Drug Monograph

Drug Name: **Skytrofa® (lonapegsomatropin-tcgd) cartridge**
Drug Class: **Endocrine and Metabolic Agents: Growth Hormone, Somatropin Agents and Analogs**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Skytrofa is available as a lyophilized powder in single-dose, dual chamber, prefilled cartridges containing lonapegsomatropin-tcgd 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.
Manufacturer:	Manufactured for: Ascendis Pharma, Inc., Palo Alto, CA 94301.
Summary of Findings:	The efficacy of Skytrofa for the treatment of growth failure due to inadequate secretion of endogenous growth hormone in pediatric patients aged 1 year and older who weigh at least 11.5 kg was evaluated in the heiGHt 52 week clinical trial. 105 treatment-naïve prepubertal patients received once weekly Skytrofa (lonapegsomatropin=tcgd) 0.24 mg hGH/kg/week while 56 received once daily Gentotropin (somatropin) 0.034 mg hGH/kg/day. Skytrofa demonstrated noninferiority over daily Genotropin for the primary endpoint of annualized height velocity (AHV; cm/year) at 52 weeks (P = 0.009).

Status Recommendation:	☐ Clinical Edit ☐ Open Access	☐ PA Required ☒ PDL
Type of PA Criteria:	☐ Appropriate Indications ☐ No PA Required	☒ Non-Preferred ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

Growth hormone deficiency (GHD) is a rare condition, but a lack of standard diagnostic criteria complicates reliable prevalence and incidence data; prevalence is estimated at 2 to 3 cases per 10,000 population (when combining both childhood-onset and adult-onset GHD). In infancy, patients may present with hypoglycemia and prolonged jaundice; however, diagnosis often occurs later: around age 5 when children begin school or may occur when puberty is delayed; around 10-13 years for females or 12-16 years for males. Pediatric presentation frequently includes short stature, poor height velocity, delayed bone age, relative weight preservation, muscle weakness, slow tooth eruption, and delayed puberty. Slow height growth of less than 1.4 inches per year after a child's third birthday is the main sign of childhood GHD. Children often present with abnormally short stature (height that is more than 2 standard deviations [SD] below the population mean) with normal body proportions.

GHD is the result of insufficient production of the peptide hormone somatropin, also known as GH, by the anterior pituitary gland. GH is secreted in a pulsatile fashion and is primarily controlled by GH-releasing hormone (GHRH), somatostatin, and ghrelin. GH acts at the epiphysis to increase linear growth by promoting differentiation of the prechondrocytes and expansion of osteoblasts. Endogenous and exogenous GH stimulates linear bone growth, increases bone mass, acts on adipose tissue to increase lipolysis, inhibit lipoprotein lipase, stimulate hormone-sensitive lipase, decrease glucose transport and decrease lipogenesis, and acts on muscle to increase transport of amino acids.

GHD may be congenital, acquired, or idiopathic. With congenital cases, GHD IA and IB are autosomal-recessive, GHD IIB is autosomal-dominant, and GHD III is X-linked. Acquired GHD may be the result of brain trauma, central nervous system infection, radiation therapy, brain (hypothalamus or pituitary) tumor, or infiltrative diseases. GHD without any otherwise identified cause are considered idiopathic. Childhood-onset GHD is commonly identified as idiopathic in nature while adult-onset GHD is most often acquired from hypothalamic-pituitary tumors or brain trauma.

Dosage Form(s) [3]

Skytrofa is available as a lyophilized powder in single-dose, dual chamber, prefilled cartridges containing lonapegsomatropin-tcgd 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.

Manufacturer [3]

Manufactured for: Ascendis Pharma, Inc., Palo Alto, CA 94301.

Indication(s) [3]

Skytrofa is indicated for the treatment of pediatric patients 1 year and older who weight at least 11.5 kg and have growth failure due to inadequate secretion of endogenous growth hormone (GH).

Clinical Efficacy [1,3,4] (mechanism of action/pharmacology, comparative efficacy)

Skytrofa is a pegylated, long-acting prodrug of the human growth hormone somatropin and is the first FDA-approved sustained-release somatropin product. The product utilizes a proprietary TransCon (transient conjugation) technology that combines three parts: an unmodified "parent drug" (somatropin), an inert methoxypolyethylene glycol (mPeG) carrier to shield it, and a linker that temporarily binds the pair. When bound, the carrier inactivates and shields the parent drug from clearance. Based on physiologic pH and temperature, the linker autohydrolyzes, releasing fully active, unmodified human GH (hGH) over a one-week period designed to allow the same tissue distribution and receptor activation as endogenous hGH.

Somatropin binds to the growth hormone receptor in the cell membrane of target cells resulting in intracellular signal transduction along with a vast number of additional pharmacodynamic effects. Somatropin has direct tissue and metabolic effects, and indirect effects mediated by insulin-like growth factor-1 (IGF-1), including stimulation of chondrocyte differentiation and proliferation, stimulation of hepatic glucose output, protein synthesis, and lipolysis. Somatropin stimulates skeletal growth in pediatric patients with GHD as a result of effects on the epiphyses (growth plates) of long bones.

Pharmacokinetics:

Absorption	T_{max}: 25 hours following subcutaneous dosage of lonapegsomatropin 0.24 mg/kg/week in pediatric patients with GHD; 12 hours for released somatropin
Metabolism	Protein catabolism via both the liver and kidneys. The methoxypolyethylene glycol carrier is cleared by the kidneys
Excretion	Clearance at steady state: 3.2 mL/hr/kg following subcutaneous administration of 0.24 mg/kg/week
Half-life	$t_{1/2}$: 30.7 hours

Clinical Trials Experience

STUDY 1 DESIGN (NCT02781727)	heiGHt trial: Multicenter, randomized, open-label, active-controlled, parallel-group, 52 week study

INCLUSION CRITERIA	• Prepubertal children with GHD (either isolated or as part of a multiple pituitary hormone deficiency) in Tanner stage 1 (Tanner 1982) aged:
	  ○ Boys: 3-12 years, inclusive
	  ○ Girls: 3-11 years, inclusive
	• Impaired height (HT) defined as at least 2.0 standard deviations (SD) below the mean height for chronological age and sex (HT SDS ≤ -2.0) according to the 2000 CDC Growth Charts for the United States Methods and Development, available at http://www.cdc.gov/growthcharts/
	• Diagnosis of GHD confirmed by 2 different GH stimulation tests, defined as a peak GH level of ≤10 ng/mL, determined with a validated assay
	• Bone age (BA) at least 6 months less than chronological age
	• Baseline IGF-1 level of at least 1 SD below the mean IGF-1 level standardized for age and sex (IGF-1 SDS ≤-1)

	• Written, signed informed consent of the parent(s) or legal guardian(s) of the subject and written assent of the subject (if the subject is able to read, understand, and sign)
EXCLUSION CRITERIA	• Children with a body weight below 12 kg • Prior exposure to recombinant hGH or IGF-1 therapy • Children with past or present intracranial tumor growth as confirmed by a sellar MRI scan (with contrast) at screening (MRI results from up to 6 months prior to screening may be accepted) • Children with psychosocial dwarfism • Children with idiopathic short stature • History or presence of malignant disease; any evidence of present tumor growth • Closed epiphyses • Major medical conditions and/or presence of contraindication to hGH treatment • Participation in any other trial of an investigational agent within 3 months prior to screening
TREATMENT REGIMEN	Treatment-naïve, prepubertal (Tanner Stage 1) children aged 3 to 13 years (males 3-12, females 3-11; mean 8.5 years) with GHD were randomized to Skytrofa 0.24 mg hGH/kg/week or Genotropin (somatropin) 0.034 mg hGH/kg/day.
RESULTS	The primary endpoint of the heiGHt trial was annualized height velocity (AHV; cm/year) at 52 weeks. Once weekly Skytrofa demonstrated noninferiority over daily Genotropin with an AHV of 11.2 versus 10.3 (P = 0.0088) and an estimated treatment difference (95% CI) of 0.9 (0.2, 1.5). Change from baseline in height standard deviation score (SDS) was utilized as a secondary endpoint. LS mean (SE) height SDS increased from baseline to week 52 by 1.10 (0.04) versus 0.96 (0.05) in the weekly Skytrofa versus daily Genotropin groups (P = 0.01)
SAFETY	Discussed in the Adverse Effects section below.

Contraindications [3]

- Acute critical illness after open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure due to the risk of increased mortality with use of pharmacologic doses of somatropin
- Hypersensitivity to somatropin or any of the excipients in Skytrofa.
- Closed epiphyses.
- Active malignancy due to risk of malignancy progression.
- Active proliferative or severe non-proliferative diabetic retinopathy which may be worsened by somatropin therapy.
- Children with Prader-Willi syndrome who are severely obese, have a history of upper airway obstruction or sleep apnea or have severe respiratory impairment due to risk of sudden death.

Warnings and Precautions [3]

- Severe hypersensitivity
- Increased risk of neoplasm
    - Somatropin increases the risk of active malignancy progression therefore, preexisting malignancies should be inactive, and treatment completed prior to initiating Skytrofa. Discontinue Skytrofa if there is evidence of malignancy.

    - Pediatric patients treated with somatropin for GHD following radiation to the brain/head for a first neoplasm are at increased risk of developing a second neoplasm, particularly meningiomas. Monitor patients with a history of GHD secondary to an intracranial neoplasm while on somatropin therapy for progression or recurrence.
- Glucose intolerance and diabetes mellitus
    - Somatropin may decrease insulin sensitivity, particularly at higher doses, and glucose levels should be monitored in all patients. Patients with preexisting diabetes (Type 1 or 2) or impaired glucose tolerance should be monitored closely during Skytrofa treatment initiation and dosage adjustments of antihyperglycemic drugs may be necessary.
- Intracranial hypertension
    - Intracranial hypertension has been reported in a small number of patients and often occurred within 8 weeks of somatropin initiation. Following somatropin discontinuation or dose reduction, signs and symptoms resolved rapidly. A fundoscopic examination to exclude papilledema should be performed prior to treatment initiation and reassessed periodically. If somatropin-induced intracranial hypertension is confirmed, Skytrofa should be stopped and restarted at a lower dose after resolution of signs and symptoms.
- Fluid retention
    - Often transient and dose dependent.
- Hypoadrenalism
    - An increased risk for reduced serum cortisol levels and/or unmasking of central (secondary) hypoadrenalism has been observed in patients receiving somatropin who have or are at risk for pituitary hormone deficiency(s). An increased maintenance or stress glucocorticoid replacement dose may be necessary in patients with previously diagnosed hypoadrenalism. Monitor cortisol levels and need for increased glucocorticoid dose in patients with known hypoadrenalism.
- Hypothyroidism
    - Central (secondary) hypothyroidism may worsen or first become evident during Skytrofa treatment. Periodic thyroid function tests should be performed, and thyroid hormone replacement therapy adjusted or initiated as necessary.
- Slipped capital femoral epiphysis
    - May occur more frequently in patients undergoing rapid growth. Perform appropriate patient evaluation if persistent hip or knee pain or new onset of limp.
- Progression of preexisting scoliosis
    - Progression of existing scoliosis can occur in patients undergoing rapid growth. Monitor patients with a history of scoliosis for disease progression.
- Pancreatitis
    - Should be considered in the setting of persistent, severe abdominal pain.
- Lipoatrophy
    - Rotation of injection sites reduces the risk of lipoatrophy associated with products administered via subcutaneous injection.
- Sudden death in pediatric patients with Prader-Willi Syndrome
    - Fatalities have been reported after somatropin therapy initiation in pediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnea, or unidentified respiratory infection. Males may be at higher risk than females.
- Abnormal Laboratory tests

- Somatropin therapy may lead to increased serum phosphate, alkaline phosphatase, and parathyroid hormone levels. Monitor as appropriate.

Adverse Effects [3]

Adverse Reaction	Skytrofa (N=105) n (%)	Daily Genotropin (N=56) n (%)
Infection, viral	16 (15%)	6 (11%)
Pyrexia	16 (15%)	5 (9%)
Cough	11 (11%)	4 (7%)
Nausea/vomiting	11 (11%)	4 (7%)
Hemorrhage	7 (7%)	1 (2%)
Diarrhea	6 (6%)	3 (5%)
Abdominal pain	6 (6%)	2 (4%)
Arthralgia and arthritis	6 (6%)	1 (2%)

Drug Interactions [3]

- Replacement glucocorticoid treatment: An increase of maintenance or stress glucocorticoid dose may be necessary following Skytrofa initiation in patients with hypoadrenalism.
- Pharmacologic glucocorticoid therapy and supraphysiologic glucocorticoid treatment: Glucocorticoid replacement dosage adjustments may be necessary to avoid hypoadrenalism and an inhibitory effect on growth.
- Cytochrome P-450-metabolized drugs: Clearance may be altered by Skytrofa and monitoring is recommended if Skytrofa is to be administered in combination with drugs metabolized by CYP450 liver enzymes.
- Oral estrogen: Higher Skytrofa doses may be necessary due to oral estrogens leading to a reduction in serum insulin-like growth factor-1 (IGF-1) response to Skytrofa.
- Insulin and/or other antihyperglycemic agents: Skytrofa may decrease insulin sensitivity, particularly at higher doses and insulin and/or other antihyperglycemic dosage adjustments may be necessary in patients with diabetes mellitus.

Dosage and Administration [3]

- For treatment-naïve patients and those switching from daily somatropin therapy: 0.24 mg/kg body weight once weekly via subcutaneous injection into the abdomen, buttock, or thigh with regular rotation of injection site. Dose is titrated based on response.

Recommended Dosing for Patients Weighing 11.5 to 100 kg and Prescribed a Dose of 0.24 mg/kg/week	
Weight (kg)	**Dose (mg)**
11.5 – 13.9	3
14 – 16.4	3.6
16.5 – 19.9	4.3
20 – 23.9	5.2
24 – 28.9	6.3
29 – 34.9	7.6
35 – 41.9	9.1

42 – 50.9	11
51 – 60.4	13.3
60.5 – 69.9	15.2 (using two cartridges of 7.6 mg each)
70 – 84.9	18.2 (using two cartridges of 9.1 mg each)
85 – 100	22 (using two cartridges of 11 mg each)

- If prescribing a dose other than 0.24 mg/kg/week, calculate the total weekly dose (in mg) and select the appropriate cartridge as follows:
  - Total weekly dose (mg) = prescribed weekly dose (mg/kg) x patient's body weight (kg).
  - Round the total weekly dose (mg) to the closest cartridge dose while also considering treatment goals and clinical response.
- When changing from daily somatropin therapy, wait at least 8 hours between the final dose of daily somatropin and the first dose of Skytrofa.
- Refrigerate cartridges at 36°F to 46°F in the outer carton to protect from light until the expiration date. Allow Skytrofa to remain at room temperature for 15 minutes prior to use. Alternatively, the outer carton containing blistered cartridges may be stored at room temperature for up to six months and can be returned to refrigeration within the six months. Skytrofa should not be used beyond the expiration date or 6 months after the date it was first removed from refrigeration (whichever is earlier).
- Discontinue Skytrofa once epiphyseal fusion has occurred.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost** / Month‡
Lonapegsomatropin-tcgd	Skytrofa® cartridge	Ascendis Pharma, Inc	0.24 mg/kg body weight SQ once weekly	$3,758
Somatropin	Gentotropin® cartridge	Pharmacia & Upjohn Co, LLC	0.16 to 0.24 mg/kg body weight per week SQ divided into 6-7 injections	$881

** Wholesale Acquisition Cost

‡ Estimated cost based on 17 kg patient

Conclusion

Skytrofa, the first FDA-approved sustained-release somatropin product is administered as a once weekly subcutaneous injection for the treatment of growth failure due to inadequate secretion of endogenous growth hormone in pediatric patients 1 year and older who weigh at least 11.5 kg. During the 52 week heiGHt clinical trial that enrolled 161 patients, once weekly Skytrofa was found to be noninferior to once daily Genotropin. Adverse reactions were also similar between the two groups, the most common (> 5%) of which were viral infection, pyrexia, cough, and nausea/vomiting.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL) as non-preferred.

References

1) IPD Analytics: New Drug Review: Skytrofa (lonapegsomatropin-tcgd). Published September 2021. Accessed January 2022.
2) Grimberg A, DiVall SA, Polychronakos C. Guidelines for Growth Hormone and Insulin-Like Growth Factor-I Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-I Deficiency. Horm Res Paediatr. 2016; 86: 361-397. https://www.karger.com/Article/Pdf/452150. Accessed January 2022.
3) Skytrofa® (lonapegsomatropin-tcgd) [package insert]. Palo Alto, CA: Ascendis Pharma, Inc.; August 2021.
4) A Phase 3 Trial of the Safety, Tolerability and Efficacy of TransCon hGH Weekly Versus Daily hGH in Children With Growth Hormone Deficiency (GHD). NCT02781727. ClingTrials.gov https://www.clinicaltrials.gov/ct2/show/NCT02781727?term=NCT02781727&draw=2&rank=1. Accessed January 2022.

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