Lonapegsomatropin-tcgd (Skytrofa™) Drug Bulletin

September 2021

Nonproprietary Name	lonapegsomatropin-tcgd
Brand Name	Skytrofa
Manufacturer	Ascendis
FDA Approval Date	August 25, 2021
Market Availability Date	To be determined (TBD)
Indication	For the treatment of pediatric patients ≥ 1 year old who weigh ≥ 11.5 kg and have growth failure due to inadequate secretion of endogenous growth hormone (GH)
Dosage Form	Lyophilized powder available in single-dose, dual-chamber, prefilled cartridges containing drug and diluent, water for injection, in the following strengths: 3 mg, 3.6 mg, 4.3 mg, 5.2 mg, 6.3 mg, 7.6 mg, 9.1 mg, 11 mg, and 13.3 mg; cartridges can be stored under refrigeration (2°C to 8°C) in the outer carton until the expiration date or the outer carton containing blistered cartridges can be stored at room temperature (up to 30°C) for up to 6 months and may be returned to refrigeration within the 6 months
Dosage	For treatment-naïve patients and patients switching from daily somatropin: 0.24 mg/kg body weight once-weekly via subcutaneous (SC) injection into the abdomen, buttock, or thigh; individualize and titrate based on response; if a different dose is used, the total weekly dose should be calculated with selection of the appropriate cartridge by rounding the total weekly dose (mg) to the closest cartridge dose; when changing from daily somatropin therapy to once-weekly lonapegsomatropin-tcgd, wait ≥ 8 hours between the final dose of daily somatropin and the first once-weekly dose; discontinue therapy once epiphyseal fusion has occurred

CLINICAL CONSIDERATIONS

- Lonapegsomatropin-tcgd (Skytrofa) is a long-acting prodrug of a human GH (HGH; somatropin) made through recombinant DNA technology using *Escherichia coli*. Lonapegsomatropin-tcgd contains somatropin conjugated to a methoxypolyethylene glycol carrier via a proprietary TransCon™ linker; this results in a pegylated form of human GH.[1]
  - Somatropin binds to the GH receptor in the cell membrane of target cells resulting in direct tissue and metabolic effects, and indirect effects through insulin-like growth factor-1 (IGF-1); it stimulates skeletal growth in pediatric patients with growth hormone deficiency (GHD) due to the effects on the epiphyses (growth plates) in long bones.

- Fully active somatropin is released via autocleavage of the TransCon linker of lonapegsomatropin-tcgd; this results in a dose-linear IGF-1 response with IGF-1 levels in the normal range for GHD patients for most of the week, similar to daily somatropin.

- Safety[2]
  - *Contraindications:* acute critical illness (e.g., after open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure due to the increased risk of mortality with use of somatropin); hypersensitivity to somatropin or any of the excipients; children with closed epiphyses; active malignancy due to the risk of malignancy progression; active proliferative or severe non-proliferative diabetic retinopathy as treatment with somatropin may worsen this condition; Prader-Willi syndrome patients who are severely obese, have a history of upper airway obstruction or sleep apnea or have severe respiratory impairment due to the risk of sudden death
  - *Warnings/Precautions:* severe hypersensitivity reactions, including anaphylactic reactions and angioedema; increased risk of neoplasms (preexisting malignancy should be inactive, and its treatment should be completed before starting therapy; risk of second neoplasms in pediatric patients; new malignancy during treatment); glucose intolerance and diabetes mellitus; reversible intracranial hypertension (e.g., papilledema, visual changes, headache, nausea, and/or vomiting); transient and dose-dependent fluid retention (e.g., edema, arthralgia, myalgia, nerve compression syndromes); hypoadrenalism; hypothyroidism; slipped capital femoral epiphysis (onset of a limp or persistent hip/knee pain); progression of preexisting scoliosis; pancreatitis; lipoatrophy; sudden death in pediatric patients with Prader-Willi syndrome; laboratory tests (e.g., phosphate, alkaline phosphatase, parathyroid hormone may increase)
  - *Monitoring:* Monitor glucose in all patients, especially in those with risk factors for type 2 diabetes mellitus (T2DM) (e.g., obesity or a family history); when starting therapy, monitor patients with preexisting type 1 diabetes mellitus (T1DM), T2DM, or impaired glucose tolerance with adjustment of antihyperglycemic drugs as warranted; perform fundoscopic examination prior to starting therapy to exclude preexisting papilledema and reevaluate periodically thereafter; monitor for decreased serum cortisol levels and/or glucocorticoid dose increases in those with hypoadrenalism; periodic thyroid function tests and start/adjust thyroid hormone replacement therapy
  - *Common adverse effects occurring in ≥ 5% of patients treated with lonapegsomatropin-tcgd versus daily somatropin, respectively:* viral infection (15% versus 11%), pyrexia (15% versus 9%), cough (11% versus 7%), nausea and vomiting (11% versus 7%), hemorrhage (7% versus 2%), diarrhea (6% versus 5%), abdominal pain (6% versus 4%), and arthralgia and arthritis (6% versus 2%); laboratory changes: phosphate levels elevated (44.2% versus 30.2%) and alkaline phosphatase levels elevated (19.2% versus 9.4%)
  - *Drug Interactions:* glucocorticoid therapy, cytochrome P450-metabolized drugs, oral estrogen, insulin and/or other antihyperglycemic agents

- *Special Populations:* data are not available on use in pregnant patients to determine the potential for adverse maternal or fetal outcomes; use in children < 1 year old has not been established

- Efficacy[3,4,5] - A multicenter, global, randomized, open-label, active-controlled, parallel-group phase 3 study (heiGHt; NCT02781727) evaluated treatment-naïve, prepubertal pediatric patients with GHD across 52 weeks. Patients were randomized 2:1 to receive either lonapegsomatropin-tcgd at a dose of 0.24 mg/kg/week (n=105) or an equivalent weekly dose of somatropin (Genotropin), administered daily (n=56). Patients enrolled were an average of 8.5 years of age (range, 3.2 to 13.1 years old) with the majority being male (82%). Patients enrolled were predominantly Caucasian and had an average baseline height standard deviation score (SDS) of -2.9. At 52 weeks, the primary endpoint of annualized height velocity (AHV) for lonapegsomatropin-tcgd was found to be non-inferior and superior to that observed with daily somatropin (least squares mean [LSM] AHV, 11.2 cm/year versus 10.3 cm/year, respectively; treatment difference, 0.9; 95% confidence interval [CI], 0.2 to 1.5, P=0.009). The secondary endpoint of change from baseline in height SDS at week 52 was also significantly improved with lonapegsomatropin-tcgd compared to daily somatropin (LSM height SDS, 1.1 versus 0.96; P=0.01). Safety (adverse events, tolerability, and immunogenicity) were comparable between study arms.
- In most cases, the diagnosis of GHD should be based on results from 2 provocative tests as recommended by the Pediatric Endocrine Society (PES).[6] The 2019 American Association of Clinical Endocrinology (AACE) Growth Hormone Task Force does not advocate use of one product over another, but they do recommend using individualized dose adjustments to improve effectiveness and minimize side effects.[7] The 2019 Growth Hormone Research Society Guidelines advise assessing the somatropin dose every 6 to 12 months, with dose adjustments based on the change in SDS and height velocity.[8]
- There are a number of recombinant human growth hormone (rHGH; somatropin) products commercially available in the United States (US). Brand-name products indicated for pediatric GHD include: Genotropin®, Humatrope®, Norditropin®, Nutropin AQ® NuSpin®, Omnitrope®, Saizen®, and Zomacton®.[9,10,11,12,13,14,15]
  - These products are also indicated for pediatric patients with other conditions, including growth failure due to Prader-Willi syndrome, small for gestational age, Turner syndrome, Noonan syndrome, idiopathic short stature, height standard deviation score less than - 2.25, and associated with growth rates unlikely to allow for attainment of adult height in the normal range; short stature or growth failure in short stature homeobox-containing gene (SHOX) deficiency, chronic kidney disease (CKD) up to the time of renal transplantation, as well as for replacement of endogenous GH in adults with GH deficiency.
  - Most growth hormone products are given 6 or 7 times weekly. Saizen and Zomacton can be dosed in pediatric patients as few as 3 times per week, as can Nutropin AQ NuSpin when treating Turner syndrome.

- Lonapegsomatropin-tcgd (Skytrofa) provides a pegylated, once-weekly, long-acting prodrug formulation of HGH (somatropin) for pediatric patients ≥ 1 year who weigh ≥ 11.5 kg and have growth failure due to inadequate secretion of endogenous GH. This Orphan Drug is the first once-weekly treatment for pediatric patients with GHD;[16] it serves as an alternative to daily somatropin injections for patients in whom it is indicated.[17]

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	Growth Hormone
Clinical Edit	**Initial Approval Criteria** ▪ Pediatric patient is ≥ 1 year old; **AND** ▪ Patient weighs ≥ 11.5 kg; **AND** ▪ Patient has growth failure secondary to growth hormone deficiency (GHD); **AND** ▪ Patient has short stature as defined by height that is ≥ 2 standard deviations below the mean for chronological age; **AND** - Patient has hypothalamic-pituitary defect§ (e.g., major congenital malformation, tumor, or irradiation) and a deficiency of ≥ 1 additional pituitary hormone❖; **OR** - Patient had an inadequate response to growth hormone (GH) provocation tests on 2 separate stimulation tests as defined as a serum peak GH concentration < 10 ng/mL; **AND** ▪ Other causes of growth failure must be ruled out (e.g., malnutrition, hypothyroidism, hypocortisolism); **AND** ▪ Patient does NOT have a current acute critical illness after open heart surgery, abdominal surgery, or multiple accidental trauma, or those with acute respiratory failure; **AND** ▪ Patient does NOT have a hypersensitivity to any somatropin product or any of the excipients; **AND** ▪ Pediatric patient must NOT have closed epiphyses; **AND** ▪ Patient does NOT have active malignancy; **AND** ▪ Patient does NOT have active proliferative or severe non-proliferative diabetic retinopathy as confirmed by a fundoscopic examination at baseline and periodically throughout treatment; **AND** ▪ Patient does NOT have, or previously had, an intracranial tumor growth as confirmed by a sellar MRI scan with contrast; **AND** ▪ Patient does NOT have Prader-Willi syndrome with ≥ 1 of the following risk factors: severe obesity, have a history of upper airway obstruction or sleep apnea or have severe respiratory impairment, or unidentified respiratory infection; **AND** ▪ Patient does NOT have idiopathic short stature; **AND** ▪ Patient must have had an intolerance to short-acting growth hormone (e.g., somatropin) prior to consideration of lonapegsomatropin-tcgd; **AND**

	▪ Therapy with lonapegsomatropin-tcgd will be supervised by a healthcare professional (HCP) who is experienced in the diagnosis and management of pediatric patients with growth failure due to GHD; **AND** ▪ Prescriber attestation will monitor glucose; when starting therapy, monitor patients with preexisting type 1 diabetes mellitus (T1DM), T2DM, or impaired glucose tolerance with adjustment of antihyperglycemic drugs as warranted; **AND** ▪ Prescriber attestation will monitor for decreased serum cortisol levels and/or the need for glucocorticoid dose increases in those with hypoadrenalism; **AND** ▪ Prescriber attestation will monitor periodic thyroid function tests. *§ Examples of Organic, Congenital, or Genetic Hypothalamic Pituitary Defects* *Organic - Suprasellar mass with previous surgery and cranial irradiation* *Congenital/Genetic - Transcription factor defects (PIT-1, PROP-1, LHX3/4, HESX-1, PITX-2); GHRH receptor-gene defects; GH-gene defects; GH-receptor/post-receptor defects; associated with brain structural defects; single central incisor; cleft lip/palate; perinatal insults* ❖ *Examples of Pituitary Hormones: adrenocorticotropic hormone (ACTH); antidiuretic hormone (ADH); follicle stimulating hormone (FSH); growth hormone (GH); luteinizing hormone (LH); thyroid stimulating hormone (TSH); prolactin* **Renewal Criteria** ▪ Patient must continue to meet the above criteria; **AND** ▪ Patient has shown a beneficial response compared to pre-treatment baseline (with lonapegsomatropin-tcgd or somatropin [if used as switch maintenance]) as evidenced by ≥ 1 of the following: - improvement in height - improvement in growth velocity; **AND** ▪ Patient has NOT experienced any treatment-restricting adverse effects (e.g., severe hypersensitivity reactions, increased risk of neoplasms or recurrence, intracranial hypertension, pancreatitis, glucose intolerance/development of diabetes mellitus, hypothyroidism, hypoadrenalism, fluid retention, slipped capital femoral epiphysis, progression of preexisting scoliosis in pediatric patients, lipoatrophy); **AND** ▪ Patient does NOT have growth velocity failure due to advanced bone age and/or antibodies to recombinant human growth hormone.
Quantity Limit	1 syringe per week for following strengths: 3 mg, 3.6 mg, 4.3 mg, 5.2 mg, 6.3 mg, and 13.3 mg 2 syringe per week for following strengths: 7.6 mg, 9.1 mg, 11 mg
Duration of Approval	Initial: 12 months

	Renewal: 12 months
Drug to Disease Hard Edit	Acute critical illness; acute respiratory failure; active malignancy; active proliferative or severe non-proliferative diabetic retinopathy; closed epiphyses; Prader-Willi syndrome (children who are severely obese or have severe respiratory impairment)

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