

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

RECENT MAJOR CHANGES

Contraindications (4) 10/2022
Warnings and Precautions (5.2) 10/2022

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: Hypersensitivity reactions, including anaphylaxis and angioedema have occurred. 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 ($\geq 5\%$) 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 Endocrinology, 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 dosing in pediatric patients 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: 10/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

[1 INDICATIONS AND USAGE](#)

[2 DOSAGE AND ADMINISTRATION](#)

[2.1 General Dosing Information](#)

[2.2 Dosage Recommendations](#)

[2.3 Missed Doses](#)

[2.4 Administrative Instructions](#)

[2.5 Preparation and Administration](#)

[3 DOSAGE FORMS AND STRENGTHS](#)

[4 CONTRAINDICATIONS](#)

[5 WARNINGS AND PRECAUTIONS](#)

[5.1 Increased Mortality in Patients with Acute Critical Illness](#)

[5.2 Severe Hypersensitivity](#)

[5.3 Increased Risk of Neoplasms](#)

[5.4 Glucose Intolerance and Diabetes Mellitus](#)

[5.5 Intracranial Hypertension](#)

[5.6 Fluid Retention](#)

[5.7 Hypoadrenalism](#)

[5.8 Hypothyroidism](#)

[5.9 Slipped Capital Femoral Epiphysis](#)

[5.10 Progression of Preexisting Scoliosis](#)

[5.11 Pancreatitis](#)

[5.12 Lipoatrophy](#)

[5.13 Sudden Death in Pediatric Patients with Prader-Willi Syndrome](#)

[5.14 Laboratory Tests](#)

[6 ADVERSE REACTIONS](#)

[6.1 Clinical Trials Experience](#)

[6.2 Immunogenicity](#)

[6.3 Postmarketing Experience](#)

[7 DRUG INTERACTIONS](#)

[8 USE IN SPECIFIC POPULATIONS](#)

[8.1 Pregnancy](#)

[8.2 Lactation](#)

[8.4 Pediatric Use](#)

[9 DRUG ABUSE AND DEPENDENCE](#)

[9.1 Controlled Substance](#)

[9.2 Abuse](#)

[9.3 Dependence](#)

[10 OVERDOSAGE](#)

[11 DESCRIPTION](#)

[12 CLINICAL PHARMACOLOGY](#)

[12.1 Mechanism of Action](#)

[12.2 Pharmacodynamics](#)

[12.3 Pharmacokinetics](#)

[13 NONCLINICAL TOXICOLOGY](#)

[13.1 Carcinogenicity, Mutagenesis, Impairment of Fertility](#)

[14 CLINICAL STUDIES](#)

[14.1 Treatment-Naïve Pediatric Patients with Growth Hormone Deficiency \(NCT02781727\)](#)

[16 HOW SUPPLIED/STORAGE AND HANDLING](#)

[16.1 How Supplied](#)

[16.2 Storage and Handling](#)

[17 PATIENT COUNSELING INFORMATION](#)

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

SKYTROFA (lonapegsomatropin-tcgd) 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).

2. DOSAGE AND ADMINISTRATION

2.1. General Dosing Information

- For subcutaneous injection, once-weekly.
- Therapy with SKYTROFA should be supervised by a physician who is experienced in the diagnosis and management of pediatric patients with growth failure due to growth hormone deficiency (GHD).
- To exclude preexisting papilledema, perform fundoscopic examination before initiating treatment with SKYTROFA and reassess periodically thereafter [*see Warnings and Precautions (5.5)*].

2.2. Dosage Recommendations

- The recommended dose of SKYTROFA for treatment-naïve patients and patients switching from daily somatropin therapy is 0.24 mg/kg body weight, given once-weekly.
- Individualize and titrate the dosage of SKYTROFA based on response.
- When changing from daily somatropin therapy to once-weekly SKYTROFA, wait at least 8 hours between the final dose of daily somatropin and the first dose of once-weekly SKYTROFA.
- Assess compliance and evaluate other causes of poor growth such as hypothyroidism, under-nutrition, advanced bone age and antibodies to recombinant human growth hormone if patients experience failure to increase height velocity, particularly during the first year of treatment.
- Discontinue SKYTROFA once epiphyseal fusion has occurred.

2.3. Missed Doses

- Administer a missed dose as soon as possible and not more than 2 days after the missed dose.
 - To avoid missed doses, SKYTROFA can be taken 2 days before or 2 days after the scheduled dosing day. Resume once-weekly dosing for the next dose at the previously scheduled dosing day.
 - If more than 2 days have passed from the scheduled day, skip the dose and administer the next dose on the regularly scheduled day.
 - At least 5 days should elapse between doses.
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2.4. Administration Instructions

SKYTROFA is available in 9 cartridges (dosage strengths in somatropin equivalents). Selection of the appropriate cartridge is based on the prescribed dose (mg/kg) and the patient's body weight (kg).

- If prescribing a dose of 0.24 mg/kg/week and the patient's weight is 11.5 to 100 kg, follow the recommended dosing in [Table 1](#).
- 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.

Table 1: Recommended Dosing for Patients Prescribed Doses 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)

2.5. Preparation and Administration

The SKYTROFA cartridge has been designed for use only with the SKYTROFA Auto-Injector.

If refrigerated, the SKYTROFA cartridge must be kept at room temperature for 15 minutes before use.

The SKYTROFA Auto-Injector provides a fully automated reconstitution of the lyophilized drug product which is followed by a manual mixing step controlled by the device. When the injection needle is inserted into the skin, the device automatically delivers the drug product. The built-in electronics and software assist the user during the entire preparation and injection sequence and provide confirmation that the full dose has been delivered.

The mixed solution should be clear and colorless to opalescent and may occasionally contain air bubbles. DO NOT inject if the solution is cloudy or contains particulate matter.

Use SKYTROFA cartridges within 4 hours after reconstitution. Discard reconstituted SKYTROFA cartridges after 4 hours when stored at room temperature up to 86°F (30°C).

Inject SKYTROFA subcutaneously into the abdomen, buttock, or thigh. Rotate injection sites between and within regions to reduce the risk of lipoatrophy.

Refer to the Instructions for Use for complete administration instructions with illustrations. The instructions can also be found on www.Skytrofa.com/IFU.

3. DOSAGE FORMS AND STRENGTHS

SKYTROFA is a white to off-white lyophilized powder available in a single-dose, dual-chamber, prefilled cartridge containing lonapegsomatropin-tcgd in one chamber and diluent, Water for Injection, in the other chamber and is available in the following strengths:

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.

4. CONTRAINDICATIONS

SKYTROFA is contraindicated in patients with:

- 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 [*see Warnings and Precautions (5.1)*].
- Hypersensitivity to somatropin or any of the excipients in SKYTROFA. Severe systemic hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported [*see Warnings and Precautions (5.2)*].
- Closed epiphyses.
- Active malignancy due to the risk of malignancy progression [*see Warnings and Precautions (5.3)*].
- Active proliferative or severe non-proliferative diabetic retinopathy because treatment with somatropin may worsen this condition.
- 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 [*see Warnings and Precautions (5.13)*].

5. WARNINGS AND PRECAUTIONS

5.1. Increased Mortality in Patients with Acute Critical Illness

Increased mortality in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure has been reported after treatment with pharmacologic doses of somatropin [*see Contraindications (4)*]. The safety of continuing SKYTROFA treatment in patients receiving

replacement doses for the approved indication who concurrently develop these illnesses has not been established.

5.2. Severe Hypersensitivity

Severe systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with postmarketing use of somatropin products, including SKYTROFA. Inform patients and/or caregivers that such reactions are possible, and that prompt medical attention should be sought if an allergic reaction occurs. SKYTROFA is contraindicated in patients with known hypersensitivity to somatropin or any of the excipients in SKYTROFA.

5.3. Increased Risk of Neoplasms

Active Malignancy

There is an increased risk of malignancy progression with somatropin treatment in patients with active malignancy [see *Contraindications (4)*]. Any preexisting malignancy should be inactive, and its treatment should be completed prior to instituting therapy with SKYTROFA. Discontinue SKYTROFA if there is evidence of recurrent malignancy.

Risk of Second Neoplasm in Pediatric Patients

In childhood cancer survivors who were treated with radiation to the brain/head for their first neoplasm and who developed subsequent growth hormone deficiency (GHD) and were treated with somatropin, an increased risk of a second neoplasm has been reported. Intracranial tumors, in particular meningiomas, were the most common of these second neoplasms. Monitor all patients with a history of GHD secondary to an intracranial neoplasm while on somatropin therapy for progression or recurrence of the tumor.

New Malignancy During Treatment

Because children with certain rare genetic causes of short stature have an increased risk of developing malignancies, thoroughly consider the risks and benefits of starting somatropin in these patients. If treatment with somatropin is initiated, carefully monitor these patients for development of neoplasms.

Monitor patients on somatropin therapy carefully for increased growth or potential malignant changes of preexisting nevi. Advise patients/caregivers to report marked changes in behavior, onset of headaches, vision disturbances and/or changes in skin pigmentation or changes in the appearance of preexisting nevi.

5.4. Glucose Intolerance and Diabetes Mellitus

Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses. Previously undiagnosed impaired glucose tolerance and overt type 2 diabetes mellitus may be unmasked. Monitor glucose levels in all patients receiving SKYTROFA, especially in those with risk factors for type 2 diabetes mellitus, such as obesity or a family history of type 2 diabetes mellitus. When initiating SKYTROFA, monitor closely patients with preexisting type 1 or type 2 diabetes mellitus or impaired glucose tolerance and adjust the doses of antihyperglycemic drugs as needed.

5.5. Intracranial Hypertension

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea, and/or vomiting has been reported in a small number of patients treated with somatropin. Symptoms usually occurred within 8 weeks after the initiation of somatropin. In all reported cases, IH-associated signs and symptoms resolved rapidly after cessation of therapy or a reduction of the somatropin dose. To exclude preexisting papilledema, perform fundoscopic examination before initiating treatment with SKYTROFA, and reassess periodically thereafter. If papilledema is observed by fundoscopy, stop somatropin treatment. If somatropin-induced IH is confirmed, restart treatment with SKYTROFA at a lower dose after IH-associated signs and symptoms have resolved.

5.6. Fluid Retention

Fluid retention during somatropin therapy may occur. Clinical manifestations of fluid retention (e.g., edema, arthralgia, myalgia, nerve compression syndromes including carpal tunnel syndrome/paresthesia) are usually transient and dose-dependent.

5.7. Hypoadrenalism

Patients receiving somatropin therapy who have or are at risk for pituitary hormone deficiency(s) may be at risk for reduced serum cortisol levels and/or unmasking of central (secondary) hypoadrenalism. In addition, patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of SKYTROFA therapy. Monitor patients for reduced serum cortisol levels and/or need for glucocorticoid dose increases in patients with known hypoadrenalism [*see Drug Interactions (7)*].

5.8. Hypothyroidism

Undiagnosed or untreated hypothyroidism may prevent optimal response to SKYTROFA. In patients with GHD, central (secondary) hypothyroidism may first become evident or worsen during SKYTROFA treatment. Therefore, perform periodic thyroid function tests in patients and initiate or appropriately adjust thyroid hormone replacement therapy when indicated.

5.9. Slipped Capital Femoral Epiphysis

Slipped capital femoral epiphysis may occur more frequently in patients undergoing rapid growth. Evaluate pediatric patients with the onset of a limp or complaints of persistent hip or knee pain.

5.10. Progression of Preexisting Scoliosis

Somatropin increases growth rate, and progression of existing scoliosis can occur in patients who experience rapid growth. Somatropin has not been shown to increase the occurrence of scoliosis. Monitor patients with a history of scoliosis for disease progression.

5.11. Pancreatitis

Pancreatitis has been reported in pediatric patients receiving somatropin. The risk may be greater in pediatric patients than adults. Consider pancreatitis in patients who develop persistent severe abdominal pain.

5.12. Lipoatrophy

When SKYTROFA is administered subcutaneously at the same site over a long period of time, lipoatrophy may result. Rotate injection sites when administering SKYTROFA to reduce this risk [see *Preparation and Administration (2.5)*].

5.13. Sudden Death in Pediatric Patients with Prader-Willi Syndrome

There have been reports of fatalities after initiating therapy with somatropin 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. Male patients with one or more of these factors may be at greater risk than females. SKYTROFA is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

5.14. Laboratory Tests

Serum levels of phosphate, alkaline phosphatase, and parathyroid hormone may increase after somatropin treatment. If a patient is found to have abnormal laboratory tests, monitor as appropriate.

6. ADVERSE REACTIONS

The following important adverse reactions are described elsewhere in the labeling:

- Increased mortality in patients with acute critical illness [see *Warnings and Precautions (5.1)*]
- Severe hypersensitivity [see *Warnings and Precautions (5.2)*]
- Increased risk of neoplasms [see *Warnings and Precautions (5.3)*]
- Glucose intolerance and diabetes mellitus [see *Warnings and Precautions (5.4)*]
- Intracranial hypertension [see *Warnings and Precautions (5.5)*]
- Fluid retention [see *Warnings and Precautions (5.6)*]
- Hypoadrenalism [see *Warnings and Precautions (5.7)*]
- Hypothyroidism [see *Warnings and Precautions (5.8)*]
- Slipped capital femoral epiphysis in pediatric patients [see *Warnings and Precautions (5.9)*]
- Progression of preexisting scoliosis in pediatric patients [see *Warnings and Precautions (5.10)*]
- Pancreatitis [see *Warnings and Precautions (5.11)*]
- Lipoatrophy [see *Warnings and Precautions (5.12)*]

- Sudden death in pediatric patients with Prader-Willi syndrome [see *Warnings and Precautions (5.13)*]

6.1. Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

SKYTROFA was studied in a 52-week, open-label, active-controlled trial in 161 treatment-naïve, prepubertal pediatric patients with growth hormone deficiency (GHD) [see *Clinical Studies (14.1)*]. The subjects ranged in age from 3.2 to 13.1 years with a mean of 8.5 years. One hundred thirty-two (82%) of the subjects were male and 29 (18%) were female. One subject was Asian, 3 were Black or African American, 152 were Caucasian, and 5 were categorized as “other.”

Table 2 shows common adverse reactions that occurred in $\geq 5\%$ of patients treated with SKYTROFA in this trial.

Table 2: Adverse Reactions Occurring in $\geq 5\%$ SKYTROFA-Treated Pediatric Patients and More Frequently than in Daily Somatropin-Treated Pediatric Patients (52 Weeks of Treatment)

Adverse Reactions	Daily Somatropin (N = 56) n (%)	SKYTROFA (N = 105) n (%)
Infection, viral	6 (11%)	16 (15%)
Pyrexia	5 (9%)	16 (15%)
Cough	4 (7%)	11 (11%)
Nausea and vomiting	4 (7%)	11 (11%)
Hemorrhage ^a	1 (2%)	7 (7%)
Diarrhea	3 (5%)	6 (6%)
Abdominal pain	2 (4%)	6 (6%)
Arthralgia and arthritis ^b	1 (2%)	6 (6%)

Adverse reactions that are medically related were grouped to a single preferred term.

^a Hemorrhage in the SKYTROFA treatment group included epistaxis (3), contusion (2), petechiae (1) and eye hemorrhage (1).

^b Arthralgia and arthritis in the SKYTROFA treatment group included arthralgia (5) and reactive arthritis (1).

Laboratory Tests

More SKYTROFA-treated patients shifted from normal baseline levels to elevated phosphate and alkaline phosphatase levels at the end of the trial compared to the daily somatropin group (44.2% vs. 30.2% and 19.2% vs. 9.4%, respectively); these laboratory changes occurred intermittently [see *Warnings and Precautions (5.14)*].

6.2. Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to SKYTROFA with the incidence of antibodies to other products may be misleading.

Anti-lonapegsomatropin-tcgd antibodies were evaluated in samples collected every 3 months in phase 3 trials in pediatric patients with GHD receiving lonapegsomatropin-tcgd. Mean duration of exposure to SKYTROFA was 70.2 weeks. Of the 304 patients with post-baseline assessments, 19 (6.3%) showed detectable binding antibodies to lonapegsomatropin-tcgd at any time. No apparent correlation of anti-lonapegsomatropin-tcgd antibodies to adverse events or loss of efficacy was observed. No neutralizing antibodies to SKYTROFA were detected.

6.3. Postmarketing Experience

The following adverse reactions have been identified during post approval use of somatropin products, including SKYTROFA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Severe systemic hypersensitivity reactions including anaphylactic reactions and angioedema

7. DRUG INTERACTIONS

Table 3 includes a list of drugs with clinically important drug interactions when administered concomitantly with SKYTROFA and instructions for preventing or managing them.

Table 3: Clinically Important Drug Interactions with SKYTROFA

Replacement Glucocorticoid Treatment	
<i>Clinical Impact:</i>	Microsomal enzyme 11 β -hydroxysteroid dehydrogenase type 1 (11 β HSD-1) is required for conversion of cortisone to its active metabolite, cortisol, in hepatic and adipose tissue. Somatropin inhibits 11 β HSD-1. Consequently, individuals with untreated growth hormone deficiency (GHD) have relative increases in 11 β HSD-1 and serum cortisol. Initiation of SKYTROFA may result in inhibition of 11 β HSD-1 and reduced serum cortisol concentrations.
<i>Intervention:</i>	Patients treated with glucocorticoid replacement for hypoadrenalism may require an increase in their maintenance or stress doses following initiation of SKYTROFA [<i>see Warnings and Precautions (5.7)</i>]
<i>Examples</i>	Cortisone acetate and prednisone may be affected more than others because conversion of these drugs to their biologically active metabolites is dependent on the activity of 11 β HSD-1.

Pharmacologic Glucocorticoid Therapy and Supraphysiologic Glucocorticoid Treatment	
<i>Clinical Impact:</i>	Pharmacologic glucocorticoid therapy and supraphysiologic glucocorticoid treatment may attenuate the growth-promoting effects of SKYTROFA in pediatric patients.
<i>Intervention:</i>	Carefully adjust glucocorticoid replacement dosing in pediatric patients receiving glucocorticoid treatments to avoid both hypoadrenalism and an inhibitory effect on growth.
Cytochrome P450-Metabolized Drugs	
<i>Clinical Impact:</i>	Limited published data indicate that somatropin treatment increases cytochrome P450 (CYP450)-mediated antipyrine clearance. SKYTROFA may alter the clearance of compounds known to be metabolized by CYP450 liver enzymes.
<i>Intervention:</i>	Careful monitoring is advisable when SKYTROFA is administered in combination with drugs metabolized by CYP450 liver enzymes.
Oral Estrogen	
<i>Clinical Impact:</i>	Oral estrogens may reduce the serum insulin-like growth factor-1 (IGF-1) response to SKYTROFA.
<i>Intervention:</i>	Patients receiving oral estrogen replacement may require higher SKYTROFA dosages.
Insulin and/or Other Antihyperglycemic Agents	
<i>Clinical Impact:</i>	Treatment with SKYTROFA may decrease insulin sensitivity, particularly at higher doses.
<i>Intervention:</i>	Patients with diabetes mellitus may require adjustment of their doses of insulin and/or other antihyperglycemic agents [<i>see Warnings and Precautions (5.4)</i>].

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

There are no available data on lonapegsomatropin-tcgd use in pregnant patients to evaluate a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Available published data over several decades for somatropin, the active component of lonapegsomatropin-tcgd, have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, there was no evidence of embryo-fetal or neonatal harm when pregnant rats were administered subcutaneous lonapegsomatropin-tcgd at doses up to 13-fold the clinical dose of 0.24 mg/kg/week (*see Data*).

The estimated background risk of birth defects and miscarriages for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

No embryonic or fetal development toxicities occurred in rats administered subcutaneous lonapegsomatropin-tcgd at doses up to 13-fold the clinical dose of 0.24 mg/kg/week.

In a peri- and post-natal developmental study in rats, there were no adverse effects on the pregnant/lactating female or on development of the conceptus and the offspring following exposure of the female from implantation through weaning to doses of a structurally related pegylated somatropin prodrug up to 13-fold the clinical dose of 0.24 mg/kg/week.

8.2. Lactation

Risk Summary

There are no data on the presence of lonapegsomatropin-tcgd in human milk, effects on the breastfed infant, or effects on milk production. High molecular weight therapeutic proteins, including lonapegsomatropin-tcgd, are expected to have low passage into human milk and limited systemic exposure in the breastfed infant. Additionally, published data indicate that exogenous somatropin does not increase normal human milk concentrations of growth hormone. No adverse effects on the breastfed infant have been reported with somatropin. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SKYTROFA and any potential adverse effects on the breastfed infant from SKYTROFA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of SKYTROFA have been established in pediatric patients 1 year and older and who weigh at least 11.5 kg. Pediatric use was established in a controlled study of 161 treatment-naïve pediatric patients ages 3 to 13 years and by supportive data in pediatric patients 1 year and older [*see Adverse Reactions (6) and Clinical Studies (14)*].

The safety and effectiveness of SKYTROFA in children less than 1 year of age have not been established.

Use of somatropin in pediatric patients with Prader-Willi syndrome has been associated with reports of sudden death. SKYTROFA is not indicated for the treatment of pediatric patients with growth failure due to genetically confirmed Prader-Willi syndrome [*see Warnings and Precautions (5.13)*].

9. DRUG ABUSE AND DEPENDENCE

9.1. Controlled Substance

SKYTROFA is a prodrug of somatropin. Somatropin is not a controlled substance.

9.2. Abuse

Inappropriate use of somatropin may result in significant negative health consequences.

9.3. Dependence

Somatropin is not associated with drug related withdrawal adverse reactions.

10. OVERDOSAGE

Acute overdosage may lead initially to hypoglycemia and subsequently to hyperglycemia. Overdose with somatropin may cause fluid retention. Long-term overdosage may result in signs and symptoms of gigantism consistent with the known effects of excess growth hormone.

11. DESCRIPTION

Lonapegsomatropin-tcgd is a long-acting prodrug of a human growth hormone (somatropin) produced by recombinant DNA technology using *E. coli*. Lonapegsomatropin-tcgd consists of a parent drug, somatropin, that is conjugated to a methoxypolyethylene glycol carrier (4 x 10 kDa mPEG) via a proprietary TransCon Linker and has a molecular weight of 63 kDa (released somatropin is 22 kDa). *In vitro* assay confirms the minimum potency of released somatropin is NLT 2.5 IU/mg.

SKYTROFA (lonapegsomatropin-tcgd) for injection is a sterile, preservative-free, white to off-white lyophilized powder available in a single-dose, dual-chamber, prefilled cartridge containing lonapegsomatropin-tcgd in one chamber and the diluent, Water for Injection, in the other chamber. SKYTROFA prefilled cartridge must be used with SKYTROFA Auto-Injector to provide an automatic mixing step for reconstitution prior to subcutaneous use.

After reconstitution, each prefilled cartridge delivers:

- 0.273 mL containing 3 mg lonapegsomatropin-tcgd, succinic acid (0.32 mg), trehalose dihydrate (22.7 mg), and tromethamine for pH adjustment to 5.
- 0.327 mL containing 3.6 mg lonapegsomatropin-tcgd, succinic acid (0.39 mg), trehalose dihydrate (27.1 mg), and tromethamine for pH adjustment to 5.
- 0.391 mL containing 4.3 mg lonapegsomatropin-tcgd, succinic acid (0.46 mg) and trehalose dihydrate (32.5 mg) and tromethamine for pH adjustment to 5.
- 0.473 mL containing 5.2 mg lonapegsomatropin-tcgd, succinic acid (0.56 mg) and trehalose dihydrate (39.3 mg) and tromethamine for pH adjustment to 5.
- 0.286 mL containing 6.3 mg lonapegsomatropin-tcgd, succinic acid (0.34 mg) and trehalose dihydrate (21.2 mg) and tromethamine for pH adjustment to 5.
- 0.345 mL containing 7.6 mg lonapegsomatropin-tcgd, succinic acid (0.41 mg) and trehalose dihydrate (25.5 mg) and tromethamine for pH adjustment to 5.
- 0.414 mL containing 9.1 mg lonapegsomatropin-tcgd, succinic acid (0.49 mg) and trehalose dihydrate (30.6 mg) and tromethamine for pH adjustment to 5.
- 0.5 mL containing 11 mg lonapegsomatropin-tcgd, succinic acid (0.59 mg) and trehalose dihydrate (37 mg) and tromethamine for pH adjustment to 5.
- 0.605 mL containing 13.3 mg lonapegsomatropin-tcgd, succinic acid (0.71 mg) and trehalose dihydrate (44.8 mg) and tromethamine for pH adjustment to 5.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

SKYTROFA is a pegylated human growth hormone (somatropin) for once-weekly subcutaneous injection [see *Pharmacokinetics (12.3)*].

Somatropin binds to the growth hormone (GH) receptor in the cell membrane of target cells resulting in intracellular signal transduction and a host of 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 growth hormone deficiency (GHD) as a result of effects on the growth plates (epiphyses) of long bones.

12.2. Pharmacodynamics

Somatropin released from SKYTROFA produces a dose linear IGF-1 response, with a change of 0.02 mg/kg on average resulting in a change in IGF-1 standard deviation score (SDS) of 0.17.

At steady-state, IGF-1 levels peak approximately 2 days post-dose, with the average weekly IGF-1 occurring approximately 4.5 days post-dose. IGF-1 levels are in the normal range for GHD patients for the majority of the week, similar to daily somatropin.

12.3. Pharmacokinetics

Absorption

Following subcutaneous dose administration, SKYTROFA releases fully active somatropin via autocleavage of the TransCon linker that follows first-order kinetics.

In pediatric patients with GHD, following subcutaneous dose administration of 0.24 mg/kg/week SKYTROFA, the observed mean (CV%) steady state peak serum concentration (C_{max}) of lonapegsomatropin-tcgd was 1230 (86.3) ng hGH/mL, and the median time to reach maximum concentrations (T_{max}) was 25 hours. For released somatropin, C_{max} was 15.2 (83.4) ng/mL with a median T_{max} of 12 hours. The mean (CV%) somatropin exposure over the one-week dose interval (area under the curve) was 500 (83.8) h*ng/mL. No significant accumulation of lonapegsomatropin-tcgd and somatropin following repeat dose administration was observed.

C_{max} of the methoxypolyethylene glycol carrier was 13.1 (28.1) µg /mL with a median T_{max} of 36 hours.

In healthy adults, following single subcutaneous dose administration in the range of 0.24 to 0.42 mg/kg of SKYTROFA, exposure of released somatropin increased greater than proportional to dose.

Distribution

In pediatric patients with GHD, the mean (CV%) steady state apparent volume of distribution of lonapegsomatropin-tcgd after subcutaneous administration of 0.24 mg/kg/week SKYTROFA was 0.13 (109) L/kg. A similar distribution pattern as observed for daily somatropin is expected once somatropin is released from lonapegsomatropin-tcgd.

Elimination

Metabolism

The metabolism of somatropin involves protein catabolism in both the liver and kidneys. The methoxypolyethylene glycol carrier is cleared by the kidneys.

Excretion

In pediatric patients with GHD, the mean (CV%) lonapegsomatropin-tcgd apparent clearance at steady state was 3.2 (67) mL/h/kg following subcutaneous administration of 0.24 mg/kg/week SKYTROFA with a mean (\pm SD) observed half-life of 30.7 (\pm 12.7) hours. The apparent half-life of somatropin released from lonapegsomatropin-tcgd was approximately 25 hours.

Specific Populations

Based on a population pharmacokinetic analysis, age, sex, race, and body weight do not have clinically meaningful effects on pharmacokinetics.

Male and Female Patients — No sex-specific pharmacokinetic studies have been performed with SKYTROFA. The available literature indicates that the pharmacokinetics of somatropin are similar in men and women.

Patients with Renal or Hepatic Impairment — No specific studies have been performed with SKYTROFA.

13. NONCLINICAL TOXICOLOGY

13.1. Carcinogenicity, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with lonapegsomatropin-tcgd.

Lonapegsomatropin-tcgd was not mutagenic in the Ames test, in the human chromosomal aberration assay or in the rat bone marrow micronucleus test.

In an animal fertility study, lonapegsomatropin-tcgd was administered via subcutaneous injection to male and female rats before cohabitation, through mating to implantation.

Lonapegsomatropin-tcgd did not affect fertility or early embryo-fetal development at doses up to 20-fold the clinical dose of 0.24 mg/kg/week.

14. CLINICAL STUDIES

14.1. Treatment-Naïve Pediatric Patients with Growth Hormone Deficiency (NCT02781727)

A multi-center randomized, open-label, active-controlled, parallel-group phase 3 study was conducted in 161 treatment-naïve, prepubertal pediatric subjects with growth hormone deficiency (GHD); 105 subjects received once-weekly SKYTROFA, and 56 received daily somatropin. The dose in both arms was 0.24 mg/kg/week. The primary efficacy endpoint was annualized height velocity at Week 52.

The subjects ranged in age from 3.2 to 13.1 years with a mean of 8.5 years. One hundred thirty-two (82%) subjects were male and 29 (18%) were female. One subject was Asian, three were

Black or African American, 152 were Caucasian, and five were categorized as “other.” The subjects had a mean baseline height SDS (standard deviation score) of -2.9.

Treatment with once-weekly SKYTROFA for 52 weeks resulted in an annualized height velocity of 11.2 cm/year. Subjects treated with daily somatotropin achieved an annualized height velocity of 10.3 cm/year after 52 weeks of treatment. Refer to [Table 4](#).

Table 4: Annualized Height Velocity at Week 52 in Pediatric Treatment-Naïve Subjects with Growth Hormone Deficiency

	Once-Weekly SKYTROFA (N=105)	Daily Somatotropin (N=56)	Estimate of Treatment Difference (95% CI) (SKYTROFA minus Daily Somatotropin)
Annualized Height Velocity (cm/year) ^a	11.2	10.3	0.9 (0.2-1.5)

^a The estimates of least square (LS) means and 95% confidence interval (CI) are from an ANCOVA model that included baseline age, peak GH levels (log transformed) at stimulation test, baseline height SDS – average SDS of parental height as covariates, and treatment and sex as factors. Missing data were imputed with multiple imputation method.

Height SDS (change from baseline) was 1.1 in the SKYTROFA arm and 0.96 in the daily somatotropin arm at Week 52. Refer to [Table 5](#).

Table 5: Height SDS over 52 Weeks in Pediatric Treatment-Naïve Subjects with Growth Hormone Deficiency

	Once-Weekly SKYTROFA (N=105)	Daily Somatotropin (N=56)
Height SDS, baseline	-2.9	-3.0
Height SDS, change from baseline ^a	1.1	0.96

Abbreviations: SDS: Standard deviation score.

^a Height SDS, change from baseline: The estimates of LS means are 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.

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1. How Supplied

SKYTROFA (lonapegsomatropin-tcgd) for injection is a sterile, preservative-free, white to off-white lyophilized powder available in a single-dose, dual-chamber, prefilled cartridge containing lonapegsomatropin-tcgd in one chamber and the diluent, Water for Injection, in the second chamber. The dual-chamber glass cartridge is available in 9 strengths (in somatotropin equivalents) as described in [Table 6](#).

Table 6: SKYTROFA Presentations

SKYTROFA	NDC
3 mg	73362-003-01
3.6 mg	73362-004-01

SKYTROFA	NDC
4.3 mg	73362-005-01
5.2 mg	73362-006-01
6.3 mg	73362-007-01
7.6 mg	73362-008-01
9.1 mg	73362-009-01
11 mg	73362-010-01
13.3 mg	73362-011-01

Each carton contains 4 single-dose prefilled cartridges and 6 sterile, single-use, disposable 0.25 mm x 4 mm (31-gauge x 5/32 inch) needles. The cartridges are for use only with the SKYTROFA Auto-Injector, packaged in a separate carton. The SKYTROFA Auto-Injector is not supplied with SKYTROFA cartridges but is available for patients with a prescription for SKYTROFA through the Ascendis Pharma Customer Support by calling the toll-free number at 1-844-442-7236 (1-844-44ASCENDIS).

16.2. Storage and Handling

- For patients: Refrigerate SKYTROFA cartridges at 36°F to 46°F (2°C to 8°C) in the outer carton to protect from light until the expiration date. Do not freeze. Alternatively, SKYTROFA outer carton containing blistered cartridges may be stored at room temperature [up to 86°F (30°C)] for up to 6 months and can be returned to refrigeration within the 6 months. Write the date first removed from the refrigerator in the space provided on the outer carton. Do not use SKYTROFA beyond the expiration date or 6 months after the date it was first removed from refrigeration (whichever is earlier).
- For pharmacy long-term storage: Store SKYTROFA cartridges refrigerated at 36°F to 46°F (2°C to 8°C) in the outer carton to protect from light until the expiration date. Do not freeze.

17. PATIENT COUNSELING INFORMATION

Administration Instructions

- Advise patients and/or caregivers to read the FDA-approved patient labeling (SKYTROFA Auto-Injector Instructions for Use (available at www.Skytrofa.com/IFU)). Advise patients and/or caregivers to call the Ascendis Pharma Customer Support toll-free number at 1-844-442-7236 (1-844-44ASCENDIS) for assistance or additional training, if needed.
- Advise patients and/or caregivers to refer to the Instructions for Use that accompanies the SKYTROFA Auto-Injector for complete mixing and administration instructions with illustrations [see *Preparation and Administration (2.5)*]. Instruct patients and/or caregivers of proper needle disposal and caution against any reuse of needles. An appropriate container for the disposal of used cartridge and needle should be used.
- Advise patients and/or caregivers to administer SKYTROFA once weekly, at any time of day. Advise patients and/or caregivers that doses can be taken 2 days before or 2 days after the scheduled dosing day. Advise patients and/or caregivers to resume once-weekly dosing

for the next dose. If more than 2 days have passed from the schedule dosing day, advise patients and/or caregivers to skip the missed dose and take the next dose on the regularly scheduled day. If subsequently changing the regular dosing day to a different day of the week, advise patients and/or caregivers to ensure that at least 5 days will elapse between the last dose and the newly established regular dosing day.

Hypersensitivity Reactions

Advise patients and/or caregivers that severe and/or serious systemic hypersensitivity reactions (anaphylaxis and angioedema) have been reported, and to seek prompt medical attention should an allergic reaction occur [*see Warnings and Precautions (5.2)*].

Neoplasms

Advise childhood cancer survivors and/or caregivers that individuals treated with brain and/or head radiation are at increased risk of secondary neoplasms and, as a precaution, need to be monitored for recurrence. Advise patients and/or caregivers to report marked changes in behavior, onset of headaches, vision disturbances and/or changes in skin pigmentation or changes in the appearance of preexisting nevi.

Glucose Intolerance/Diabetes Mellitus

Advise patients and/or caregivers that new onset impaired glucose intolerance/type 2 diabetes mellitus or exacerbation of preexisting diabetes mellitus can occur and monitoring of blood glucose during treatment with SKYTROFA may be needed.

Intracranial Hypertension

Advise patients and/or caregivers to report to their healthcare provider any visual changes, headache, and nausea and/or vomiting.

Fluid Retention

Advise patients and/or caregivers that fluid retention during SKYTROFA replacement therapy may occur. Inform patients and/or caregivers of the clinical manifestations of fluid retention (e.g., edema, arthralgia, myalgia, nerve compression syndromes including carpal tunnel syndrome/paresthesia) and to report to their healthcare provider if any of these signs or symptoms occur during treatment with SKYTROFA.

Hypoadrenalism

Advise patients and/or caregivers that patients who have or who are at risk for pituitary hormone deficiency(s) that hypoadrenalism may develop and to report to their healthcare provider if they experience hyperpigmentation, extreme fatigue, dizziness, weakness, or weight loss.

Hypothyroidism

Advise patients and/or caregivers that undiagnosed/untreated hypothyroidism may prevent an optimal response to SKYTROFA. Advise patients/caregivers that patients may require periodic thyroid function tests.

Pancreatitis

Advise patients and/or caregivers that pancreatitis may develop and to report to their healthcare provider any new onset abdominal pain.

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PATENT INFORMATION: www.ascendispharma.us/products/patents

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