiency for neonates and infants. Growth hormone deficiency in neonates is a medical emergency and recurrent hypoglycaemia may lead to sequelae. The long-term effects of moderate and severe neonatal hypoglycemia are irreversible neurological damage and delayed psychomotor development. However, there is no direct evidence from randomized controlled trials that treatment of hypoglycemia improves long-term neurodevelopmental outcomes[1]. The application states that there is no evidence of effectiveness of rhGH therapy on hypoglycemia in neonates, but that this would be self-evident, because rhGH would be administered to correct the very deficiency that leads to hypoglycemia. However, the indication on the application is not GHD, but hypoglycaemia (secondary to), and there are other alternatives for treatment with reasonable evidence. GH has been linked to cell proliferation and recovery of lost motor functions after brain injuries. There are some studies that propose positive action of this hormone in children in cases of cerebral palsy, asphyxia during delivery, after traumatic brain injury or with congenital malformations[5]. Although the physiology of GHD has been understood and described, including resulting hypoglycaemia, evidence of effectiveness of treatment with rhGH specifically for hypoglycaemia has not been forthcoming. There are several case reports and case series, some cohorts[5], but no trials or RCTs. Other options for treating hypoglycaemia in neonates and infants – IV dextrose (as infusion of 8 mg.kg-1.min−1, or as bolus at 200 mg/kg), most widely used in all settings, oral diazoxide and glucagon (already on the EMLc) and buccal dextrose gel (40%). Buccal dextrose gel (40%) at 200mg/kg, probably increases correction of hypoglycaemic events in newborns s (rate ratio 1.08, 95% (CI) 0.98 to 1.20), and may result in a slight reduction in the risk of major neurological disability at age two years or older (RR 0.46, 95% CI 0.09 to 2.47); but certainty of evidence is low. Dextrose gel is probably an effective and safe first-line treatment for infants with neonatal hypoglycaemia in high-income settings[6,7,8]. In a SR of 7 studies involving 348 infants, six studies involving glucagon (N = 323) produced results of increased blood glucose concentration at 1–2h by 2.3 mmol/L (95% CI 2.1,2.5) (low certainty evidence). In neonates, the benefits and risks of glucagon have not been systematically evaluated, and there are concerns that glucagon may be less effective due to reduced glycogen stores and higher insulin concentrations. Glucagon is already included in the EMLc, but there is paucity of evidence to support guidelines[7].

Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☐ Yes ☒ No ☐ Not applicable Comments: There is some evidence but not enough long-term evidence, and certainly not for newborns who may undergo treatment for the first two years of life. Harms and toxicity of rhGH have been assessed through patient registries in the absence of long-term randomized trials. When used as replacement therapy in children and adolescents side effects of rhGH include rash and pain at injection site, transient fever, prepubertal gynecomastia, arthralgia, edema, benign intracranial hypertension, insulin resistance, progression of scoliosis, and slipped capital femoral epiphysis[9]. Because rhGH stimulates cell proliferation, neoplasms are a possible AE. A recent cohort of 23,984 patients treated rhGH in eight European countries did not support carcinogenic effects of the drug. The Childhood Cancer Survival Study (CCSS) followed up 13,539 survivors of childhood cancer. A nested cohort of 361 patients treated with rhGH, showed an increased risk of developing a second neoplasm RR 3.21 (95% CI, 1.88-5.46)[9]. The National Cooperative Growth Study (NCGS) of 54,996 children receiving rhGH between 1985 and 2006, reported few adverse effects (but table presented in the application is not very straightforward).
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Apart from rhGH, for any of the treatments, no adverse events have been reported in studies; however, there is evidence that a rapid increase in blood glucose, by any therapy, or to concentrations above the normal physiological range may exacerbate neuronal injury[8].

Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: *For GHD* Diagnosis of GHD include auxology, radiographic assessment of bone age, measurement of insulin-like growth factor 1 (IGF-I) and IGF binding protein 3 (IGFBP-3), provocative growth hormone (GH) testing, cranial magnetic resonance imaging (MRI), and, genetic testing. Growth velocity and the degree of short stature are primary considerations[2]. The diagnosis of GHD differs markedly between neonates, children, and adolescents. In neonates, diagnostic criteria re based on a range of tests physical (micro-penis in boys, midline defects i.e. optic nerve hypoplasia, cleft palate, clinical signs of associated pituitary hormone deficiencies and prolonged jaundice); biochemical (blood glucose, hyperbilirubinemia); hormonal (growth hormone stimulation test such as a glucagon or an arginine test may be needed to confirm the diagnosis as well as the presence of other hormonal deficiencies); radiological (cerebral ultrasound to validate defective brain structures). In summary, GHD diagnosis in neonates is primarily based on a combination of clinical signs including recurrent hypoglycemic episodes, and on GH determination. Recombinant human Growth Hormone (rhGH) is administered as a subcutaneous injection, and available as a powder (reconstituted with a diluent) or a liquid solution, usually in pre-filled pens or cartridges (5mg). Different brands are considered interchangeable even if injection devices differ in quality and strengths. After opening flask it remains stable for 21 days at room temperature or 28 days under refrigeration. Dose is weight-based or weight-based or body surface area-based. An initial rhGH dose is 0.16-0.24 mg/kg/week (22–35 µg/kg/day) but some patients may require larger doses. The administration of daily rhGH may be performed at home. It does not require a skilled health professional if the caregiver has been fully instructed in advance. However, monitoring (2-4 times a yr) involves physical examination and hormonal tests. In high-resource settings monitoring IGF 1 (somatomedin C), produced by the liver in response to GH or rhGH treatment, is usually employed to titrate the dose. In low-income settings IGF-1 testing may not be available. *For Hypoglycaemia* To prevent brain injury, the gold standard would be to determine if an infant has neuroglycopenia, for which currently there is not a diagnostic test[1]. So, diagnosis involves not only *prima-facie* determination of GHD but also of hypoglycaemia and neuroglycopenia. Once recognized, if so, treatment is only necessary during the first 2 years of life, although case reports of children diagnosed with GHD up to the age of 7 have been reported. Screening infants at risk of hypoglycaemia and treating those with hypoglycaemic episodes to maintain the BGC ≥ 2.6 mmol/L appears to preserve cognitive function. However, screening is difficult, as almost 30% of babies would be at risk for hypoglycaemia, from a number of causes[8].

Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: There is the issue of no evidence. As the application admits, there are no data on cost-effectiveness of rhGH treatment in neonates and infants with hypoglycemia. A simple costing estimate in the application, for the monthly cost for rhGH in the indication: Newborn: 56 USD; 6-month-old infant:120 USD; 2 year old toddler:240 USD, which presents the drug as relatively affordable by middle and high-income settings.
Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☒ Yes ☐ No ☐ Not applicable Comments: The drug has been on the market for over 35 years and is produced by various manufacturers. In LMIC the drug may not be publicly funded. Recombinant GH has been largely used for non-sanctioned practices (illegal in sports and in certain jurisdictions), and to increase vitality (performance enhancement), due to its role as an anabolic agent. Once included it must be considered that it may be directed to other potential uses. It may prove difficult to direct the use proposed by the application[3,4].
Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments: No WHO guidelines are available.

Additional References

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