IGF-1 Plays an Essential Role in Growth

He reached the water fountain

The only FDA-approved treatment for Severe Primary IGF-1 Deficiency (SPIGFD)

The proper diagnosis matters

She rode the BIG rollercoaster

Actor portrayals are for illustrative purposes only

INDICATION

INCRELEX® (mecasermin) is indicated for the treatment of growth failure in pediatric patients aged 2 years and older with severe primary IGF-1 deficiency* (IGFD), or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH.

Limitations of use: INCRELEX is not a substitute to GH for approved GH indications. INCRELEX is not indicated for use in patients with secondary forms of IGFD, such as GH deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory corticosteroids.

*Severe primary IGFD is defined by height standard deviation score ≤ -3.0 and basal IGF-1 standard deviation score ≤ -3.0 and normal or elevated GH.

IMPORTANT SAFETY INFORMATION

Contraindications

- **Hypersensitivity** to mecasermin (rhIGF-1), any of the inactive ingredients in INCRELEX or who have experienced a severe hypersensitivity to INCRELEX. Allergic reactions have been reported, including anaphylaxis requiring hospitalization.
- **Intravenous Administration**
- **Closed Epiphyses**
- **Malignant Neoplasia** in pediatric patients with malignant neoplasia or a history of malignancy

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The Relationship Between GH and IGF-1 in Body Growth

IGF-1—an Essential Hormone for Growth

Insulin-like growth factor-1 (IGF-1) is a 70-amino acid peptide hormone and growth factor considered one of the most important hormonal regulators of postnatal growth.[1,2] The major regulator of circulating IGF-1 is growth hormone (GH).[2]

She was able to reach the sink

He chose his own ice cream flavor

Actor portrayals are for illustrative purposes only

IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions

- **Hypoglycemia:** INCRELEX should be administered 20 minutes before or after a meal or snack and should not be administered when the meal or snack is omitted. Glucose monitoring and INCRELEX dose titration are recommended until a well-tolerated dose is established and as medically indicated.
- **Intracranial Hypertension:** Funduscopic examination is recommended at the initiation of and periodically during the course of therapy.
- **Lymphoid Tissue Hypertrophy:** Patients should have periodic examinations to rule out potential complications.
- **Slipped Capital Femoral Epiphysis:** Carefully evaluate any pediatric patient with the onset of a limp or hip/knee pain during INCRELEX therapy.

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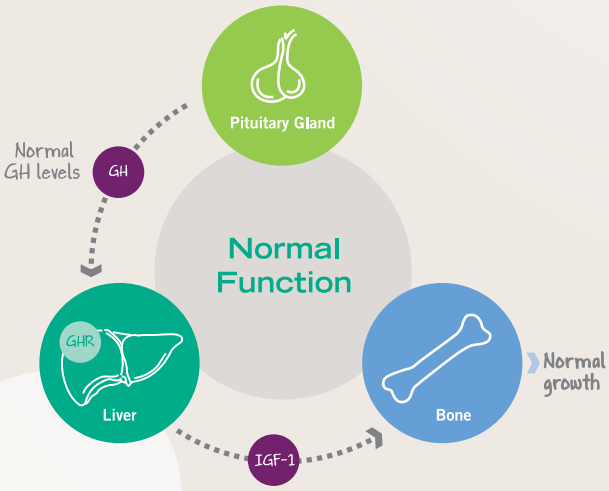
GH Stimulates the Production and Secretion of IGF-1

GH is secreted from the pituitary gland and binds to the GH receptor (GHR) in many tissues, including the growth plate and the liver.[1,3] Although GH has direct effects at the growth plate, its major growth-promoting action is mediated through the GHR in the liver, which stimulates the production of IGF-1.[3] IGF-1 is released from the liver into the peripheral tissues, where it has a direct impact on linear bone growth and bone remodeling (Figure 1).[1,3,4]

FIGURE 1: GH AND IGF-1 ACTIVITY IN THE NORMAL GROWTH PROCESS[1,3,5]



IGF-1 and GH are major hormonal factors involved in normal growth.[1]

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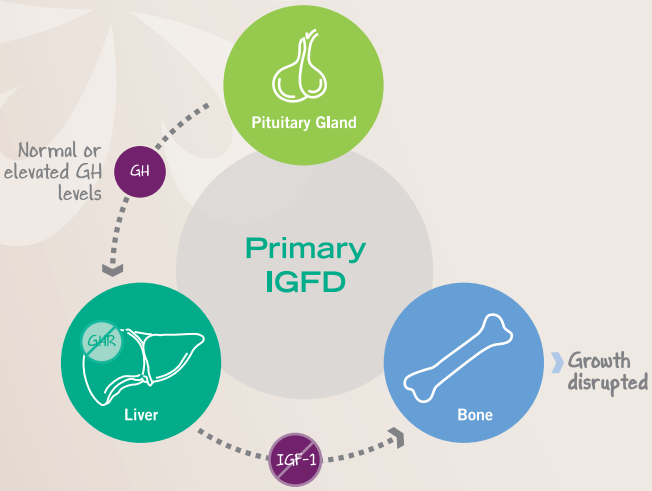
The Relationship Between GH and IGF-1 in Body Growth

Primary IGF-1 Deficiency Leads to Growth Failure

Deficiency in IGF-1 may lead to short stature in children and adolescents.[6] Primary IGF-1 deficiency (IGFD) is characterized by abnormally low levels of IGF-1 in the presence of normal or elevated GH levels. Normal growth becomes disrupted due to the inability of IGF-1 to mediate the growth-promoting activity of GH (Figure 2).[1,7]

FIGURE 2: DISRUPTION OF NORMAL GROWTH IN PRIMARY IGFD[1,3,5,8]



IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions (continued)

- **Progression of Scoliosis:** Patients with a history of scoliosis, treated with INCRELEX, should be monitored.
- **Malignant Neoplasia:** There have been postmarketing reports of malignant neoplasia in pediatric patients who received treatment with INCRELEX. The tumors were observed more frequently in patients who received INCRELEX at higher than recommended doses or at doses that produced serum IGF-1 levels above the normal reference ranges for age and sex. Monitor all patients receiving INCRELEX carefully for development of neoplasms. If malignant neoplasia develops, discontinue INCRELEX treatment.
- **Risk of Serious Adverse Reactions in Infants due to Benzyl Alcohol Preserved Solution:** Serious and fatal adverse reactions including "gasping syndrome" can occur in neonates and infants treated with benzyl alcohol-preserved drugs. Use of INCRELEX in infants is not recommended.

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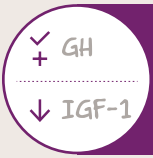
Various Causes of Primary IGFD

Primary IGFD arises from a deficiency of either the production or peripheral action of IGF-1 on linear growth.[6] These defects may arise from a number of causes, including[6,8,9]:

- GHR mutations or deletions
- GHR abnormalities
- Post-GHR signaling defects
- Bioinactive IGF-1
- Primary defects of synthesis and action of IGF-1



Children with Primary IGFD have normal or elevated levels of GH and low IGF-1 levels.[1]

Olive, actual Increlex® patient

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Identifying Severe Primary IGF-1 Deficiency

Clinical Features of Primary IGF-1 Deficiency

A patient with Primary IGFD may exhibit a number of unique clinical features in addition to having short stature, including[6,10]:

- Hypoglycemia
- Obesity (with abdominal adiposity)
- Undeveloped muscles
- Midfacial hypoplasia
- High-pitched voice
- Osteoporosis
- Small genitalia since birth
- Delayed puberty

Olive, actual Increlex® patient, and her mother, Renee

IMPORTANT SAFETY INFORMATION (continued)

Adverse Reactions

Common adverse reactions include hypoglycemia, local and systemic hypersensitivity, and tonsillar hypertrophy.

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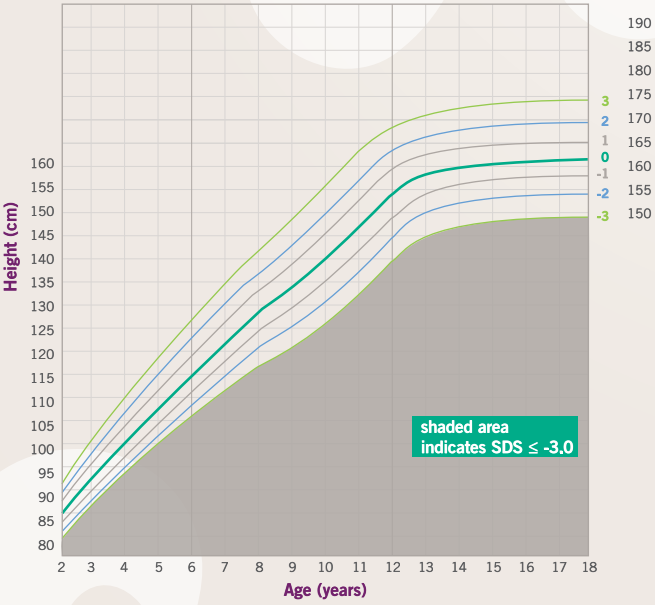
Criteria for a Diagnosis of SPIGFD

SPIGFD may be the cause of a severe impairment in growth. The diagnosis of SPIGFD is made when a patient meets the following criteria (Figure 3)[9]:

- Height standard deviation score (SDS) ≤ -3.0
- IGF-1 concentration SDS ≤ -3.0
- GH is normal or elevated

FIGURE 3: SPIGFD PATIENTS HAVE HEIGHT SDS ≤ -3.0[9]



Data and formula from Centers for Disease Control and Prevention.[11]

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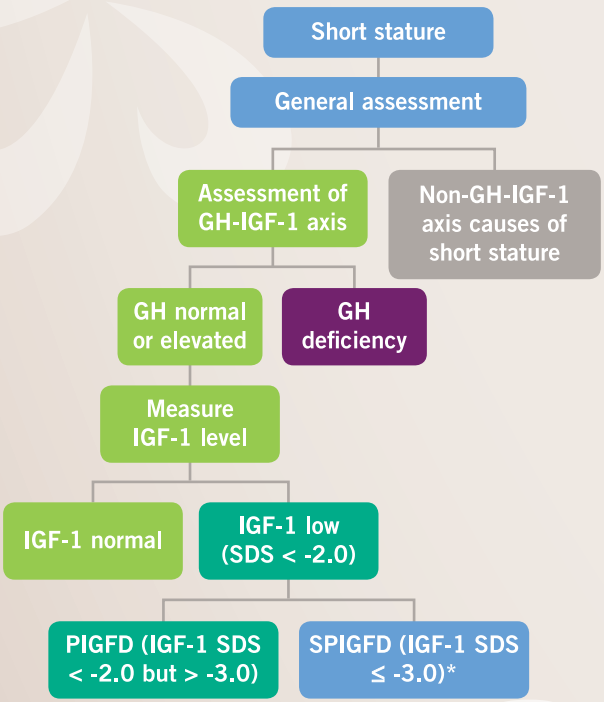
Identifying Severe Primary IGF-1 Deficiency

Endocrine Investigation of a Patient With Short Stature

After the general assessment of a patient with short stature (which may include a review of the patient's growth history and medical history, physical examination, or general laboratory test) to investigate chronic illness and other causes, an investigation may then be conducted to assess the growth hormone-IGF-1 axis prior to the initiation of therapy.[2,7,9]

FIGURE 4: POSSIBLE DEFECTS IN GH AND IGF-1 LEVELS[7,9]



*Severe Primary IGF-1 deficiency (IGFD) is defined by[9]:

- height standard deviation score ≤ -3.0 and
- basal IGF-1 standard deviation score ≤ -3.0 and
- normal or elevated growth hormone (GH)

IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions

- **Hypoglycemia:** INCRELEX should be administered 20 minutes before or after a meal or snack and should not be administered when the meal or snack is omitted. Glucose monitoring and INCRELEX dose titration are recommended until a well-tolerated dose is established and as medically indicated.

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The Importance of a Proper Diagnosis

Testing for Primary IGF-1 deficiency in children with short stature and suspected defect in the GH-IGF-1 axis is essential because these children have a limited time to reach full growth potential with treatment before epiphyseal fusion. Proper diagnosis allows for the condition to be treated from the start.[2,9]

As GH concentrations are normal or elevated in SPIGFD, these patients cannot be expected to respond adequately to exogenous GH treatment.[1,9]

Olive, actual Increlex® patient

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Increlex®—The ONLY Treatment for SPIGFD

Improve Growth Rates in Children With SPIGFD

Increlex, which contains human IGF-1 produced by recombinant DNA technology, is the only FDA-approved treatment for SPIGFD.[9] Increlex is not a substitute to GH for approved GH indications.[9] Patients with SPIGFD who are treated with Increlex may achieve a greater final adult height than in the absence of therapy.[6,9]

Actor portrayals are for illustrative purposes only

IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions (continued)

- **Intracranial Hypertension:** Funduscopic examination is recommended at the initiation of and periodically during the course of therapy.
- **Lymphoid Tissue Hypertrophy:** Patients should have periodic examinations to rule out potential complications.
- **Slipped Capital Femoral Epiphysis:** Carefully evaluate any pediatric patient with the onset of a limp or hip/knee pain during INCRELEX therapy.

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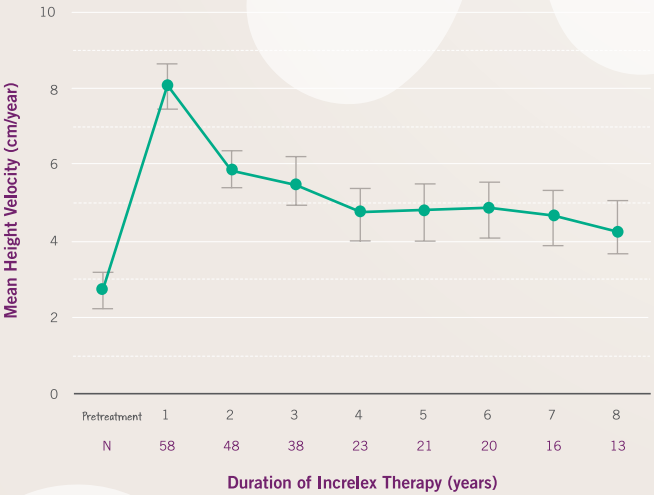
Growth in Patients With SPIGFD Improved Significantly With Increlex

In clinical studies with Increlex, mean height velocity nearly tripled over baseline in the first year of treatment ($P<0.0001$), and mean height velocity increased to a mean of 8 cm/year from a baseline of 2.8 cm/year ($P<0.0001$) (Figure 5).[9*]

FIGURE 5: GROWTH RATE WITH INCRELEX OVER 8 YEARS[9*†]



*Data shown are from an integrated analysis of individuals treated continuously in 5 clinical studies (4 open label and 1 double blind, placebo controlled) conducted in 71 pediatric subjects with SPIGFD. Pretreatment height velocity was available for 58 subjects.[9]

†95% confidence intervals are shown.

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IGF-1 Plays an Essential Role in Growth

The Proper Diagnosis of SPIGFD Matters

- IGF-1 is one of the most important hormonal regulators of growth, and IGF-1 deficiency leads to short stature in children and adolescents[1,2,6,7]
- SPIGFD is defined by a height SDS ≤ -3.0, basal IGF-1 SDS ≤ -3.0, and normal or elevated GH[9]
- Increlex® contains human IGF-1 produced by recombinant DNA technology[9]

Olive, actual Increlex patient

Please visit www.increlex.com for more information.

Please see Important Safety Information throughout this brochure and Full Prescribing Information in pocket.

References: 1. Backeljauw PF, Chernausek SD. Treatment of severe IGF-1 deficiency with recombinant human IGF-1 (mecasermin). *Curr Med Lit.* 2009;2(3):69-74. **2.** Cohen J, Blethen S, Kuntze J, Smith SL, Lomax KG, Mathew PM. Managing the child with severe primary insulin-like growth factor-1 deficiency (IGFD): IGFD diagnosis and management. *Drugs R D.* 2014;14(1):25-29. **3.** Kemp SF. Insulin-like growth factor-I deficiency in children with growth hormone insensitivity: current and future treatment options. *BioDrugs.* 2009;23(3):155-163. **4.** Yakar S, Rosen CJ, Beamer WG, et al. Circulating levels of IGF-1 directly regulate bone growth and density. *J Clin Invest.* 2002;110(6):771-781. **5.** Le Roith D, Scavo L, Butler A. What is the role of circulating IGF-I? *Trends Endocrinol Metab.* 2001;12(2):48-52. **6.** Fintini D, Brufani C, Cappa M. Profile of mecasermin for the long-term treatment of growth failure in children and adolescents with severe primary IGF-1 deficiency. *Ther Clin Risk Manag.* 2009;5(3):553-559. **7.** Savage MO, Burren CP, Rosenfeld RG. The continuum of growth hormone IGF-I axis defects causing short stature: diagnostic and therapeutic challenges. *Clin Endocrinol (Oxf).* 2010;72(6):721-728. **8.** Backeljauw P, Bang P, Dunger DB, Juul A, Le Bouc Y, Rosenfeld R. Insulin-like growth factor-I in growth and metabolism. *J Pediatr Endocrinol Metab.* 2010;23(1-2):3-16. **9.** Increlex full Prescribing Information. Cambridge, MA: Ipsen Biopharmaceuticals, Inc; December 2019. **10.** Wit JM, Kiess W, Mullis P. Genetic evaluation of short stature. *Best Pract Res Clin Endocrinol Metab.* 2011;25(1):1-17. **11.** Centers for Disease Control and Prevention Stature-For-Age Charts. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Health Statistics. https://www.cdc.gov/growthcharts/percentile_data_files.htm. Accessed November 14, 2018.

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