1. **Title page:**

Application for inclusion of somatropin (recombinant human Growth Hormone) in neonates, infants and young children with hypoglycemia secondary to growth hormone deficiency on the WHO Model List of Essential Medicines for Children (April 2023)

Submitted by:

Jean-Pierre Chanoine, MD, FRCPC (Academic)
Clinical Professor
Endocrinology and Diabetes Unit K4-206
British Columbia Children's Hospital
4480 Oak Street
Vancouver BC V6H 3V4, Canada
Email: jchanoine@cw.bc.ca; Phone: 1-604-8752624; Fax: 1-604-8753231

Niyoosha Yoosefi
Research Assistant
Endocrinology and Diabetes Unit K4-206
British Columbia Children's Hospital
4480 Oak Street
Vancouver BC V6H 3V4
Canada
Email: Niyoosha.Yoosefi1@bcchr.ca

To:

24th WHO Expert Committee on the Selection and Use of Essential Medicines
World Health Organization, Geneva

Co-Authors:

Sallianne Kavanagh MPharm, MRPharmS
Clinical Pharmacist
Department of Pharmacy, University of Huddersfield
Huddersfield, HD1 3DH, United Kingdom
Email: S.Kavanagh@hud.ac.uk

Mark E. Molitch, M.D.
Professor Emeritus
Division of Endocrinology, Metabolism & Molecular Medicine
Northwestern University Feinberg School of Medicine
645 N. Michigan Avenue, Suite 530
Chicago, IL 60611
Email: molitch@northwestern.edu

Jamie Harvey, Co-founder, Chief Executive Officer
International Coalition of Organizations Supporting Endocrine Patients
The MAGIC Foundation
4200 Cantera Drive #106
Warrenville, Illinois USA 60555
Email : jamie@icosep.org; Phone : 1-630-836-8200

2. Summary statement of the proposal for inclusion, change or deletion
This proposal requests the inclusion of somatropin (**recombinant human Growth Hormone or rhGH) as an individual medicine for the management of hypoglycemia in neonates, infants and young children with growth hormone deficiency (GHD) up to the age of 2 years to the complementary list of EMLc.**

Diagnosis and management of GHD in the pediatric age group are mostly performed by pediatric endocrinologists, and, in some countries, by general pediatricians.

3. Consultation with WHO technical departments
To the best of our knowledge, there is no technical department with expertise in growth hormone.

4. Other organizations consulted and/or supporting the submission
This submission is part of a larger project by a group of endocrinologists with worldwide representation who met regularly for 12 months (2020-2021) with the goal of performing an in-depth review of the essential medicines included in Section 18. of the EML and the EMLc ("Medicines for endocrines disorders"). The group included both adult and pediatric endocrinologists: Drs. Chanoine (Canada) and Molitch (USA) (co-Chairs) and Drs. von Oettingen (Canada), Villarroel (Bolivia), Kalra (India), Paulose (India), Abodo (Ivory Coast), Ramaiya (Tanzania), Donaghue (Australia), Junfen Fu (China) and de Beaufort (Luxembourg). In addition, we worked with economists (Drs. Ewen and Beran from Switzerland), pharmacists (Drs. Kavanagh and Gray from UK and Karekezi from Kenya) and a dietitian (Dr. Besancon from Mali).

This application is supported by Global Pediatric Endocrinology and Diabetes (GPED, Letter of support #a), the International Consortium for Pediatric Endocrinology and Diabetes (ICPE, Letter of support #b), the Endocrine Society (Letter of support #c) and the MAGIC Foundation (Letter of support #d).

5. Key information for the proposed medicine
- International Non-proprietary Name (INN)

INN: Somatropin

- Anatomical Therapeutic Chemical (ATC) code of the medicine

ATC: H01AC01

- Dosage form(s) and strength(s) of the proposed medicine(s)

Somatropin (Recombinant human Growth Hormone or rhGH) is offered as a powder (that requires reconstitution with a diluent provided by the manufacturer) or as a liquid solution and is given as a daily subcutaneous injection. It is manufactured and distributed by a number of pharmaceutical companies around the world. rhGH is considered as interchangeable between manufacturers. It comes most commonly in cartridges inserted in reusable pens or in disposable, pre-filled pens. 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. Considering the low weight of the patients in this submission, the smallest cartridge marketed by the

pharmaceutical manufacturer is the most appropriate. The smallest cartridge offered by several main manufacturers in Canada is included below **as an example** (alphabetical order, current as of March 1, 2022) (more manufacturers are likely present in other countries):

Eli Lilly (Humatrope®): 6 mg cartridge (P/F)
Novo Nordisk (Norditropin®): 5 mg cartridge (P/RT and F)
Pfizer (Genotropin®): 5.3 mg Go Quick (P/F)
Roche (Nutropin®): 5 mg cartridge (L/F)
Sandoz (Omnitrope®): 5 mg cartridge (P/F)
Serono (Saizen®) : 6 mg cartridge (L/F)

(L: liquid form; P: powder form/RT: stable 21 days at room temperature after first use; F: stable in fridge 28 days after opening)

- Indications

Management of hypoglycemia in neonates, infants and young children with growth hormone deficiency.
ICD-11 codes: 5A61.3 Growth hormone deficiency
KB60.4Y: Neonatal hypoglycaemia, specified

- Suggested wording:

18.6 Medicines for hypoglycaemia	
Complementary list	
Somatropin (once a day formulation)	Injection: 5 mg cartridges (powder or liquid) or 5 mg pre-filled pens

Somatropin should be listed under "hypoglycemia" in the complementary list to emphasize the fact that its essential indication is not growth. A note emphasizing that the indication is "hypoglycemia specifically due to growth hormone deficiency" could be added.
The content and concentration of the rhGH (somatropin) varies across manufacturers. It is suggested that the smallest available cartridge be used (usually 5 mg).

6. Proposal for an individual medicine or representative of a pharmacological class/therapeutic group

This application is requested as an individual medicine (somatropin). The authors consider that all somatropins available on the market from different manufacturers are equivalent. Preference should be given to the most affordable.

7. Information supporting the public health relevance

Indications of growth hormone

Recombinant somatropin has been available since 1985, primarily for the management of short stature secondary to growth hormone deficiency in children and adolescents. The minimum prevalence rate of idiopathic GH deficiency in the USA and UK is between 1 in 3,400 and 4,000 (this is similar to the prevalence of congenital hypothyroidism) (1). Specific incidence data are to our knowledge not available for the neonatal period. Since then, it has become an approved

medicine in many countries for the management of a number of indications, including adult growth hormone deficiency, Turner syndrome, Noonan syndrome, Prader Willi syndrome, small for gestational age (SGA), idiopathic short stature (ISS) and chronic renal failure. These latter indications are not relevant to the present submission.

Target population
As a reminder, this proposal specifically focuses the inclusion of **rhGH for the management of hypoglycemia in neonates, infants and young children with growth hormone deficiency** to avoid neurological damage as a consequence of hypoglycemia. Treatment is only necessary during the first 2 years of life.

Growth hormone deficiency (GHD): context
Growth hormone deficiency (GHD) results from insufficient production of growth hormone (GH) by the pituitary gland. Accordingly, GHD is caused by medical conditions that involve the pituitary gland, including congenital brain abnormalities (i.e. septo-optic dysplasia) and, rarely, gene deletions in the hormonal cascade that leads to the production of GH. These conditions are present at birth and are often recognized in infancy. Furthermore, brain tumors and their treatment, radiation therapy, can also cause GH deficiency, usually in older children. In addition to GH, the anterior pituitary can also be deficient in other hormones (ACTH, LH, FSH, TSH). Growth hormone deficiency is commonly associated with short stature during childhood, adolescence and adulthood. In neonates, infants and young children (see below), GHD can also cause severe hypoglycemia that only responds to rhGH. Therefore, it is important to treat this life-threatening disorder based on its underlying pathogenesis, through rhGH replacement (2,3).

In most high-income countries, rhGH, which is available in its recombinant hormone since 1985 (4), is funded by the local health authorities for the indication of GHD in the pediatric age-group.

Growth hormone deficiency in infants and severe hypoglycemia
The presentation, diagnosis and management of GHD differs markedly in the neonate compared to the older child and the adolescent (5, 6, 7, 8). In 30-85% (8), neonatal GHD is associated with severe hypoglycemia that is successfully managed with rhGH (10, 24). It is rarely seen beyond two years of age although case reports of children diagnosed with GHD up to the age of 7 have been reported (9, 10, 11, 12). If an upper age limit is required, we suggest based on the literature that it be set at 2 years, with flexibility based on individual situations.

The long-term effects of moderate and severe neonatal hypoglycemia on irreversible neurological damage and delayed psychomotor development are well documented (13, 14, 15, 16) and cerebral sequelae on the brain MRI are well described (17). Pilders et al (13) observed that, compared to controls, a significantly larger number of children with hypoglycemia during the first week of life n had IQ scores below 86 at 5 to 7 years of age. However, the average IQ for the 2 groups was similar. Wickström et al (14) demonstrated that between 2-6 years of age, infants with who experienced neonatal hypoglycemia during the first 6 weeks of life had a double risk of any neurological or neurodevelopmental adverse outcome and a tripled risk of cognitive developmental delay, compared to normoglycemic infants. In New Zealand, McKinley et al (15) assessed the neurodevelopmental function at age 4.5 years of a cohort of children with a history of neonatal hypoglycemia (< 47 mg/dl or 2.6 mmol/L) was associated with a dose-

dependent increased risk of poor executive function and visual motor function but not with an increased risk of combined neurosensory impairment at 4.5 years. Finally, in a large series, Kaiser et al (16) observed that transient hypoglycemia was associated with decreased probability of proficiency on literacy and mathematics fourth-grade achievement tests compared to controls. In the above studies (where hypoglycemia was not secondary to GH deficiency), hypoglycemia was not sustained and was regarded as a transient failure to perform the physiological postnatal transition (which includes a surge in GH (18)), contrasting with the situation in neonates with GH deficiency where the hypoglycemia is recurrent until rhGH is initiated.

8. Treatment details (requirements for diagnosis, treatment and monitoring).

Requirements for diagnosis

The diagnosis of GHD differs markedly between neonates, children and adolescents. In children and adolescents, it is based on auxology (short stature and decreased height velocity), biochemical investigations (low insulin-like growth hormone and GH levels and insufficient GH response to GH stimulation tests [arginine, glucagon, insulin, others] and radiological investigations (delayed bone age and, as appropriate, and abnormal pituitary imaging) (8, 17).

In contrast, the diagnosis of GHD in neonates and infants is based on (5, 6, 8, 20):

- Physical examination: micro-penis (boy), midline defects (i.e. optic nerve hypoplasia, cleft palate), clinical signs of associated pituitary hormone deficiencies and prolonged jaundice
- Biochemical investigations: blood glucose, hyperbilirubinemia
- Hormonal investigations: the neonatal period is the only period during which a random GH determination is useful. Indeed, during the shift from the fetal to the postnatal period, GH secretion is constitutionally activated during the first week of life. A growth hormone stimulation test such as a glucagon or an arginine test may be needed to confirm the diagnosis. The presence of additional hormonal deficiencies of the anterior pituitary further supports the diagnosis.
- Radiological investigations: thanks to the open fontanels, a cerebral ultrasound can demonstrate abnormal brain structures and support he diagnosis of pituitary dysfunction even though the cerebral ultrasound does not visualize the pituitary. We do not routinely perform a cerebral MRI in neonates (as a tumor is highly unlikely) and this does not prevent or delay the initiation of rhGH treatment.

Determination of insulin-like growth factor (IGF-1), a marker of growth hormone secretion, is not useful in neonates and infants as normal values are very low. Bone age is also not useful in this age group.

Thus, GHD diagnosis in neonates is primarily based on a combination of clinical signs including, recurrent hypoglycemic episodes, on GH determination with or without the presence of other pituitary hormone deficiencies or midline defects.

Treatment of GHD in neonates and infants

Growth hormone deficiency in neonates is a medical emergency and needs to be treated as soon as it is recognised to prevent the permanent neurological sequelae due to recurrent hypoglycemia.

To our knowledge there are no WHO guidelines for management of GHD in neonates. See reference 21 for the most recent international guidelines for rhGH treatement.

A weight-based rhGH dosing is commonly used in neonates with GHD, with an initial GH dose of 0.16-0.24 mg/kg/week (22–35 µg/kg/day) (21).

The administration of daily rhGH is routinely performed at home through subcutaneous injections (similar to an injection of insulin) using a pen. It does not require the presence of a skilled healthcare provider if the caregiver has been fully instructed in advance. Although specific recommendations vary from manufacturer to manufacturer, rhGH is kept in the fridge until the cartridge is opened and kept at room temperature (up to 25C) or in the fridge thereafter. For insulin, several studies have demonstrated that in the absence of a fridge, insulin can be kept in a clay pot without significant loss of activity (22, 23). To our knowledge, no such studies have been performed for growth hormone.

Monitoring of rhGH treatment in neonates

Follow up of neonates and young children includes (2-4 times a year): physical examination, and, as appropriate, monitoring of other pituitary hormones. Once the treatment with rhGH is initiated and that hypoglycemia has resolved, home glucose monitoring is not commonly required. IGF-1 determination is commonly used to optimize the dose of rhGH in high income countries where it is usually readily available. Pediatric endocrinologists aim at keeping the IGF-1 value in the upper normal range. However, as discussed in the International Pediatric Guidelines (21), this attitude is not evidence-based and the use of IGF-1 is a "conditional recommendation" (see 3.3 below):

"3. Dosing of GH Treatment for Patients with GHD

3.1. We recommend the use of weight-based or body surface area (BSA)-based GH dosing in children with GHD. (Strong recommendation, ●●●○) Technical Remark: We cannot make a recommendation regarding IGF-I-based dosing because there are no published adult height data using this method. The rationale is logical, but the target IGF-I level has not been established to optimize the balance between adult height gain, potential risks, and cost;

3.2. We recommend an initial GH dose of 0.16–0.24 mg/kg/week (22–35 µg/kg/day) with individualization of subsequent dosing. (Strong recommendation, ●●○○) Technical Remark: Some patients may require higher doses;

3.3. We suggest measurement of serum IGF-I levels as a tool to monitor adherence and IGF-I production in response to GH dose changes. We suggest that the GH dose be lowered if serum IGF-I levels rise above the laboratory-defined normal range for the age or pubertal stage of the patient. (Conditional recommendation, ●○○○)

To our knowledge, there are no studies on the role of IGF-1 determination in preventing hypoglycaemias and no recommendations in low-income countries, where IGF-1 determination may not be readily available.

Thus, we recommend a starting dose of 0.16-0.24 mg/kg/week followed by adjustment based on weight, growth and on the absence of hypoglycemia, and, if available, on IGF-1 determination if available.

9. Review of benefits: summary of evidence of comparative effectiveness
Since it is ethically unreasonable to not treat patients diagnosed with GHD, there is a lack of randomized placebo-controlled trials to compare the effectiveness of rhGH therapy on hypoglycemia in neonates. However, clinical experience demonstrates that hypoglycemia in neonates and infants with GHD responds very well to rhGH. It is a correction of a deficiency.

10. Review of harms and toxicity: summary of evidence of safety
As mentioned earlier, treatment of neonatal hypoglycemia secondary to growth hormone deficiency consists in replacing a hormone that is missing, with the goal of achieving an effect that is similar to endogenous growth hormone.

In the absence of long-term randomized trials, the harm and toxicity of rhGH has been assessed through several registries mandated by health authorities over the world.

To our knowledge, short-and potential long-term side effects reported in older children and adolescents have not been reported in neonates and infants (25). In older children and adolescents, rhGH treatment has been associated with the development of intracranial hypertension, slipped capital femoral epiphysis (SCFE), and increased scoliosis progression.

There have been concerns about the long-term safety of rhGH and in particular an increased risk of malignancies. The results of a recent study conducted on a cohort of 23,984 patients treated with recombinant human GH (rhGH) in eight European countries do not support a carcinogenic effect of rhGH. A recent review of the data of two large registries by Savendhal et al (26) found no indication of increased mortality risk nor AE incidence related to GH dose in any risk group.

The following table summarizes the frequencies (in percentage) of more commonly reported adverse and serious adverse events on a report from the national cooperative growth study (NCGS) of 54996 children receiving rhGH between 1985 and 2006.

Table 1.
Incidence of targeted events by indication

	All NCGS	IGHD	OGHD	TS	CRI	ISS	Other
n	54,996	23,393	8,351	5,127	1,778	9,778	6,569
AE	6.2	4.4	12.0	7.6	10.9	3.6	7.3
SAE	2.4	1.2	6.8	1.9	6.5	0.7	3.1
Deaths	0.3	0.1	1.0	0.1	1.2	0.0	0.5
Malignancy[a]	0.1	0.0	0.1	0.1	0.0	0.0	0.0
IC tumor recurrence	0.3	0.0	1.8	0.0	0.1	0.0	0.0
Leukemia[a,b]	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Second neoplasm	0.1	0.0	0.5	0.0	0.1	0.0	0.0
AI[b]	0.0	0.0	0.1	0.0	0.0	0.0	0.0
DM	0.1	0.0	0.1	0.2	0.2	0.1	0.2
IH	0.1	0.1	0.2	0.2	0.3	0.0	0.1
SCFE	0.1	0.1	0.4	0.2	0.3	0.0	0.1
Scoliosis	0.4	0.2	0.5	0.7	0.1	0.2	0.6
Pancreatitis	0.0	0.0	0.0	0.1	0.0	0.0	0.0

Data are expressed as percentage. IGHD, Idiopathic GHD; IC, intracranial.
a New onset, no risk factors.
b Based on fewer than 15 reports.

Figure: Incidence of targeted events by GHD indications (27)

Abbreviations: AE, Adverse event; AI, adrenal insufficiency; CNS, central nervous system; CRI, chronic renal insufficiency; DM, diabetes mellitus; IGHD idiopathic GHD; IH, Intracranial hypertension; ISS, idiopathic short stature; OGHD, organic GHD; SAE, serious AE; SCFE, slipped capital femoral epiphysis; TS, Turner syndrome.

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.
Several cost effectiveness studies on rhGH have been published. They focus on the benefits of height and are irrelevant to the present submission (26). To our knowledge, there are no data on cost-effectiveness of rhGH treatment in neonates and infants with hypoglycemia. However, a recent publication from New Zealand provides the following estimate for the cost of hypoglycemia (irrespective of the cause): *"Over an 80-year time horizon a subject who experienced neonatal hypoglycaemia had a combined hospital and post-discharge cost of NZ$72,000* (=USD$48,290) *due to the outcomes modelled, which is NZ$66,000* (=USD$44,266) *greater than a subject without neonatal hypoglycaemia. The net monetary benefit lost due to neonatal hypoglycaemia, using a value per QALY of NZ$43,000* (=USD$ 28,840), *is NZ$180,000* (=USD$ 120,726) *over an 80-year time horizon" (29)*.

The cost of growth hormone (per mg) varies from country to country and is as follows:
Canada: $27.90 to 46.15 CAD (=20.67 to 34.2 USD)
Argentina: $46.5 to 62.1 USD
India: 160 INR (= 6.55 USD)
Mexico: 510 pesos (=26.3 USD)

The cost of the minimal effective dose of rhGH in neonates, infants and children for 2 years can be estimated as follows (Assumptions: 1 mg = 25 USD, approximate weight 50% percentile for boys ad girls at 0, 6, 12, 24 months are 3.5, 7.5, 10.5, 15 kg)
Dose: 0.16 mg/kg/week: 3874 USD

Using the same assumption, the monthly cost for rhGH is as follows:
Newborn: 56 USD
6 month old infant:120 USD
2 year old toddler:240 USD

12. Summary of regulatory status and market availability of the medicines
Growth hormone is readily available in all high-income countries and are usually funded by the Government for the indication of growth hormone deficiency. In LMICs, rhGH is not always readily available and is rarely funded by the health authorities.

13. Availability of pharmacopoeial standards
U.S. Food and Drug Administration (FDA):
Somatropin injections are on the approved product list (Orange book). The active ingredient is approved by brand formulations available in the USA.

European Medicines Agency (EMA):
Somatropin injections are approved for use in the EMA regions and for inclusion on the list of nationally approved medicinal products.

Health Canada:
Somatropin is on the drug product list of approved medicines. The active ingredient is approved by brand formulations available in Canada.

Japanese Pharmaceuticals and Medical Devices Agency:
Somatropin injection is included in the PMDA list of approved medicines.

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