LA LIBERTAD DE LA SOMATROPINA ADMINISTRADA UNA VEZ POR SEMANA

SKYTROFA®:

MÁS DÍAS SIN INYECCIONES
con dosis de somatropina una vez por semana frente al tratamiento diario con somatropina

CONSERVACIÓN PRÁCTICA SIN CONSERVANTES
ya que no es necesario refrigerarlo hasta por 6 meses*

UN MAYOR ÍNDICE DE CRECIMIENTO†
tras 1 año en un ensayo clínico, en comparación con el tratamiento diario con somatropina‡

PROPORCIONA SOMATROPINA,
que se utiliza en inyecciones diarias de la hormona del crecimiento

*Conserve SKYTROFA en el envase original para protegerlo de la luz. No lo congele. SKYTROFA puede conservarse a temperatura ambiente (que no supere los 86 °F [30 °C]) hasta por 6 meses. Como alternativa, SKYTROFA puede conservarse refrigerado entre 36 °F y 46 °F (2 °C y 8 °C) hasta la fecha de vencimiento. Si se refrigera, déjelo a temperatura ambiente durante 15 minutos antes de usarlo. No use SKYTROFA después de la fecha de vencimiento o 6 meses después de la fecha en la que se haya sacado del refrigerador por primera vez (lo que suceda antes).

†En un ensayo clínico en el que se comparó SKYTROFA administrado una vez por semana con una somatropina de administración diaria en 161 niños con carencia de hormona del crecimiento (GHD) pediátrica que no habían recibido tratamiento anteriormente. El criterio principal de valoración del ensayo clínico era la medición de la velocidad de crecimiento estatural anualizada (annualized height velocity, AHV) a las 52 semanas.

‡11.2 cm/año para SKYTROFA frente a 10.3 cm/año para la somatropina administrada diariamente.

— ¿Para qué se utiliza SKYTROFA®?

SKYTROFA es un medicamento de venta con receta para el reemplazo de la hormona del crecimiento en niños de 1 año de edad o mayores que pesan al menos 26 libras (11.5 kilogramos) y que tienen carencia de hormona del crecimiento (growth hormone deficiency, GHD).

— ¿Qué advertencias debo saber sobre SKYTROFA?

Se han notificado muertes durante el uso de tratamientos como SKYTROFA en pacientes con enfermedad crítica, a causa de complicaciones después de determinadas cirugías, lesiones graves o en personas con insuficiencia respiratoria.

Consulte la Información de seguridad importante en todo este folleto y la Información de prescripción completa que se adjunta.

Once-weekly
Skytrofa®
lonapegsomatropin-tcgd

Entender la GHD pediátrica

Si le diagnosticaron GHD pediátrica a su hijo, significa que:

Su hipófisis no produce suficiente hormona del crecimiento para estimular el crecimiento del cuerpo

Es posible que note que su hijo

NO MANTIENE LA CURVA

en su gráfico de crecimiento porque está

creciendo a una velocidad más lenta

— **¿Qué advertencias debo saber sobre SKYTROFA? (continuación)**

Se ha informado de reacciones de hipersensibilidad graves, incluidas reacciones anafilácticas e hinchazón debajo de la piel, mientras se administraban tratamientos como SKYTROFA. Busque atención médica de inmediato si se producen los acontecimientos siguientes después de la administración de SKYTROFA: urticaria, dificultad para respirar e hinchazón del rostro, los ojos, los labios o la boca. No debe utilizarse si hay antecedentes de reacciones de hipersensibilidad a cualquiera de los componentes de SKYTROFA.

Los supervivientes de cáncer infantil que han recibido radioterapia en el cerebro o la cabeza corren un mayor riesgo de presentar cánceres secundarios y, por precaución, deben vigilarse para detectar una recidiva. Debe evaluarse con el profesional médico cualquier cambio en la conducta, así como dolores de cabeza o alteraciones de la visión recientes, o cambios en el color de la piel, las marcas de nacimiento o los lunares.

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Además de la baja estatura, la GHD pediátrica podría afectar a su hijo de otras maneras

Podría tener un aspecto más joven en comparación con sus amigos de la misma edad y sexo

La pubertad podría retrasarse o no presentarse

También podría verse afectado el funcionamiento metabólico, la fortaleza ósea y el desarrollo muscular, ya que la hormona del crecimiento es importante para estos factores

Estos son algunos motivos importantes para tratar la GHD pediátrica.

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¿Por qué comenzar con SKYTROFA®?

SKYTROFA es el primer y único tratamiento semanal aprobado por la FDA que proporciona somatropina para la GHD pediátrica, la cual se usa en tratamientos de hormona del crecimiento de administración diaria.

Un mayor índice de crecimiento a la semana 52 en un ensayo clínico

Ya sea que su hijo apenas esté iniciando el tratamiento o que haya estado recibiendo tratamiento con somatropina todos los días, se ha comprobado que SKYTROFA administrado una vez por semana ayuda a aumentar la estatura.

Obtenga más información sobre los resultados de los ensayos clínicos

SKYTROFA proporciona un mayor índice de crecimiento promedio frente a la somatropina administrada diariamente, a las 52 semanas*

Los ensayos clínicos demostraron que SKYTROFA fomenta el crecimiento en niños que no habían recibido tratamiento anteriormente y en niños a los que se les cambia el tratamiento de somatropina administrada diariamente†

— ¿Qué advertencias debo saber sobre SKYTROFA? (continuación)

Los niños que tienen baja estatura causada por determinados factores genéticos raros corren un mayor riesgo de presentar cáncer. Hable con el profesional médico sobre los riesgos y beneficios de iniciar el tratamiento con SKYTROFA.

Los pacientes podrían presentar una intolerancia a la glucosa o diabetes de tipo 2, o su diabetes podría empeorar mientras reciben SKYTROFA. Podría ser necesario ajustar la dosis de los antidiabéticos durante el tratamiento con hormona del crecimiento.

Consulte la Información de seguridad importante en todo este folleto y la Información de prescripción completa que se adjunta.

Más días sin inyecciones

Los niños a los que se les cambie el tratamiento de inyecciones diarias podrían disfrutar hasta **313 días sin inyecciones por año**, lo que significa hasta un **86% menos de días de inyección** que con el uso diario de somatropina.

Conservación práctica, sin refrigeración

No es necesario refrigerar los cartuchos de SKYTROFA hasta por 6 meses, lo cual brinda más flexibilidad para conservarlo.‡

No contiene conservantes

Cada cartucho de dosis única contiene **solo** lonapegsomatropina-tcgd, diluyente y agua estéril.

Perfil de seguridad establecido

SKYTROFA, administrado una vez por semana, está aprobado por la FDA y cuenta con un **perfil de seguridad establecido**.

- En un ensayo clínico, algunos niños que recibían SKYTROFA una vez por semana tuvieron reacciones leves en el lugar de inyección
- Entre los efectos secundarios que se produjeron con mayor frecuencia que con somatropina administrada diariamente se encuentran infección viral, fiebre, tos, náuseas y vómitos, sangrado, diarrea, dolor abdominal, y dolor articular y artritis

*En un ensayo clínico en el que se comparó SKYTROFA administrado una vez por semana con una somatropina de administración diaria en 161 niños con GHD pediátrica que no habían recibido tratamiento anteriormente. El criterio principal de valoración del ensayo clínico era la determinación de la AHV a las 52 semanas. La AHV a las 52 semanas fue de 11.2 cm/año para SKYTROFA frente a 10.3 cm/año para la somatropina administrada diariamente.

†SKYTROFA se estudió en un ensayo clínico de 26 semanas de duración en el que se investigó la seguridad, tolerabilidad y eficacia de SKYTROFA administrado una vez por semana a niños con GHD pediátrica. El ensayo incluyó a 3 niños que no habían recibido tratamiento anteriormente y 143 niños que habían recibido tratamientos de hormona del crecimiento administrado diariamente durante ≤130 semanas. Los criterios principales de valoración fueron la seguridad y la tolerabilidad.

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Autoinyector de SKYTROFA®: innovación en sus manos

SKYTROFA es la primera y única inyección pediátrica semanal aprobada por la FDA que proporciona somatropina, la cual se usa en tratamientos de hormona del crecimiento de administración diaria. El innovador autoinyector de SKYTROFA ofrece instrucciones claras en cada paso del proceso, con un mezclado preciso e inyección automatizada.

— ¿Qué advertencias debo saber sobre SKYTROFA? (continuación)

Se informó de aumentos en la presión del cerebro en una pequeña cantidad de pacientes que recibían tratamientos como SKYTROFA, que puede causar alteraciones de la visión, dolor de cabeza, náuseas o vómitos. Puede reducirse o suspenderse el tratamiento si se presenta cualquiera de estos síntomas.

SKYTROFA puede hacer que el cuerpo retenga líquidos, lo que podría ocasionar hinchazón, dolor articular o dolor muscular, y suele desaparecer cuando se suspende el tratamiento o se reduce la dosis.

Los pacientes que reciben SKYTROFA y han tenido carencia de hormonas hipofisarias, o están en riesgo de tenerla, podrían correr el riesgo de presentar concentraciones séricas reducidas de cortisol y/o desenmascaramiento de hipoadrenalismo central. Deberá examinarse periódicamente a los pacientes para detectar concentraciones séricas bajas de cortisol y/o determinar la necesidad de aumentar la dosis de los glucocorticoides que están recibiendo.

Consulte la Información de seguridad importante en todo este folleto y la Información de prescripción completa que se adjunta.

No es necesario seleccionar la dosis

SKYTROFA viene en **cartuchos listos para usar codificados por color**, para administrar la dosis recetada. Durante la administración, el autoinyector proporciona la dosis completa, sin desperdiciar medicamento.

- Todos los cartuchos son compatibles con el autoinyector de SKYTROFA
- SKYTROFA está disponible en distintas concentraciones de dosis. El médico puede ajustar fácilmente la dosis recetada para su hijo a medida que el niño crece

No es necesario refrigerarlo, no contiene conservantes

No es necesario refrigerar los cartuchos de SKYTROFA hasta por 6 meses.* SKYTROFA **no contiene conservantes**. Cada cartucho de dosis única contiene solo lonapegsomatropina-tcgd, diluyente y agua estéril.

Se eligió una aguja pequeña, pensando en la comodidad de su hijo

Se utiliza una **aguja delgada de calibre 31** que se proporciona a los pacientes con cada entrega de cartuchos de SKYTROFA.

- El autoinyector de SKYTROFA cuenta con un protector de aguja que cubre la aguja durante la inyección

Desconecte, inyecte y listo

El autoinyector es **reutilizable y recargable**. Reduce el desperdicio de las plumas inyectoras y baterías desechables. Una carga completa dura 4 semanas, con 1 inyección por semana. El autoinyector está diseñado para durar aproximadamente 4 años o administrar 210 inyecciones, lo que suceda antes.

Reciba un mensaje de texto cuando sea el momento de inyectar

El **servicio de mensajería de Ascendis Signature Access Program™ (A·S·A·P)** está diseñado para ayudarle a mantenerse en curso durante la administración de SKYTROFA. Debido a que SKYTROFA tiene menos días de inyección que los tratamientos de administración diaria, los recordatorios semanales pueden ser útiles al inicio del tratamiento. Regístrese en Skytrofa.com para recibir recordatorios de inyección enviados directamente a su teléfono.

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Once-weekly Skytrofa® lonapegsomatropin-tcgd

Ascendis Signature Access Program™: apoyo personalizado para pacientes

A·S·A·P

ASCENDIS SIGNATURE ACCESS PROGRAM™

Visite Skytrofa.com para obtener más información sobre el apoyo personalizado para pacientes con A·S·A·P

A·S·A·P es posibilitado por enfermeros, que le brindan apoyo en cada paso del proceso

En la inscripción, los conectarán a usted y a su hijo con su propio **enfermero asesor** y tendrán acceso a cursos de capacitación sobre el autoinyector de SKYTROFA® durante todo el tratamiento. Esto también incluye ayuda personalizada para abordar asuntos relacionados con la cobertura, asistencia económica e información sobre los reembolsos.

— ¿Qué advertencias debo saber sobre SKYTROFA? (continuación)

Debe vigilarse la función de la tiroides, ya que los niveles tiroideos bajos pueden inhibir la acción de SKYTROFA. Pueden volverse evidentes o empeorar los niveles bajos de las hormonas tiroideas durante el tratamiento con SKYTROFA.

Los niños que tienen un crecimiento acelerado podrían presentar cojera o dolor de cadera o rodilla. Si un niño que recibe tratamiento con SKYTROFA comienza a cojear o tiene dolor de cadera o rodilla, deberá notificarse esto al médico del niño y el niño deberá ser examinado.

En los niños que tienen un crecimiento acelerado, puede empeorar la curvatura de la columna, conocida como escoliosis. Los pacientes con escoliosis deben ser revisados con frecuencia para asegurarse de que su estado no empeore durante el tratamiento con SKYTROFA.

Consulte la Información de seguridad importante en todo este folleto y la Información de prescripción completa que se adjunta.

Su propio enfermero asesor:

- Ofrece apoyo sobre la cobertura de seguro y/o ayuda para buscar asistencia económica para pagar SKYTROFA
- Lo conecta con un instructor clínico de A·S·A·P para enseñarles a usted y su hijo cómo usar el autoinyector de SKYTROFA en una sesión de capacitación en persona o virtual
- Responder cualquier pregunta que tenga

El enfermero asesor lo ayuda a abordar las barreras relacionadas con los seguros, que incluye:

- Verificación de los beneficios, aprobación de autorizaciones previas (AP) y apelaciones
- Ayuda con información sobre los reembolsos
- Ayuda con la inscripción en el programa de copagos de SKYTROFA, si es elegible
- Coordinación de la inscripción en el programa FastStart para que comience a recibir SKYTROFA durante el proceso de reembolso por parte de los seguros
- Garantizar que no haya interrupciones del tratamiento causadas por cambios en la situación laboral o vencimiento de las AP mediante el programa SKYTROFA Bridge
- Acceso a un sistema de apoyo para familias sin seguro

SKYTROFA se entrega a domicilio con la ayuda del enfermero asesor, quien:

- Garantiza que el autoinyector de SKYTROFA y el kit básico lleguen directamente a su puerta
- Coordina la entrega de SKYTROFA desde la farmacia especializada
- Proporciona manejo de casos general

Cómo inscribirse en el A·S·A·P: su médico iniciará la inscripción en el A·S·A·P después de recetar SKYTROFA.

Once-weekly Skytrofa® lonapegsomatropin-tcgd

Notas para su próxima visita al médico

— ¿Qué advertencias debo saber sobre SKYTROFA? (continuación)

SKYTROFA puede causar inflamación del páncreas que podría producir dolor en el abdomen.

El uso continuo de SKYTROFA puede causar pérdida de tejido graso alrededor del lugar de inyección. Debe alternarse el lugar de inyección cada vez que se administre SKYTROFA a fin de evitar este riesgo.

Debido al riesgo de muerte, SKYTROFA no debe usarse en pacientes con síndrome de Prader-Willi muy obesos o que tienen problemas respiratorios graves. SKYTROFA no está indicado para el tratamiento del síndrome de Prader-Willi.

Preguntas útiles para hacerle a su médico

Utilice nuestra guía de conversación en su próxima visita para hablar con su médico sobre SKYTROFA® administrado una vez por semana.

Escanee el código QR para descargar la guía de conversación.

Información y recursos disponibles en Skytrofa.com

Escanee el código QR y visite Skytrofa.com para obtener más información sobre SKYTROFA administrado una vez por semana, lo que incluye un video sobre cómo usar el autoinyector de SKYTROFA.

— No debe usar SKYTROFA si:

- Ha tenido una enfermedad crítica inmediatamente después de someterse a una cirugía del corazón o del abdomen, si ha sufrido un traumatismo por accidente o si tiene problemas respiratorios intensos (insuficiencia respiratoria);
- Ha tenido una reacción a SKYTROFA o a cualquiera de sus componentes;
- Tiene huesos que han dejado de crecer;
- Tiene cáncer;
- Tiene problemas de la visión a causa de la diabetes;
- Tiene una enfermedad llamada síndrome de Prader-Willi y sobrepeso; tiene antecedentes de problemas respiratorios de las vías superiores, tiene apnea del sueño, o ha tenido problemas respiratorios graves, debido a que existe el riesgo de muerte repentina

— ¿Cuáles son los efectos secundarios de SKYTROFA?

Algunos de los efectos secundarios más frecuentes son infección viral, fiebre, tos, náuseas y vómitos, sangrado, diarrea, dolor abdominal, y dolor articular y artritis.

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LA LIBERTAD DE LA SOMATROPINA ADMINISTRADA UNA VEZ POR SEMANA

Más días sin inyecciones con dosis de somatropina administradas una vez por semana frente a los tratamientos diarios con somatropina

Conservación práctica sin conservantes ya que no es necesario refrigerarlo hasta por 6 meses*

Un mayor índice de crecimiento† tras 1 año en un ensayo clínico, en comparación con el tratamiento diario con somatropina‡

Proporciona somatropina, la cual se usa en tratamientos de hormona del crecimiento inyectados de administración diaria

Integrantes de su equipo con apoyo personalizado de un enfermero asesor

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† En un ensayo clínico en el que se comparó SKYTROFA administrado una vez por semana con una somatropina de administración diaria en 161 niños con GHD pediátrica que no habían recibido tratamiento anteriormente. El criterio principal de valoración del ensayo clínico era la determinación de la media de la AHV de los mínimos cuadrados (MC) a las 52 semanas.

‡ 11.2 cm/año para SKYTROFA frente a 10.3 cm/año para la somatropina administrada diariamente; diferencia entre los tratamientos en la AHV de 0.9 cm/año (media de MC por análisis de covarianza).

Visite Skytrofa.com para obtener más información sobre SKYTROFA administrado una vez por semana, lo que incluye un video sobre cómo usar el autoinyector de SKYTROFA. ¿Tiene preguntas? Llame al 1-844-442-7236

— ¿Qué otros medicamentos podrían interactuar con SKYTROFA?

Asegúrese de informar a su profesional médico de todos los medicamentos que utilice, incluidos los corticoesteroides o productos que contengan estrógenos (como determinados anticonceptivos), así como los antidiabéticos. Estos no son todos los fármacos que podrían interactuar con SKYTROFA.

Estos no son todos los efectos secundarios posibles de SKYTROFA. Llame a su médico para pedirle asesoramiento acerca de los efectos secundarios. **Le recomendamos que notifique los efectos secundarios a la FDA llamando al 1-800-FDA-1088 o escribiendo a www.fda.gov/medwatch. También puede notificar los efectos secundarios a Ascendis Pharma llamando al 1-844-442-7236.**

Consulte la Información de prescripción completa adjunta para SKYTROFA.

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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 (≥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

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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. 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 ≥5% of patients treated with SKYTROFA in this trial.

Table 2: Adverse Reactions Occurring in ≥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	
Clinical Impact:	Microsomal enzyme 11β-hydroxysteroid dehydrogenase type 1 (11βHSD-1) is required for conversion of cortisone to its active metabolite, cortisol, in hepatic and adipose tissue. Somatropin inhibits 11βHSD-1. Consequently, individuals with untreated growth hormone deficiency (GHD) have relative increases in 11βHSD-1 and serum cortisol. Initiation of SKYTROFA may result in inhibition of 11βHSD-1 and reduced serum cortisol concentrations.
Intervention:	Patients treated with glucocorticoid replacement for hypoadrenalism may require an increase in their maintenance or stress doses following initiation of SKYTROFA *[see Warnings and Precautions (5.7)]*
Examples	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 11βHSD-1.

Pharmacologic Glucocorticoid Therapy and Supraphysiologic Glucocorticoid Treatment	
Clinical Impact:	Pharmacologic glucocorticoid therapy and supraphysiologic glucocorticoid treatment may attenuate the growth-promoting effects of SKYTROFA in pediatric patients.
Intervention:	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	
Clinical Impact:	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.
Intervention:	Careful monitoring is advisable when SKYTROFA is administered in combination with drugs metabolized by CYP450 liver enzymes.
Oral Estrogen	
Clinical Impact:	Oral estrogens may reduce the serum insulin-like growth factor-1 (IGF-1) response to SKYTROFA.
Intervention:	Patients receiving oral estrogen replacement may require higher SKYTROFA dosages.
Insulin and/or Other Antihyperglycemic Agents	
Clinical Impact:	Treatment with SKYTROFA may decrease insulin sensitivity, particularly at higher doses.
Intervention:	Patients with diabetes mellitus may require adjustment of their doses of insulin and/or other antihyperglycemic agents *[see Warnings and Precautions (5.4)]*.

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 (±SD) observed half-life of 30.7 (±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

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

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 Endocrinology, Inc.
902 Carnegie Center Boulevard
Princeton, New Jersey 08540, USA
1-844-442-7236 (1-844-44ASCENDIS)
www.Skytrofa.com