Somatropin

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 18. Medicines for endocrine disorders

EMLc | ATC codes: H01AC01

Indication	Hypoglycaemia without associated diabetes ICD11 code: 5A41
INN	Somatropin
Medicine type	Biological agent
List type	Core
Formulations	**Parenteral > General injections > SC:** 5 mg in cartridge powder for injection ; 5 mg per mL in 2 mL cartridge
EML status history	Application rejected in 2023 (TRS 1049)
Sex	All
Age	Children (1 month - 12 years)
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Somatropin
DrugBank	Somatropin (Somatotropin)

Expert Committee recommendation

The Expert Committee noted that growth hormone deficiency, both congenital and acquired, has been reported to affect between 1 in 4000 to 10 000 people globally. However, the incidence and prevalence of hypoglycaemia due to growth hormone deficiency, the indication for which listing of somatropin is requested, was not reported in the application. The Committee acknowledged that management of hypoglycaemia, of any etiology, in neonates and infants was critical to prevent permanent neurological sequelae. The Committee noted that the application did not identify specific evidence from clinical trials of the efficacy and harms of somatropin in the management of hypoglycaemia due to growth hormone deficiency, but acknowledged limited evidence from case reports and cohort studies that have reported the effectiveness of rhGH therapy for this indication. The Committee noted that the Model Lists currently include diazoxide, glucagon and glucose for use in the management of hypoglycaemia. The Committee considered that comparative evidence for somatropin versus these medicines, including information on the comparative costs and cost–effectiveness would be necessary to inform any future consideration of somatropin for this indication The Expert Committee therefore did not recommend the inclusion of somatropin on the complementary list of the EMLc for the management of hypoglycaemia secondary to growth hormone deficiency in neonates, infants and young children.

Background

Somatropin has not been previously considered for inclusion on the Model Lists for the proposed nor any other

indication. Diazoxide and glucagon were recommended for inclusion on the EMLc in 2021 and 2011, respectively, for use in the treatment of hypoglycaemia in children. Diazoxide was recommended specifically for management of hypoglycaemia secondary to prolonged hyperinsulinism (1).

Public health relevance

The prevalence of idiopathic growth hormone deficiency in the United Kingdom and United States of America is estimated to be between 1 in 3400 and 4000 (2). Other estimates report a worldwide prevalence of growth hormone deficiency of between 1 in 4000 to 1 in 10 000 (3). Growth hormone deficiency occurs when the pituitary gland fails to produce enough growth hormone. This deficiency is typically associated with medical conditions that affect the pituitary gland, such as congenital brain abnormalities (e.g. septo-optic dysplasia), and in rare cases, gene deletions in the hormonal pathway responsible for growth hormone production. These conditions are usually present at birth and often diagnosed in infancy. Additionally, growth hormone deficiency can be caused by brain tumours and their treatment, including radiation therapy, which typically affects older children. Growth hormone deficiency is frequently linked to short stature throughout childhood, adolescence and adulthood. The presentation, diagnosis, and management of growth hormone deficiency differ substantially between neonates and older children or adolescents (4–7). Neonatal growth hormone deficiency is associated with severe hypoglycaemia in 30–85% of cases and can be managed with recombinant human growth hormone treatment (8,9). Neonatal growth hormone deficiency is rarely observed beyond 2 years of age, although there have been occasional reports in children up to the age of 7 years (8,10–12). Long-term consequences of moderate and severe neonatal hypoglycaemia include irreversible neurological damage and delayed psychomotor development (13–16).

Benefits

No evidence for the benefits of rhGH in the treatment of hypoglycaemia secondary to growth hormone deficiency was presented in the application. The application stated that randomized, placebo-controlled trials evaluating the effectiveness of rhGH therapy on hypoglycaemia in neonates were lacking because it is ethically unreasonable not to treat patients diagnosed with growth hormone deficiency with growth hormone replacement therapy. Several case reports, case series and cohort studies have reported the effectiveness of rhGH therapy in addressing hypoglycaemia in neonates and infants with human growth hormone deficiency (10). No evidence was presented in the application on potential alternative treatments for hypoglycaemia in neonates and infants, such as dextrose, diazoxide and glucagon.

Harms

In the absence of long-term randomized trials, evaluation of the potential harms and toxicity of rhGH has been conducted through various registries mandated by health authorities worldwide. When used as replacement therapy in children and adolescents side-effects of rhGH include rash and pain at injection site, transient fever, prepubertal gynaecomastia, arthralgia, oedema, benign intracranial hypertension, insulin resistance, progression of scoliosis and slipped capital femoral epiphysis (17). A review of data from two observational studies of the long-term safety of growth hormone treatment in children found no indication of an increased risk of mortality or adverse events related to the dose of growth hormone in any risk group (18). The application stated that short- and long-term adverse effects associated with rhGH reported in older children and adolescents have not been reported in neonates or infants (19). Because rhGH stimulates cell proliferation, concerns exist that treatment might be associated with an increased risk of malignancies. A 2017 cohort study of 23 984 patients treated with rhGH in eight European countries since 1984 found a significantly increased incidence in bone and bladder cancer in rhGH-treated patients without previous cancer. For patients treated with rhGH after previous cancer, cancer mortality risk was significantly increased with increasing rhGH dose. The incidence of Hodgkin lymphoma increased significantly with longer follow-up in all patients and in patients without previous cancer (20). The United States National Cooperative Growth Study evaluated the safety and efficacy of rhGH in 54 996 children between 1985 and 2006. No increased risk in the development of leukaemia was observed in children treated with rhGH compared with an age-matched general population. Intracranial and extracranial malignancies were not

significantly more frequent in patients without risk factors. An increased risk of secondary malignancies in patients previously treated with radiation was observed (21). The Childhood Cancer Survival Study followed up 13 539 survivors of childhood cancer. A nested cohort of 361 cancer survivors treated with rhGH showed no significantly increased risk of disease recurrence (relative risk (RR) 0.83, 95% confidence interval (CI) 0.37 to 1.86). An increased risk of development of secondary neoplasms (all solid tumours and no secondary leukaemias) was observed (RR 3.21, 95% CI 1.88 to 5.46) (22).

Additional evidence

The evidence provided by the applicants was incomplete and was supplemented by the reviewers and Secretariat.

Cost / cost effectiveness

Data specifically addressing the cost–effectiveness of rhGH treatment in neonates and infants with hypoglycaemia secondary to growth hormone deficiency are lacking. The application reported the cost of growth hormone (per mg) as US$ 46.50 to 62.10 in Argentina, US$ 20.67 to 34.20 in Canada, US$ 6.55 in India and US$ 26.30 in Mexico. The monthly treatment costs (assuming a price of US$ 25/mg and approximate weight of the 50% centile of 3.5 kg for neonates, 7.5 kg for 6-month-old infants and 15 kg for 24-month-old infants) were estimated in the submission to be US$ 56, US$ 120 and US$ 240, respectively.

WHO guidelines

WHO guidelines for the management of hypoglycaemia secondary to growth hormone deficiency are not currently available.

Availability

Somatropin is manufactured and distributed by several pharmaceutical companies around the world. Manufacturers differ by the appearance and quality of the injection devices and by the different strengths and concentrations of the cartridges to suit all ages. The availability of and financial support for rhGH treatment in low- and middle-income countries are generally limited compared with high-income countries, potentially leading to disparities in access to this therapy for individuals with growth hormone deficiency in those regions.

Other considerations

Treatment with rhGH requires specialized diagnostic and monitoring facilities as well as medical care by a paediatric endocrinologist or, if not available, by a paediatrician knowledgeable in paediatric endocrine diseases. The misuse of rhGH for performance enhancement is a serious concern. This is primarily due to the hormone’s anabolic properties, which can potentially lead to unauthorized off-label use.

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