Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Update with New Drug Evaluation: Growth Hormones

Date of Review: December 2021

Date of Last Review: June 2021 (updated PA criteria and FDA indications); September 2017 (literature scan)

Dates of Literature Search: 10/01/2017 - 09/14/2021

Generic Name: lonapegsomatropin-tcgd

Brand Name (Manufacturer): Skytrofa (Ascendis Pharma, Inc.)

Dossier Received: no

Current Status of PDL Class:
See **Appendix 1**.

Research Questions:

1. Is there new comparative evidence that growth hormone (GH) agents differ in efficacy or effectiveness in pediatric patients with growth hormone deficiency or related funded conditions?
2. Is there any new comparative evidence that GH agents differ in harms?
3. Are there specific subpopulations for which one GH agent is better tolerated or more effective than other available agents?
4. What is the evidence for efficacy and harms for the new GH agent, lonapegsomatropin, recently approved to treat pediatric patients with growth failure due to inadequate secretion of endogenous GH?

Conclusions:

- There is no new evidence that there is any difference in efficacy/effectiveness or safety between the different somatropin (i.e., GH) products and formulations.
- There is no new evidence to support that one GH agent is better tolerated or more effective than other available agents for specific subpopulations.
- The Food and Drug Administration (FDA) approval of lonapegsomatropin was based on efficacy data from one Phase 3 clinical trial (heiGHt; study 301) of 161 patients with growth hormone deficiency (GHD).[1-4] The FDA-approved indication is for the treatment of pediatric patients 1 year and older who weigh at least 11.5 kg and have growth failure due to inadequate secretion of endogenous GH.[2-5]
- The heiGHt trial (study 301) reported that once weekly lonapegsomatropin for 52 weeks was non-inferior to daily somatropin as demonstrated by a 11.2 cm/year annualized height velocity compared to 10.3 cm/year, respectively[Estimated treatment difference (ETD) 0.9 cm/year (95% CI 0.2 to 1.5; p=0.009)[1-5] Although statistical significance for non-inferiority was demonstrated, the ETD of 0.9 cm/yr was relatively small and was >50% smaller in magnitude than the non-inferiority margin (2 cm/yr), therefore it is unclear whether this statistical difference is clinically meaningful.
- The safety of lonapegsomatropin in pediatric patients with GHD was primarily evaluated based on data from the pivotal active-controlled phase 3 trial (study-301). There were no serious adverse events (SAEs) observed. The most common adverse events associated with lonapegsomatropin treatment and

Author: David Engen, PharmD

≥4% more frequently than daily somatropin included pyrexia (15%), viral infection (15%), cough (11%), nausea/vomiting (11%), arthralgia/arthritis (7%), and hemorrhage (7%).[1-5]

- There is insufficient evidence to assess long-term safety of lonapegsomatropin beyond one year or once adult height, as determined by bone age, is achieved.[2]
- With the studied population primarily pediatric (mean age of 8.5 years), male (82%), and white (94%), it is unclear whether lonapegsomatropin would demonstrate similar safety and efficacy in subpopulations of different ages, gender, race or ethnic backgrounds represented in Oregon Medicaid.[1-5]

Recommendations:

- Maintain lonapegsomatropin as non-preferred in the Growth Hormone PDL class.
- Update prior authorization (PA) criteria for GH agents to include lonapegsomatropin.
- After evaluate of comparative costs in executive session, no PDL changes were recommended.

Summary of Prior Reviews and Current Policy

- In June 2021, prior authorization criteria for the Growth Hormone PDL class was updated to align fee-for-service PA criteria with the latest Health Evidence Review Commission (HERC) guidance for use of GH and its FDA-approved indications.
- Somapacitan-beco was added to Growth Hormone PDL class and made non-preferred.
- Treatment for adult human growth hormone deficiency is currently not listed as a funded condition on the prioritized list of health services.

Background:

Growth Hormone (GH) influences many of the metabolic processes performed by somatic cells and triggers protein synthesis in a wide range of bodily tissues.[6-8] The anterior pituitary secretes GH in short busts at different times throughout the night and daily following meals, after exercise, and during stress.[6-8] GH increases growth in children by its direct action on growth plates and indirectly stimulates cell proliferation by production of various growth factors such as insulin-like growth factor-1 (IGF-1) in the liver and peripheral tissues.[6-8] Although prenatal growth is not dependent upon GH, its indirect effects on IGF-1 production is crucial for prenatal and postnatal development, especially in a child's first year of life.[6-8] GH also reduces the utilization of glucose in peripheral tissues and stimulates lipolysis as well as growth of skeletal muscle and cartilage.[6-8] Hypoglycemia, hypothyroidism, and/or defective primary or secondary sexual development may be other signs of pituitary dysfunction which can be a result of hormone deficiencies such as adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), or gonadotropin.[6-8] There are a variety of disorders in which endogenous growth hormone production is inadequate to meet the developmental demands required for specification, organization, and maturation of somatotropic cells.[6-8]

There are several pediatric conditions where growth may be severely compromised. Early GH therapy has been used to improve height velocity and normalize childhood growth in children with growth hormone deficiency (GHD).[9-12] GHD is a result of pituitary gland dysfunction that occurs in roughly 1:4000 – 10000 live births.[7] Overall, the clinical manifestations of GHD vary among individual patients, and the diagnostic process is a complex, multistep process involving clinical history, physical examination with detailed growth pattern assessment, biochemical testing, and pituitary imaging.[9-12] GHD is the most common endocrine cause of short stature, which is defined as a height 2 standard deviations below the average for age, sex, and race. GHD may be isolated or may exist with other pituitary hormone deficiencies.[9-12] Pediatric patients with absolute GHD typically present with normal birth weight, then begin to show early growth failure at 6-12 months followed by notable decreases in growth velocity until 3 years of age.[6-8] Patients with GHD may also display signs such as delayed bone age, jaundice, central obesity, and craniofacial abnormalities.[6-8, 10] Congenital GHD is rare and is typically caused as a result of genetic mutation or structural brain

malformations.[8-12] Acquired GHD may occur in either child- or adulthood secondary to pituitary or hypothalamic tumors, head injury, central nervous system (CNS) infection, or due to other conditions which lead to an insufficient production of GH.[7-10] Some medications, such as glucocorticoids and stimulants, may result in transient GH deficiency and short stature.[6-11] Besides short stature, GHD leads to risk of hypoglycemia due to the patients' high sensitivity to insulin and loss of counter-regulatory mechanisms.[6-11] **Table 1** outlines GH Research Society consensus guidelines for times to consider immediate investigation into GHD.[9-11]

Table 1: Considerations for immediate investigation of potential GHD[9-11]

Height: ▪ 3 SD below mean for age (severe short stature) ▪ 2 SD below mean for age and height velocity > 1 SD below mean for chronological age over past year or decrease in height SD > 0.5 over past year in children > 2 years old ▪ > 1.5 SD below mid-parental height
Height Velocity: ▪ > 2 SD below mean over past year or > 1.5 SD below mean over past 2 years
Signs of intracranial lesion
Signs of multiple pituitary hormone deficiency
Neonatal signs of GHD

GHD=growth hormone deficiency; SD=standard deviations

Growth failure in children may be the result of isolated GHD, but compromised growth may also be present in those with chronic illness, genetic syndromes, or skeletal disorders.[11 9] Recombinant GH (rGH) is a first-line agent for GHD and is also approved for treatment of many other pediatric conditions that affect growth (**Table 2**).[8,9] Somatropin is the standard rGH preparation and is typically administered daily by subcutaneous injection.[8-12] When appropriate, rGH is generally initiated at an early age due to a more robust growth response and therapy is continued until growth has ceased.[9-12]

Table 2: FDA-approved Uses for Recombinant Growth Hormone

Condition	Etiology/Pathology	Clinical Manifestations	rGH Function	Approved rGH Preparation	Population Indication
GHD[6,7]	Impaired production of GH from congenital malformations/genetic defects or acquired causes (e.g. trauma, infection, malignancy)	Early growth failure at 6-12 months with decreased growth velocity until 3 years of age, delayed bone age, jaundice, central obesity, craniofacial abnormalities, hypoglycemia, hypothyroidism, defective primary or secondary sexual development	In children, used to normalize adult height and avoid extreme shortness in children and adolescents with GHD. In adults, decreased visceral fat and increased muscle mass, and increased exercise capacity	Genotropin™ Humatrope™ Norditropin™ Nutropin AQ™ Omnitrope™ Saizen™ Zomacton™ Skytrofa™ Sogroya™	Pediatric; Adult Pediatric Adult

PWS[13]	Deletions or unexpressed regions of paternal chromosome 15 (15q11-13) leads to generalized hypothalamic insufficiency	Short stature, mental retardation, hyperphagia with obesity, and hyperflexibility	Foster linear growth, improve muscle mass, enhance satiety and reduce weight gain	Genotropin™ Norditropin™ Omnitrope™	Pediatric
Noonan Syndrome[14]	Mutation in the RAS-MAPK signaling pathway which disrupts numerous hormones, cytokines, and growth factors that control cell proliferation, migration, differentiation, and survival	Face dysmorphology, short stature, congenital heart defect (e.g. pulmonary valve stenosis, hypertrophic cardiomyopathy), and developmental delays	Correction of short stature and improve growth	Norditropin™	Pediatric
Turner Syndrome[15]	Complete, partial absence, or structural abnormality of 1 X chromosome (45,X) in phenotypic female	Lymphedema, excess skin folds on neck, failure to thrive, slow growth, amenorrhea, and infertility	Improve short-term growth and increase final height; prevent short stature (females <4 years old)	Genotropin™ Humatrope™ Norditropin™ Nutropin AQ™ Omnitrope™ Zomacton™	Pediatric
Idiopathic Short Stature[10]	Unknown	Low to normal height velocity (< 5 cm/year from age 5 years until puberty), height below midparental centile range (height > 2 standard deviations below population mean for age and gender)	Increase short-term height velocity, and may increase final height in children	Genotropin™ Humatrope™ Norditropin™ Nutropin AQ™ Omnitrope™ Zomacton™	Pediatric
SHOX Deficiency[16]	Missing gene that encodes transcription factor expressed for developing skeletal tissue for long-bone growth	Short stature, skeletal dysplasia and severe limb deformity	Appears to increase height velocity and linear growth in prepubertal children	Humatrope™ Zomactron™	Pediatric
CKD with Growth Failure[17]	Reduced GFR leading to growth retardation	Reduced height velocity and stunted growth	Reported to improve growth during the first year of administration	Nutropin AQ™	Pediatric
Small Gestational Age [9]	Maternal/placental or genetic factors that result in a fetus or newborn infant	Persistent short stature; Higher mortality rate due to cardiovascular disease	To accelerate linear growth, improve body composition,	Genotropin™ Humatrope™ Norditropin™	Pediatric

	whose weight and/or crown-heel length is less than (2 SD below mean) expected for their gestational age and sex		blood pressure, and lipid metabolism	Omnitrope™ Zomacton™	
HIV Associated Cachexia[18]	Altered metabolism and malabsorption due to HIV infection	Weight loss, anorexia, muscle atrophy, fatigue and weakness	To increase lean body mass, body weight and improve physical endurance	Serostim™	Pediatric, Adult
Short Bowel Syndrome[19]	Reduction of functional intestinal surface area from intestinal resection or tissue damage leads to malabsorption of nutrients, fluid, and/or electrolytes.	Diarrhea, dehydration, electrolyte abnormalities, weight loss, confusion and apathy	To increase weight, lean/fat-free body mass, and nutritional absorption	Zorbtive™	Adult

Abbreviations: CKD = chronic kidney disease; FDA = Food and Drug Administration; GFR = glomerular filtration rate; GHD = growth hormone deficiency; HIV = human immunodeficiency virus; PWS= Prader-Willi syndrome; rGH = recombinant growth hormone; SHOX = Short stature homeobox-containing gene

Although most GH products are FDA approved to treat pediatric patients, not every GH formulation is identical.[20-28] For example, somatropin exists under 9 different brand names that are not always interchangeable.[20-28] Clinical practice guidelines do not distinguish among the various preparations of GH as there is limited evidence of differences in clinical outcomes from one brand to another.[9-12] Each formulation may have a different strength, administration device, and/or storage requirement.[20-28] Dosing frequency may also vary among different products and conditions.[20-28] The choice of preparation is individualized based on therapeutic needs, patient response, as well as adherence.[20-28] If more than one product is suitable, the most cost-effective product should be chosen.[12] GH is indicated for children who need GH therapy and who have open epiphyses.[9-12] Therapy is started at low doses then increased gradually to the minimum effective dose that results in normalized IGF-1 levels without major adverse effects.[8] The treatment of somatropin should be discontinued if growth velocity increases less than 50% from baseline in the first year of treatment, final height is approached and growth velocity is less than 2 cm total growth in 1 year, adherence issues, or if final height is attained.[8-12] The decision to stop treatment should be made in consultation with the patient and/or caregivers by a pediatrician with specialist expertise in managing growth hormone disorders in children or an adult endocrinologist.[12]

Adult GHD (AGHD) is most often due to hypopituitarism secondary to head trauma, tumor of the hypothalamus or pituitary gland, or the consequences of cancer treatment such as surgery or radiation.[30-31] Growth hormone deficiency is characterized by decreased lean body mass and bone mineral density, increased visceral adiposity, abnormal lipid profile, decreased muscle strength and decreased exercise endurance.[30-31] The diagnosis of GH deficiency is confirmed if other pituitary hormones such as thyroid stimulating hormone (TSH), corticotropin (ACTH), and gonadotropins are also diminished.[30-31] A subnormal serum insulin-like growth factor-1 (IGF-1) concentration or subnormal serum GH response to a stimulation test also assists in confirming AGHD.[30-31] The insulin tolerance test (ITT) and GHRH-arginine test are two tests recommended by the Endocrine Society to establish diagnosis of AGHD.[30-31] However, GH stimulation testing is invasive, time consuming, and can have increased risks in patients with seizure disorders or cardiovascular disease.[30-31]

The Health Evidence Review Commission (HERC) guidance currently restricts use of GH to funded diagnoses where there is medical evidence of effectiveness and safety.[32] HERC guidance continues to specify that treatment with GH for children with conditions such as gonadal dysfunction, panhypopituitarism, iatrogenic and other pituitary disorders should only continue until adult height, as determined by bone age, is achieved.[32] There are only 3 conditions for which GH therapy

is FDA approved for use in adults: cachexia associated with AIDS (Serostim®)[26], short bowel syndrome (Zorbtive®)[28] and GH deficiency.[20-25,29] HIV associated with cachexia and short bowel syndrome are OHP-covered conditions for adults by their respective FDA-approved GH agents.[32] However, treatment for adult human growth hormone deficiency is currently not a funded condition on the HERC prioritized list of health services.[32]

During 2020 in the OHP FFS population, the most common indications identified based on medical claims for GHD-related diagnosis included short stature in children and hypopituitarism. Patients with diagnoses for other conditions such as Turner's syndrome, Prader-Willi syndrome, and other congenital malformations associated with short stature were relatively infrequent. There were 28 patients with claims for growth hormone agents in quarter 2 of 2021, which represents a moderate expenditure to the Oregon Health Authority. Of these claims, 82% were for preferred therapies.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
No new high-quality systematic reviews were identified.

After review, 3 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:
No new high-quality practice guidelines were identified.

Additional Guidelines for Clinical Context:
In 2019, the American Association of Clinical Endocrinologists and American College of Endocrinology released guidelines for management of growth hormone deficiency in adults and patients transitioning from pediatric to adult care. Due to lack of details on guideline methodology and a significant portion of the professional practice committee members having conflicts of interest with industry, the guidelines will not be reviewed in detail or relied upon for policy making decisions.[33]

After review, 2 guidelines were excluded due to poor quality or for lack of applicability to the OHP population.

New Formulations or Indications:
No new formulations or indications were identified since the last review.

New FDA Safety Alerts:
There were numerous safety alerts released by the FDA over the last 3 years regarding the use of various somatropin formulations. The main alerts are summarized in **Table 4**.

Table 4: Description of New FDA Safety Alerts[34]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Somatropin	Humatrope (H) Zomacton (Z) Norditropin (N)	10/2019 7/2018 2/2018	Warning	-Increased mortality in patients with acute critical Illness due to complications from open heart surgery, abdominal surgery, accidental trauma, or respiratory failure (H) -Cases of pancreatitis (especially children; females with Turner syndrome) (N,Z) -Increased risk of malignancy/neoplasms (H,Z) -Progression of preexisting scoliosis (N,H) -Patients with Turner syndrome have an increased risk of developing autoimmune thyroid disease and primary hypothyroidism (Z)
			Contraindication	-Acute critical illness after open heart surgery, trauma, etc due to increased mortality (N) -Pediatric patients 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 the risk of sudden death (N) -Active malignancy (H)

Randomized Controlled Trials:
A total of 71 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION:

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Lonapegsomatropin is a long-acting pegylated prodrug formulation of somatropin, or recombinant hGH, approved for the treatment of pediatric patients 1 year and older who weigh at least 11.5 kg and have growth failure due to inadequate secretion of endogenous growth hormone (GH).[2-5] Lonapegsomatropin is covalently bonded to a methoxypolyethylene glycol carrier via a TransCon linker, and is designed to be given once weekly subcutaneously via a specialized glass auto injector.[2-5] Lonapegsomatropin slowly releases hGH via hydrolysis and is deigned to maintain the same mode of action and distribution in the body as daily somatropin.[2-5] Upon release, hGH stimulates the GH-receptor in tissues and increases hepatic production of IGF-1 which leads to GH activity such as growth stimulation, increased lean body mass, and improved metabolic actions.[1-5] The FDA approved lonapegsomatropin based on study 310 ("heiGHt" trial), a pivotal phase 3, open-label, active controlled, parallel-group study of 162 patients with GHD.[1-5] The trial consisted of a screening period (up to 6 weeks plus up to 2 weeks between randomization and visit 1) and a treatment period (52 weeks of dosing with a total of 6 trial visits).[1-5] The patients were randomized 2:1 to either lonapegsomatropin (n=106) or Genotropin (n=56), respectively.[2-5] Study participants were primarily white (94%), male (82%), had a mean baseline height velocity of 3.9 cm/year, a height standard deviation score (SDS) of -3 and a mean age of 8.5 years.[2-5] Baseline demographics were overall similar between groups in all major areas and baseline characteristics of height velocity and height SDS also appeared evenly distributed.[2-5] Patients with prior exposure to GH or IGF-1 therapies; a history of malignancy, evidence of malnourishment, idiopathic short stature, small for gestational age, or other non-GHD related causes of short stature were excluded.[1-4] The primary endpoint was annualized height velocity (AHV; cm/year) after 52 weeks based on a wall-mounted, calibrated stadiometer.[1-5] The AHV calculation used was AHV = (change in height [cm] ÷ change in time[days]) x 365 days.[1-4] The pre-specified non-inferiority margin was 2 cm/year, and the investigators planned a test for superiority if non-inferiority was achieved.[1-5] Secondary end points included AHV, height SDS, numerous IGF-1 lab measurements, and bone age assessed at predefined timepoints over 52 weeks.[1-5] Lonapegsomatropin 0.24 mg/kg was administered once weekly subcutaneously in 105 patients while 56 patients received once daily somatropin 0.034 mg hGH/kg.[1-5] The FDA also evaluated safety data from 2 other Phase 3 studies with pediatric GHD: CT-302 which was a 26-week, multi-site, open-label, uncontrolled trial with 146 patients from 24 international sites and CT-301EXT, an ongoing, long term open-label, uncontrolled extension trial which enrolled 296 patients at 63 international sites.[2-4] There were no endpoints specified for study CT-302 or CT-301EXT.[2-4]

Patients treated with once weekly lonapegsomatropin for 52 weeks achieved 11.2 cm/year annualized height velocity while patients treated with once daily somatropin achieved an annualized height velocity of 10.3 cm/year which was considered statistically significant using the sponsor's pre-specified ANCOVA method (Estimated treatment difference (ETD) 0.9 cm/year; 95% CI 0.2 to 1.5; p=0.009).[1-5] With the upper boundary of the 95% CI less than the non-inferiority margin of 2, non-inferiority was attained.[1-4] Based on the pre-specified analysis, statistical superiority was also achieved as the lower limit of the two-sided CI of the treatment difference greater than or equal to 0 cm/year..[1-4] Lonapegsomatropin also demonstrated a relatively small but statistically significant change in Height SDS compared to placebo (1.10 vs. 0.96, respectively; ETD 0.14 (95% CI, 0.03 to 0.26; p=0.015).[1-5] The data used by the study sponsor to calculate Height SDS changes were from an ANCOVA model that included baseline age, peak GH levels (log transformed) at stimulation test and baseline height SDS as covariates, and treatment and sex as factors.[1-4]

This trial had some inherent limitations. Because lonapegsomatropin was administered once weekly compared to Genotropin given once daily, neither patients nor investigators were blinded to treatment. Due to the controlled nature of the study, it is unknown whether a once-weekly formulation would increase or decrease adherence compared to daily dosing if patients were to self-administer. Although statistical significance for non-inferiority was demonstrated, the treatment difference (0.9 cm/yr) between lonapegsomatropin and Genotropin was relatively small and was >50% smaller in magnitude than the non-inferiority margin (2 cm/yr). It is unclear whether this statistical difference is clinically meaningful. The lower boundary margin was set at >0, therefore statistical superiority was established. However, since the rationale for non-inferiority margin was not described it is unclear whether there was sufficient evidence available to warrant statistical (and clinical) superiority versus the standard of care.

Clinical Safety:

The safety population included 305 patients from 3 studies who had received at least one dose of lonapegsomatropin.[2-5] In study 301, adverse events related to treatment occurred in 12 patients (11%) in the lonapegsomatropin group compared to 10 patients (18%) in the Genotropin arm.[2-5] There were no serious adverse events (SAEs) observed that were related to treatment.[2-5] There were 3 treatment emergent adverse events (TEAEs) overall, 2 in the lonapegsomatropin group (lipoatrophy, urticaria) and one in the Genotropin arm (injection site-related swelling) that led to a dose reduction. No TEAEs resulted in drug discontinuation or death.[2-5] In the single-arm CT-302 safety study, there was one SAE and 4% of patients experienced a TEAE related to the study drug. There were no treatment discontinuations due to adverse events in the lonapegsomatropin group.[2-5] The most common adverse events associated with treatment included pyrexia, hemorrhage, viral infection, arthralgia/arthritis, cough, nausea and vomiting (see **Table 5**).[2-5]

Table 5. Adverse Reactions Occurring in ≥5% Lonapegsomatropin-Treated Patients and ≥4% More Frequently than in Somatropin-Treated Patients. [2,5]

	Lonapegsomatropin-tcgd (N=105) n (%)	Genotropin (N=56) n (%)
Pyrexia	16 (15%)	5 (9%)
Infection, viral	16 (15%)	6 (11%)
Cough	11 (11%)	4 (7%)
Nausea and vomiting	11 (11%)	4 (7%)
Hemorrhage	7 (7%)	1 (2%)
Arthralgia and arthritis	6 (7%)	1 (2%)

Adverse events of special interest (AESI) included on the FDA label included injections site reactions, increased risk of neoplasms, glucose intolerance, intracranial hypertension, fluid retention, hypoadrenalism, hypothyroidism, slipped capital femoral epiphyses, progression of pre-existing scoliosis, pancreatitis, and lipoatrophy.[2,5] The AESI listed on the label are consistent with the known hGH class specific side effects and not limited to lonapegsomatropin.[2-5] Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with post-marketing use of somatropin products. [2, 5] Lonapegsomatropin is contraindicated in patients with acute critical illness, active malignancies and with hypersensitivity to the drug.[5] FDA labeling has also limited the indication of lonapegsomatropin to patients 1 year or older with a body weight >11.5 kg due to the lowest available dosage strength available in that formulation.[5]

Look-alike / Sound-alike Error Risk Potential: None identified.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Final height
2) Growth/height velocity
3) Health-related quality of life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Annualized height velocity (AHV; cm/year) after 52 weeks

Table 6: Pharmacology and Pharmacokinetic Properties.[2,3]

Parameter	
Mechanism of Action	A long-acting, pegylated prodrug of a human growth hormone (somatropin) that binds to the GH receptor in the cell membrane of target cells resulting in intracellular signal transduction and numerous pharmacodynamic effects on tissues and metabolic processes.
Oral Bioavailability	N/A
Distribution and Protein Binding	Vd=0.13 L/kg; Protein binding not available
Elimination	3.2 mL/hour/kg
Half-Life	30.7 hours
Metabolism	Protein catabolism in both liver and kidneys

Abbreviations: GH=growth hormone; kg=kilogram; ml=milliliters; Vd=volume of distribution

Table 7: Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
Thornton, et al. [1] 2021 Phase 3, OL, R, AC, PG	1. Lonapegsomatropin 0.24 mg hGH/kg/wk 2. Genotropin (somatropin) 0.034 mg hGH/kg/ day	Demographics: 1. Mean age: 8.5 years 2. Mean height: 112.7 cm 3. Mean bone age: 5.9 years 4. Mean height velocity: 3.9 cm/yr 5. Mean height SDS: -3 6. Male: 82% 7. Ethnic group: White (94.4%) Key Inclusion Criteria: -Prepubertal Tanner stage 1, GH therapy naïve -Boys: 3-12 yrs; Girls 3-11 yrs -Height SDS ≤ -2, standardized for chronological age/sex or height SDS less than 1.5 below the mid-parental height -BMI within ±2 SD of mean BMI for chronological age and sex -Confirmed GHD by 2 different GH stimulation tests. -Bone age 6 months less than chronological age -Baseline IGF-1 SDS ≤ -1, standardized for age and sex -Normal fundoscopy at screening	ITT: 1. 105 2. 56 Attrition: 1. 2 (2%) 2. 0 (0%)	Primary Endpoint: AHV (cm/yr) at Week 52 1. 11.2 2. 10.3 ETD=0.9 (95% CI, 0.2 to 1.5) p-value=0.009 Secondary Endpoints: Change in height SDS at 52 weeks 1. 1.10 2. 0.96 ETD=0.14 (95% CI, 0.03 to 0.26); P = 0.01	N/A for all	No serious adverse effects reported at 52 weeks TEAEs 1. 2/105 (2%) 2. 1/56 (2%)	N/A for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Unclear) Subjects were centrally randomized in a 2:1 ratio but no details on methods. Baseline demographics similar in both treatment groups. Performance Bias: (High) Open label study due to inability to conceal once weekly versus daily formulation and lack of double-dummy use. Doses could be adjusted at the discretion of the investigator after discussion with the medical monitor due to symptoms or lab results. Detection Bias: (Unclear) Bone age was read by a blinded central bone age reader and auxology performed by the same blinded auxologist at each visit when possible. Method of blinding was not reported. Attrition Bias: (Low) Similar rates of study withdrawal in both arms with similar reasons for discontinuation. Reporting Bias: (Unclear) Study protocol not available. Not all secondary outcomes reported (e.g. IGFBP-3 and IGFBP-3 SDS values) Other Bias: (Unclear) Sponsored by the manufacturer Ascendis Pharma, who directly employed or provided financial support to several authors through grants or personal fees. One primary author is an advisory board consultant for the manufacturer.

		Key Exclusion Criteria: -Children with a body weight<12kg -Tanner stage >1 -Prior exposure to recombinant hGH or IGF-1 therapy -Children w/ past or present intracranial tumor growth or malignancy -Children born small for gestational age, with idiopathic short stature, with psychosocial dwarfism, or other causes of short stature -Children with malnutrition -Any clinically significant abnormality likely to affect growth or the ability to evaluate growth -Poorly controlled DM, defined as hemoglobin A1c ≥ 8% or diabetic complications -chromosomal abnormalities -Closed epiphyses						**Applicability**: Patient: Appropriate diagnostic criteria were used, including evaluation of bone age, height at baseline; subjects underwent testing with 2 different GH stimulation tests in order to confirm the GHD diagnosis. However, exclusion of diabetics (A1c ≥8%) and inclusion of mostly males and white race may limit applicability to females and other racial or ethnic subgroups in the OHP population. Intervention: Fixed doses of rhGH were used Subjects started at a dose of 0.24 mg hGH/kg/week; starting dose consistent with recommended initial rhGH dose of 0.16-0.24 mg/kg/week Comparator: Genotropin (somatropin) appropriate standard of care and dosed reasonably at 0.034 mg hGH/kg/day Outcomes: AHV is a surrogate endpoint that has been accepted by the FDA for the approval of several other rhGH products for treatment of pediatric subjects with growth failure due to GHD Setting: 54 sites including Armenia, Australia, Belarus, Bulgaria, Georgia, Greece, Italy, New Zealand, Poland, Romania, Russia, Turkey, Ukraine, United States
Abbreviations: AC=active comparator; AHV=annualized height velocity; ARR = absolute risk reduction; BMI = body mass index; CI = confidence interval; DM = diabetes mellitus; ETD=estimated treatment difference; GH=growth hormone; GHD=growth hormone deficiency; (r)hGh=(recombinant)human growth hormone; IGF-1=insulin-like growth factor-1; ITT = intention to treat; kg=kilogram; mITT = modified intention to treat; N = number of subjects; N/A = not applicable; NNH = number needed to harm; NNT = number needed to treat; OL=open label; PG=parallel group; PP = per protocol; R=randomized; SD = standard deviation; SDS=standard deviation score								

References:

1. Thornton PS, Maniatis AK, Aghajanova E, et al. Weekly Lonapegsomatropin in Treatment-Naïve Children With Growth Hormone Deficiency: The Phase 3 heiGHt Trial. *The Journal of Clinical Endocrinology & Metabolism*. 2021.
2. US Food and Drug Administration (FDA) Center for Drug Evaluation and Research. Skytrofa Summary Review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761177Orig1s000SumR.pdf Accessed October 1, 2021.
3. US Food and Drug Administration (FDA) Center for Drug Evaluation and Research. Skytrofa Clinical Review(s). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761177Orig1s000MedR.pdf Accessed October 1, 2021.
4. US Food and Drug Administration (FDA) Center for Drug Evaluation and Research. Skytrofa Statistical Review.https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761177Orig1s000StatR.pdf Accessed October 1, 2021.
5. Skytrofa (lonapegsomatropin subcutaneous injection) [Prescribing Information]. Palo Alto, CA. Ascendis Pharma, Inc. August 2021.
6. Chinoy A, Murray PG. Diagnosis of growth hormone deficiency in the paediatric and transitional age. *Best Practice & Research Clinical Endocrinology & Metabolism*. 2016;30(6):737-747.
7. Stanley T. Diagnosis of growth hormone deficiency in childhood. Curr Opin Endocrinol Diabetes Obes. 2012;19(1):47-52.
8. Rogol AD, Hayden GF. Etiologies and Early Diagnosis of Short Stature and Growth Failure in Children and Adolescents. *The Journal of Pediatrics*. 2014;164(5, Supplement):S1-S14.e16.
9. Clayton PE, Cianfarani S, Czernichow P, Johannsson G, Rapaport R, Rogol A. Management of the Child Born Small for Gestational Age through to Adulthood: A Consensus Statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society. *The Journal of Clinical Endocrinology & Metabolism.* 2007;92(3):804-810.
10. Cohen P, Rogol AD, Deal CL, et al. Consensus Statement on the Diagnosis and Treatment of Children with Idiopathic Short Stature: A Summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. *The Journal of Clinical Endocrinology & Metabolism*. 2008;93(11):4210-4217.
11. Grimberg A, DiVall SA, Polychronakos C, et al. 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. *Hormone Research in Paediatrics*. 2016;86(6):361-397.
12. National Institute for Health and Clinical Excellence (NICE). Human growth hormone (somatropin) for the treatment of growth failure in children. London (UK): National Institute for Health and Clinical Excellence, 2010 May. https://www.nice.org.uk/guidance/ta188 Accessed Oct 1, 2021
13. Driscoll DJ, Miller JL, Schwartz S, et al. Prader-Willi Syndrome. 1998 Oct 6 [Updated 2017 Dec 14]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1330/
14. Allanson JE, Roberts AE. Noonan Syndrome. 2001 Nov 15 [Updated 2019 Aug 8]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1124/
15. Pinsker JE. Turner Syndrome: Updating the Paradigm of Clinical Care. *The Journal of Clinical Endocrinology & Metabolism*. 2012;97(6):E994-E1003.
16. Rappold G, Blum WF, Shavrikova EP, et al. Genotypes and phenotypes in children with short stature: clinical indicators of SHOX haploinsufficiency. *J Med Genet.* 2007;44(5):306-313.
17. Hodson EM, Willis NS, Craig JC. Growth hormone for children with chronic kidney disease. The Cochrane database of systematic reviews. 2012;2012(2):CD003264-CD003264.
18. Grunfeld C. What Causes Wasting in AIDS? *New England Journal of Medicine*. 1995;333(2):123-124.
19. Jeppesen PB. Growth Factors in Short-Bowel Syndrome Patients. *Gastroenterology Clinics of North America*. 2007;36(1):109-121.
20. Genotropin® [prescribing information]. Pfizer, Inc.; New York (NY); 2016 Sep.

21. Humatrope® [prescribing information]. Lilly USA, LLC: 2016 Dec.
22. Norditropin® [prescribing information]. Novo Nordisk Inc.; Plainsboro (NJ); 2018 Feb.
23. Nutropin AQ® [prescribing information]. Genentech, Inc.; San Francisco (CA); 2016 Dec.
24. Omnitrope® [prescribing information]. Sandoz, Inc.; Princeton (NJ); 2016 Dec.
25. Saizen® [prescribing information]. EMD Serono, Inc.; Rockland (MA); 2018 May.
26. Serostim® [prescribing information]. EMD Serono, Inc.; Rockland (MA); 2018 May.
27. Zomacton® [prescribing information]. Ferring Pharmaceuticals, Inc.; Parsippany (NJ); 2018 Jan.
28. Zorbtive® [prescribing information]. EMD Serono, Inc.; Rockland (MA); 2017 May.
29. Sogroya ® {prescribing information]. Novo Nordisk Inc.; Plainsboro, New Jersey; 2021 Oct
30. Hoffman AR. Treatment of the adult growth hormone deficiency syndrome: Directions for future research. *Growth Hormone & IGF Research*. 2005;15:48-52.
31. Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Vance ML. Evaluation and Treatment of Adult Growth Hormone Deficiency: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*. 2011;96(6):1587-1609.
32. Health Evidence Review Commission. Searchable Prioritized List, Guideline Notes, Multisector Interventions and Services Recommended for Non-Coverage. Available at https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Searchable-List.aspx Accessed 10/1/2021.
33. Yuen KCJ, Biller BMK, Radovick S, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Growth Hormone Deficiency in Adults and Patients Transitioning from Pediatric to Adult Care. *Endocrine Practice*. 2019;25(11):1191-1232.
34. Food and Drug Administration (FDA) Alert -Drug Safety-related Labeling Change. Available at https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchResult.page. Accessed 10/8/2021.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
somatropin	GENOTROPIN	CARTRIDGE	Y
somatropin	GENOTROPIN	SYRINGE	Y
somatropin	NORDITROPIN FLEXPRO	PEN INJCTR	Y
somatropin	NUTROPIN AQ NUSPIN	PEN INJCTR	Y
somatropin	HUMATROPE	CARTRIDGE	N
somatropin	HUMATROPE	VIAL	N
somatropin	OMNITROPE	CARTRIDGE	N
somatropin	OMNITROPE	VIAL	N
somatropin	SAIZEN	VIAL	N
somatropin	SAIZEN-SAIZENPREP	CARTRIDGE	N
somatropin	SEROSTIM	VIAL	N
somatropin	ZOMACTON	VIAL	N
somatropin	ZORBTIVE	VIAL	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to September 14, 2021>

1	somapacitan.mp.	15
2	somatropin.mp.	279
3	somatotropin.mp.	8163
4	humatrope.mp.	27
5	nutropin.mp.	25
6	serostim.mp.	39
7	zomacton.mp.	5
8	saizen.mp.	38
9	norditropin.mp.	91
10	zorbtive.mp.	3
11	genotropin.mp.	117
12	omnitrope.mp.	54
13	growth hormone.mp. or Growth Hormone/75581	
14	human growth hormone.mp. or Human Growth Hormone/19768	
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14/76289	
16	limit 15 to (full text and humans and yr="2018 -Current" and (clinical trial, all or controlled clinical trial or meta analysis or "systematic review"))	71

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SKYTROFA™ safely and effectively. See full prescribing information for SKYTROFA™.

SKYTROFA™ (lonapegsomatropin-tcgd) for injection, for subcutaneous use

Initial U.S. Approval: 2021

----------INDICATIONS AND USAGE----------

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

----------DOSAGE AND ADMINISTRATION----------

SKYTROFA should be administered subcutaneously into the abdomen, buttock, or thigh with regular rotation of the injection sites (2.5).
The recommended dose is 0.24 mg/kg body weight once-weekly.

See Full Prescribing Information for instructions on preparation and administration of drug (2.4, 2.5).

----------DOSAGE FORMS AND STRENGTHS----------

SKYTROFA is a lyophilized powder available in single-dose, dual-chamber, prefilled cartridges containing lonapegsomatropin-tcgd and diluent, Water for Injection, as follows:
For injection: 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 (3).

----------CONTRAINDICATIONS----------

- Acute critical illness (4)
- Hypersensitivity to somatropin or any of the excipients in SKYTROFA (4)
- Children with closed epiphyses (4)
- Active malignancy (4)
- Active proliferative or severe non-proliferative diabetic retinopathy (4)
- Children with Prader-Willi syndrome who are severely obese or have severe respiratory impairment due to risk of sudden death (4)

----------WARNINGS AND PRECAUTIONS----------

- Severe Hypersensitivity: Serious hypersensitivity reactions may occur. In the event of an allergic reaction, seek prompt medical attention (5.2).
- Increased Risk of Neoplasms: Monitor patients with preexisting tumors for progressions or recurrence. Increased risk of a second neoplasm in childhood cancer survivors treated with somatropin – in particular meningiomas in patients treated with radiation to the head for their first neoplasm (5.3).
- Glucose Intolerance and Diabetes Mellitus: May be unmasked. Periodically monitor glucose levels in all patients. Doses of concurrent antihyperglycemic drugs in diabetics may require adjustment (5.4).
- Intracranial Hypertension: Exclude preexisting papilledema. May develop and is usually reversible after discontinuation or dose reduction (5.5).
- Fluid Retention (i.e., edema, arthralgia, carpal tunnel syndrome): May occur. Reduce dose as necessary (5.6).
- Hypoadrenalism: Monitor patients for reduced serum cortisol levels and/or need for glucocorticoid dose increases in those with known hypoadrenalism (5.7).
- Hypothyroidism: May first become evident or worsen (5.8).
- Slipped Capital Femoral Epiphysis: May develop. Evaluate children with the onset of a limp or persistent hip/knee pain (5.9).
- Progression of Preexisting Scoliosis: May develop (5.10).
- Pancreatitis: Consider pancreatitis in patients with persistent severe abdominal pain (5.11).

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥5%) in pediatric patients include: viral infection, pyrexia, cough, nausea and vomiting, hemorrhage, diarrhea, abdominal pain, and arthralgia and arthritis (6).

To report SUSPECTED ADVERSE REACTIONS, contact Ascendis Pharma, Inc., at 1-844-442-7236 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Replacement Glucocorticoid Treatment: Patients treated with glucocorticoid for hypoadrenalism may require an increase in their maintenance or stress doses following initiation of SKYTROFA (7).
- Pharmacologic Glucocorticoid Therapy and Supraphysiologic Glucocorticoid Treatment: Adjust glucocorticoid replacement dosing in pediatric patients receiving glucocorticoid treatment to avoid both hypoadrenalism and an inhibitory effect on growth (7).
- Cytochrome P450-Metabolized Drugs: SKYTROFA may alter the clearance. Monitor carefully if used with SKYTROFA (7).
- Oral Estrogen: Larger doses of SKYTROFA may be required (7).
- Insulin and/or Other Antihyperglycemic Agents: Dose adjustment of insulin or antihyperglycemic agent may be required (7).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 8/2021

Appendix 4: Key Inclusion Criteria

Population	Children and adolescents with GHD or GHD-related diagnosis
Intervention	Drugs listed in Appendix 1
Comparator	Drugs listed in Appendix 1 or placebo
Outcomes	Final height, growth/height velocity, health-related quality of life
Timing	Weeks to years
Setting	Outpatient

Appendix 5: Prior Authorization Criteria

Growth Hormones

Goal(s):

- Restrict use of growth hormone (GH) for funded diagnoses where there is medical evidence of effectiveness and safety.

NOTE: Treatment with GH in children should continue only until adult height, as determined by bone age, is achieved. Treatment is not included for isolated deficiency of human growth hormone in adults.

Length of Authorization:

- Up to 12 months

Requires PA:

- All GH products require prior authorization for OHP coverage. Treatment of human growth hormone deficiency for adults is not funded by the OHP.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Initial Approval Criteria		
1. What is the diagnosis being treated?	Record ICD10 code	
2. Is the request for an FDA approved indication?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is this a request for initiation of growth hormone?	**Yes:** Go to #4	**No:** Go to **Renewal Criteria**
4. Is the agent being prescribed by, or in consultation with, a pediatric endocrinologist or pediatric nephrologist?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the patient an adult (>18 years of age)?	**Yes:** Go to #10	**No:** Go to #6
6. Is the diagnosis funded?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the diagnosis promotion of growth delay in a child with 3rd degree burns?	**Yes:** Document and send to DHS Medical Director for review and pending approval	**No:** Go to #8
8. If male, is bone age <16 years? If female, is bone age <14 years?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Is there evidence of non-closure of epiphyseal plate?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness

Initial Approval Criteria		
10. Is the request for the treatment of isolated human growth hormone deficiency in an adult (E23.0) or short stature due to an endocrine disorder (E34.3), or another unfunded condition? Per Guideline Note 74, treatment with GH for children with conditions such as panhypopituitarism, iatrogenic and other pituitary disorders, as well as gonadal dysfunction, should only continue until adult height, as determined by bone age, is achieved.	**Yes:** Pass to RPh. Deny; not funded by the OHP.	**No:** Go to #11
11. Is the request for a pediatric patient with Prader-Willi syndrome who has: • Severe obesity? or • A history of upper airway obstruction or sleep apnea? or • Severe respiratory impairment? Note: Recombinant somatropin is contraindicated in these patients due to the risk of sudden death.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to # 12
12. Is the requested product preferred?	**Yes:** Approve for up to 12 months	**No:** Go to #13

Initial Approval Criteria		
13. Will the prescriber consider a change to a preferred product that is FDA-approved for the condition? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months.	**No:** Go to #14
14. Is the request for lonapegsomatropin?	**Yes:** Go to #15	**No:** Approve for up to 12 months
15. Is the request for a pediatric patient 1 year or older with a body weight >11.5 kg?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Document approximate date of initiation of therapy and diagnosis (if not already done).		
2. Was treatment with this agent initiated in patient prior to reaching adulthood (<18 years of age)?	**Yes:** Go to #3	**No:** Go to #5
3. Is growth velocity greater than 2.5 cm per year?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is male bone age <16 years or female bone age <14 years?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the request for isolated human growth hormone deficiency in an adult (E23.0), short stature due to an endocrine disorder (E34.3), or another unfunded condition?	**Yes:** Pass to RPh. Deny; not funded by the OHP.	**No:** Go to #6
6. Is the product requested preferred?	**Yes:** Approve for up to 12 months	**No:** Go to #7

7. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months	**No:** Approve for up to 12 months

P&T Review: 12/21 (DE); 6/21; 11/18 ; 9/17; 9/16; 9/15; 9/14; 9/10; 5/10; 9/08; 2/06; 11/03; 9/03
Implementation: 1/1/22; 1/1/19; 10/13/16; 1/1/11, 7/1/10, 4/15/09, 10/1/03, 9/1/06; 10/1/03