

GAINS BEYOND GROWTH



SKYTROFA[®] delivers:

MORE INJECTION-FREE DAYS

with once-weekly dosing
compared with daily therapies

CONVENIENT STORAGE

with no required refrigeration
for up to 6 months*

HIGHER GROWTH RATE[†]

after 1 year in a clinical trial compared
with a daily somatotropin therapy[‡]

— **What is SKYTROFA[®] used for?**

SKYTROFA is a prescription medication for the replacement of growth hormone in children 1 year old or older who weigh at least 26 pounds (11.5 kilograms) with growth hormone deficiency (GHD).

— **What Warnings should I know about SKYTROFA?**

There have been reports of death when using treatments like SKYTROFA in patients with critical illness due to complications following certain surgeries, severe injury, or in people with respiratory failure.

*Store SKYTROFA in the original package to protect from light. Do not freeze. SKYTROFA can be stored at room temperature (not to exceed 86°F [30°C]) for up to 6 months. Alternatively, SKYTROFA can be stored under refrigeration at 36°F to 46°F (2°C to 8°C) until the expiration date. If refrigerated, keep at room temperature for 15 minutes before use. Do not use SKYTROFA beyond the expiration date or 6 months after the date it was first removed from refrigeration (whichever is earlier).

[†]In a clinical trial that compared once-weekly SKYTROFA with a daily somatotropin in 161 children with pediatric growth hormone deficiency (GHD) who previously had not been on treatment. The primary endpoint from the clinical trial was measuring annualized height velocity (AHV) at 52 weeks.

[‡]11.2 cm/year for SKYTROFA versus 10.3 cm/year for a daily somatotropin.

**Please see Important Safety Information throughout
and accompanying full Prescribing Information.**

Once-weekly
Skytrofa[®]
lonapegsomatropin-tcqd

Understanding pediatric GHD



If your child has been diagnosed with pediatric GHD, it means:

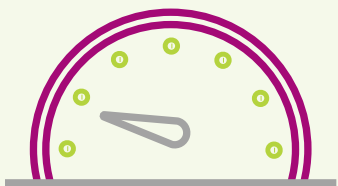


Their pituitary gland does not produce enough growth hormone to stimulate their body to grow

Your child is likely growing at a

SLOWER RATE
than other children

which will be noticeable
on their growth chart



— What Warnings should I know about SKYTROFA? (continued)

Severe hypersensitivity reactions including anaphylactic reactions and swelling underneath the skin, have been reported during use with treatments like SKYTROFA. Seek medical help right away if the following happen after administering SKYTROFA: hives, trouble breathing, and swelling of the face, eyes, lips, or mouth. Do not use if there is any history of hypersensitivity reactions to any ingredients in SKYTROFA.

Childhood cancer survivors treated with brain/head radiation are at increased risk of secondary cancers and, as a precaution, need to be monitored for recurrence. Changes in behavior, new headaches, vision disturbances or changes in skin color or changes in birthmarks or moles should be discussed with the healthcare provider.

Please see Important Safety Information throughout and accompanying full Prescribing Information.

In addition to short stature, pediatric GHD may impact your child in other ways.



They may look younger when compared with friends of the same age and gender



Puberty may be delayed or absent



Normal metabolism, bone strength, and muscle development may also be affected as growth hormone is important for these

These are some of the important reasons for treating pediatric GHD.

Once-weekly
Skytrofa
lonapegsomatropin-tcqd

Why start with SKYTROFA®?

SKYTROFA is the first and only FDA-approved once-weekly treatment of pediatric GHD delivering somatotropin, which is used in daily growth hormone therapies.

Higher growth rate at week 52 in a clinical trial

Whether your child is just starting treatment or has been treated with daily somatotropin, once-weekly SKYTROFA is proven to help increase height



SKYTROFA provides a higher average growth rate versus daily somatotropin at 52 weeks



Based on clinical data, pediatric patients treated with daily somatotropin may be switched to SKYTROFA

— What Warnings should I know about SKYTROFA? (continued)

Children with certain rare genetic causes of short stature have an increased risk of developing cancer. Talk with the healthcare provider about risks and benefits of starting SKYTROFA.

Patients may develop impaired glucose tolerance or Type 2 diabetes or have a worsening of diabetes when using SKYTROFA. Dosage of diabetes medicines may need to be adjusted during growth hormone treatment.

Please see Important Safety Information throughout and accompanying full Prescribing Information.



More injection-free days

Children switching from daily injections can enjoy up to **313 injection-free days per year**, which means up to **86% fewer injection days** than daily somatotropin



Convenient storage

SKYTROFA cartridges **do not need to be refrigerated** for up to 6 months, allowing more flexibility for storage*



No preservatives

Each single-dose cartridge contains **only** lonapegsomatropin-tcgd, diluent, and sterile water



Established safety profile

Once-weekly SKYTROFA has **established safety**, with no serious side effects due to treatment, as reported in a clinical study

- In a clinical study, some children taking once-weekly SKYTROFA had mild injection-site reactions
- None of those children stopped taking SKYTROFA during the study
- Side effects occurring more frequently than with daily somatotropin included viral infection, fever, cough, nausea and vomiting, bleeding, diarrhea, stomach area pain, and joint pain and arthritis

*Store SKYTROFA in the original package to protect from light. Do not freeze. SKYTROFA can be stored at room temperature (not to exceed 86°F [30°C]) for up to 6 months. Alternatively, SKYTROFA can be stored under refrigeration at 36°F to 46°F (2°C to 8°C) until the expiration date. If refrigerated, keep at room temperature for 15 minutes before use. Do not use SKYTROFA beyond the expiration date or 6 months after the date it was first removed from refrigeration (whichever is earlier).

Once-weekly
Skytrofa
lonapegsomatropin-tcgd

SKYTROFA® Auto-Injector— innovation in your hands

SKYTROFA is the first and only FDA-approved once-weekly pediatric injection that delivers somatotropin, which is used in daily growth hormone therapies. The innovative SKYTROFA Auto-Injector provides clear direction at every step of the process with precise mixing and automated injection.

Needle guard

Starts injection when pressed against skin

Check mark

Indicates injection is successfully completed

Eye

Indicates mixed medicine is ready for inspection in window

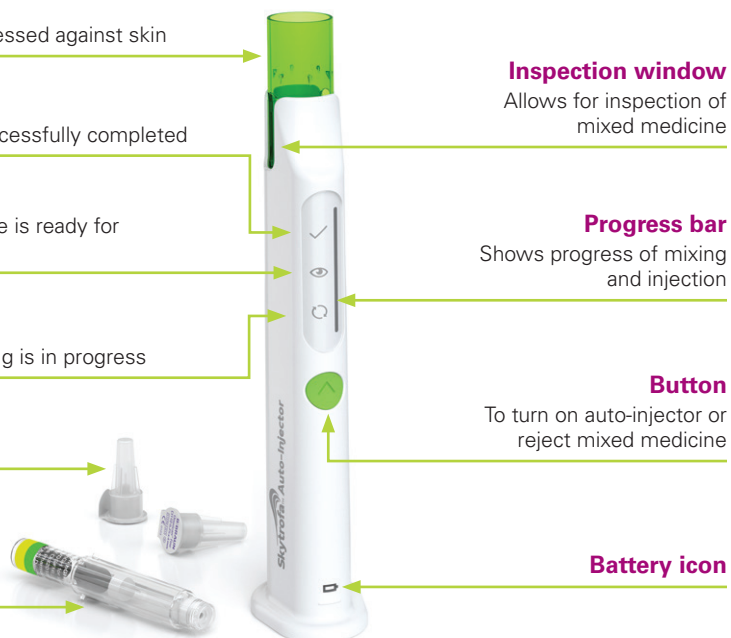
Mixing

Indicates medicine mixing is in progress

Needle

Cartridge

Contains medicine and water for injection



— What Warnings should I know about SKYTROFA? (continued)

Increased pressure in the brain has been reported in a small number of patients taking treatments like SKYTROFA, which can cause changes in vision, headache, nausea or vomiting. Treatment may be reduced or stopped if any of these conditions occur.

SKYTROFA can cause the body to retain fluid which may cause swelling, joint pain, or muscle pain, and usually goes away after treatment is stopped or dose is reduced.

Patients taking SKYTROFA who have or are at risk for pituitary hormone deficiencies may be at risk for reduced serum cortisol levels and/or unmasking of central hypoadrenalism. Patients should be checked regularly for low serum cortisol levels and/or the need to increase the dose of the glucocorticoids they are taking.

Please see Important Safety Information throughout and accompanying full Prescribing Information.



No need to dial the dose

SKYTROFA comes in ready-to-use, color-coded cartridges for the prescribed dose. During administration, the Auto-Injector delivers the entire dose without wasting medicine

- All cartridges work in the SKYTROFA Auto-Injector



Convenient storage

SKYTROFA cartridges do not need to be refrigerated for up to 6 months*



Small needle size selected with your child's comfort in mind

Uses a thin, 31-gauge needle provided to patients with every SKYTROFA cartridge delivery

- The SKYTROFA Auto-Injector has a needle guard that covers the needle during injections



Unplug, inject, and go

The Auto-Injector is reusable and rechargeable. It reduces the waste of disposable injector pens and batteries. A full charge lasts for 4 weeks, with 1 injection per week. The Auto-Injector is designed to last for approximately 4 years or 210 injections, whichever comes first



Ways to remember your injection

- Create a weekly calendar reminder
- Set an alarm on your smartphone—you can even choose a unique ringtone
- Use voice commands with your smart home devices
- Schedule text reminders
- Explore the app store for medication reminder apps

*Store SKYTROFA in the original package to protect from light. Do not freeze. SKYTROFA can be stored at room temperature (not to exceed 86°F [30°C]) for up to 6 months. Alternatively, SKYTROFA can be stored under refrigeration at 36°F to 46°F (2°C to 8°C) until the expiration date. If refrigerated, keep at room temperature for 15 minutes before use. Do not use SKYTROFA beyond the expiration date or 6 months after the date it was first removed from refrigeration (whichever is earlier).

Once-weekly
Skytrofa
lonapegsomatropin-tcqd

Ascendis Signature Access Program™ — personalized patient support

A·S·A·P ASCENDIS SIGNATURE ACCESS PROGRAM™



A·S·A·P offers support services that have you and your child supported at every step of the way. At enrollment, you and your child are connected with a dedicated Nurse Advocate and can access SKYTROFA® Auto-Injector training throughout treatment. This also includes personalized help with navigating coverage issues, financial assistance, and reimbursement education.

— What Warnings should I know about SKYTROFA? (continued)

Thyroid function should be monitored as low thyroid levels can cause SKYTROFA to not work. Low thyroid hormone levels may become apparent or worsen during SKYTROFA treatment.

In children experiencing rapid growth, limping or hip or knee pain may occur. If a child being treated with SKYTROFA starts to limp or gets hip or knee pain, the child's doctor should be notified and the child should be examined.

In children experiencing rapid growth, curvature of the spine may worsen, known as scoliosis. Patients with scoliosis should be checked regularly to make sure their scoliosis does not get worse during treatment with SKYTROFA.

Please see Important Safety Information throughout and accompanying full Prescribing Information.



Provides a dedicated Nurse Advocate who will:

- Offer insurance support and/or help with seeking financial assistance to pay for your SKYTROFA
- Schedule an in-person or virtual training session with an A·S·A·P nurse educator to teach you and your child how to use the SKYTROFA Auto-Injector
- Answer any questions you may have



Navigate insurance barriers, including:

- Benefits verification, prior authorization (PA) approvals, and appeals
- Assisting with reimbursement education
- Helping you enroll in the Co-Pay Program for SKYTROFA, if eligible
- Coordinating product shipments through the SKYTROFA FastStart Program while awaiting commercial insurance authorization
- Ensuring there is no gap in treatment caused by job changes or PA expirations through the SKYTROFA Bridge Program
- Accessing support for uninsured families



Delivered to your doorstep:

- Ensure the SKYTROFA Auto-Injector and Starter Kit are shipped right to your door
- Coordinate delivery of your SKYTROFA medicine from the Specialty Pharmacy
- Provide overall case management

How to enroll in A·S·A·P

As a caregiver whose child has been prescribed SKYTROFA, you will be enrolled in A·S·A·P by your healthcare provider.

You can also fill out the patient consent form at SKYTROFA.com and fax it to 1-888-436-0193 or email it to info@ascendissupport.com. For any questions or comments, please call 1-844-442-7236.



To download the A·S·A·P patient consent form, please scan the QR code to the left. Learn more about A·S·A·P at SKYTROFA.com.

Once-weekly
Skytrofa
lonapegsomatropin-tcqd





Use our doctor discussion guide at your next visit to talk with your doctor about once-weekly SKYTROFA®.

To download the doctor discussion guide, please scan the QR code to the left. Learn more about SKYTROFA at SKYTROFA.com.

– **What Warnings should I know about SKYTROFA? (continued)**

SKYTROFA can cause inflammation of the pancreas which may cause pain in the area of the stomach.

SKYTROFA can cause loss of fat tissue around the injection site with continued use. Injection sites should be different each time SKYTROFA is administered to prevent this risk.

SKYTROFA should not be used in patients with Prader-Willi syndrome who are very overweight or who have severe breathing problems due to risk of death. SKYTROFA is not indicated for treatment of Prader-Willi syndrome.

– **You should not use SKYTROFA if you have:**

- Critical illness immediately after open heart surgery, abdominal surgery, or accidental trauma, or those with severe breathing problems known as respiratory failure;
- Had a reaction to SKYTROFA or any of its ingredients;
- Bones that have stopped growing;
- Cancer;
- Eye vision problems due to diabetes;
- A condition known as Prader-Willi syndrome and are overweight; have a history of upper airway breathing problems, have sleep apnea, or have severe breathing problems, due to the risk of sudden death

– **What are the side effects of SKYTROFA?**

The most common side effects include viral infection, fever, cough, nausea and vomiting, bleeding, diarrhea, stomach area pain, and joint pain and arthritis.

GAINS BEYOND GROWTH



MORE INJECTION-FREE DAYS

with once-weekly dosing compared with daily therapies



CONVENIENT STORAGE

with no required refrigeration for up to 6 months*



HIGHER GROWTH RATE[†]

after 1 year in a clinical trial compared with a daily somatropin therapy[†]



PEOPLE ON YOUR TEAM

with personalized support from a Nurse Advocate

*Store SKYTROFA in the original package to protect from light. Do not freeze. SKYTROFA can be stored at room temperature (not to exceed 86°F [30°C]) for up to 6 months. Alternatively, SKYTROFA can be stored under refrigeration at 36°F to 46°F (2°C to 8°C) until the expiration date. If refrigerated, keep at room temperature for 15 minutes before use. Do not use SKYTROFA beyond the expiration date or 6 months after the date it was first removed from refrigeration (whichever is earlier).

[†]In a clinical trial that compared once-weekly SKYTROFA[®] with a daily somatropin in 161 children with pediatric GHD who previously had not been on treatment. The primary endpoint from the clinical trial was measuring least squares (LS) mean AHV at 52 weeks.

[‡]11.2 cm/year for SKYTROFA versus 10.3 cm/year for a daily somatropin; treatment difference in AHV of 0.9 cm/year (LS mean by analysis of covariance).



Learn more about SKYTROFA. Please call 1-844-442-7236 or visit SKYTROFA.com for more information, including a video on how to use the SKYTROFA Auto-Injector.

— What other medication might interact with SKYTROFA?

Make certain to tell your healthcare provider about all medicines you take including corticosteroids, estrogen containing products, including certain birth control medications, or medicine for diabetes. These are not all of the drugs that may interact with SKYTROFA.

These are not all of the possible side effects of SKYTROFA. Call your doctor for medical advice about side effects. **You are encouraged to report side effects to FDA at 1-800-FDA-1088 or at www.fda.gov/medwatch. You may also report side effects to Ascendis Pharma at 1-844-442-7236.**

Please see accompanying full Prescribing Information for SKYTROFA.

© October 2021 Ascendis Pharma Endocrinology, Inc. All rights reserved. SKYTROFA[®], Ascendis Signature Access Program[™], Ascendis[®], the Ascendis Pharma logo and the company logo are trademarks owned by the Ascendis Pharma Group.

US-COMMGHP-2100284 10/21

ascendis
pharma

Once-weekly

Skytrofa[®]
lonapegsomatropin-tcqd

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

FULL PRESCRIBING INFORMATION: CONTENTS*

1	INDICATIONS AND USAGE	7	DRUG INTERACTIONS
2	DOSAGE AND ADMINISTRATION	8	USE IN SPECIFIC POPULATIONS
2.1	General Dosing Information	8.1	Pregnancy
2.2	Dosage Recommendations	8.2	Lactation
2.3	Missed Doses	8.4	Pediatric Use
2.4	Administrative Instructions	9	DRUG ABUSE AND DEPENDENCE
2.5	Preparation and Administration	9.1	Controlled Substance
3	DOSAGE FORMS AND STRENGTHS	9.2	Abuse
4	CONTRAINDICATIONS	9.3	Dependence
5	WARNINGS AND PRECAUTIONS	10	OVERDOSAGE
5.1	Increased Mortality in Patients with Acute Critical Illness	11	DESCRIPTION
5.2	Severe Hypersensitivity	12	CLINICAL PHARMACOLOGY
5.3	Increased Risk of Neoplasms	12.1	Mechanism of Action
5.4	Glucose Intolerance and Diabetes Mellitus	12.2	Pharmacodynamics
5.5	Intracranial Hypertension	12.3	Pharmacokinetics
5.6	Fluid Retention	13	NONCLINICAL TOXICOLOGY
5.7	Hypoadrenalism	13.1	Carcinogenicity, Mutagenesis, Impairment of Fertility
5.8	Hypothyroidism	14	CLINICAL STUDIES
5.9	Slipped Capital Femoral Epiphysis	14.1	Treatment-Naïve Pediatric Patients with Growth Hormone Deficiency (NCT02781727)
5.10	Progression of Preexisting Scoliosis	16	HOW SUPPLIED/STORAGE AND HANDLING
5.11	Pancreatitis	16.1	How Supplied
5.12	Lipoatrophy	16.2	Storage and Handling
5.13	Sudden Death in Pediatric Patients with Prader-Willi Syndrome	17	PATIENT COUNSELING INFORMATION
5.14	Laboratory Tests		
6	ADVERSE REACTIONS		
6.1	Clinical Trials Experience		
6.2	Immunogenicity		

*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.
-

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. Systemic hypersensitivity reactions have been reported with post-marketing use of somatropin products [*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

Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with post-marketing use of somatropin products. Inform patients and caregivers that such reactions are possible, and that prompt medical attention should be sought if an allergic reaction occurs [see *Contraindications (4)*]. Do not use SKYTROFA 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 studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies 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.

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 [see <i>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, somatotropin, 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 somatotropin is 22 kDa). *In vitro* assay confirms the minimum potency of released somatotropin 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 (somatotropin) 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. Somatotropin 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. Somatotropin 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) μ g/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 somatropin 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 Somatropin (N=56)	Estimate of Treatment Difference (95% CI) (SKYTROFA minus Daily Somatropin)
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 somatropin 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 Somatropin (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 somatropin equivalents) as described in [Table 6](#).

Table 6: SKYTROFA Presentations

SKYTROFA	NDC
3 mg	73362-003-01
3.6 mg	73362-004-01
4.3 mg	73362-005-01
5.2 mg	73362-006-01
6.3 mg	73362-007-01
7.6 mg	73362-008-01

SKYTROFA	NDC
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

- Provide appropriate instructions for injection to the patient/caregiver, by providing the SKYTROFA Auto-Injector Instructions for Use (available at www.Skytrofa.com/IFU). Patients/caregivers and healthcare providers may also 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/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/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/caregivers to administer SKYTROFA once weekly, at any time of day. Advise patients/caregivers that doses can be taken 2 days before or 2 days after the scheduled dosing day. Advise patients/caregivers to resume once-weekly dosing for the next dose. If more than 2 days have passed from the schedule dosing day, advise patients/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/caregivers to ensure that at least 5 days will elapse between the last dose and the newly-established regular dosing day.

- Neoplasms – Advise childhood cancer survivors/caregivers that individuals treated with brain/head radiation are at increased risk of secondary neoplasms and, as a precaution, need to be monitored for recurrence. 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.
- Glucose Intolerance/Diabetes Mellitus – Advise patients/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/caregivers to report to their healthcare provider any visual changes, headache, and nausea and/or vomiting.
- Fluid Retention – Advise patients/caregivers that fluid retention during SKYTROFA replacement therapy may occur. Inform patients/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/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/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/caregivers that pancreatitis may develop and to report to their healthcare provider any new onset abdominal pain.
- Hypersensitivity Reactions – Advise patients/caregivers that serious systemic hypersensitivity reactions (anaphylaxis and angioedema) are possible, and to seek prompt medical attention should an allergic reaction occur.
- Administration: Counsel patients/caregivers that they should never share the SKYTROFA Auto-Injector with another person, even if the needle is changed. Sharing of the Auto-Injector between patients may pose a risk of transmission of infection.

© 2021 Ascendis Pharma. All rights reserved. SKYTROFA™, Ascendis®, TransCon®, the Ascendis Pharma logo and the company logo are trademarks owned by the Ascendis Pharma Group.

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

Manufactured by:
Ascendis Pharma Endocrinology Division A/S
Tuborg Boulevard 12 Hellerup Denmark DK-2900

U.S. License Number 2165

For information about SKYTROFA contact:

Ascendis Pharma, Inc.

500 Emerson Street

Palo Alto, CA 94301, USA

1-844-442-7236 (1-844-44ASCENDIS)

www.Skytrofa.com
