Each Patient Is Unique

Measure IGF-1 Levels Early in Your Patients With Growth Failure

Actual Increlex® patient, Olive.

She rode the BIG rollercoaster

The ONLY treatment for Severe Primary IGF-1 Deficiency (SPIGFD)

He reached the water fountain

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.

Please see Important Safety Information throughout and Full Prescribing Information.

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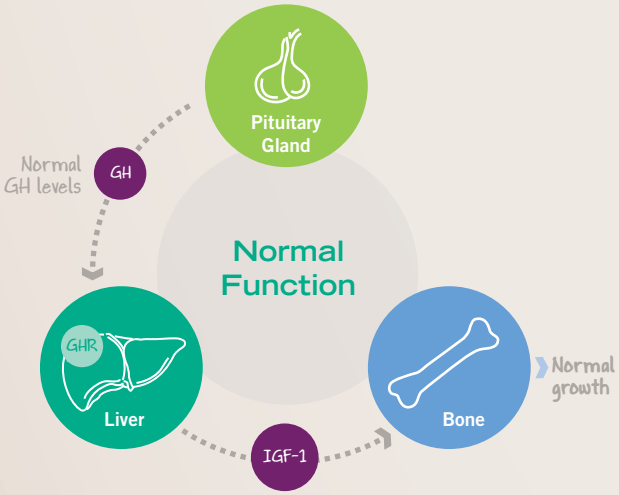
Identifying the GH–IGF-1 Relationship

Insulin-like growth factor-1 (IGF-1) is an important hormonal regulator of growth in humans[1]

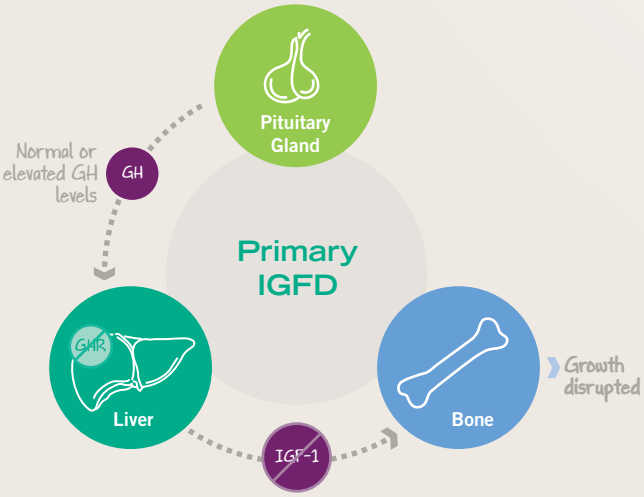
IGF-1 production is stimulated by growth hormone (GH) and primarily occurs in the liver[2]

Primary IGF-1 Deficiency (IGFD) is defined by low IGF-1 concentrations despite the presence of normal or elevated GH concentrations[1,3]

THE ROLE OF GH AND IGF-1 TO PROMOTE GROWTH[1,4]



- GH activates GHR in the liver to stimulate IGF-1 production and release
- Circulating IGF-1 promotes normal growth



- GH is unable to activate the GHR in the liver or the GHR signalling is defective
- IGF-1 is not stimulated and growth rate is affected

GHR=growth hormone receptor.

IMPORTANT SAFETY INFORMATION (continued)

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

Please see Important Safety Information throughout and Full Prescribing Information.

Making a Difference With the Proper Diagnosis

Testing for Primary IGF-1 Deficiency in children with short stature is essential because:

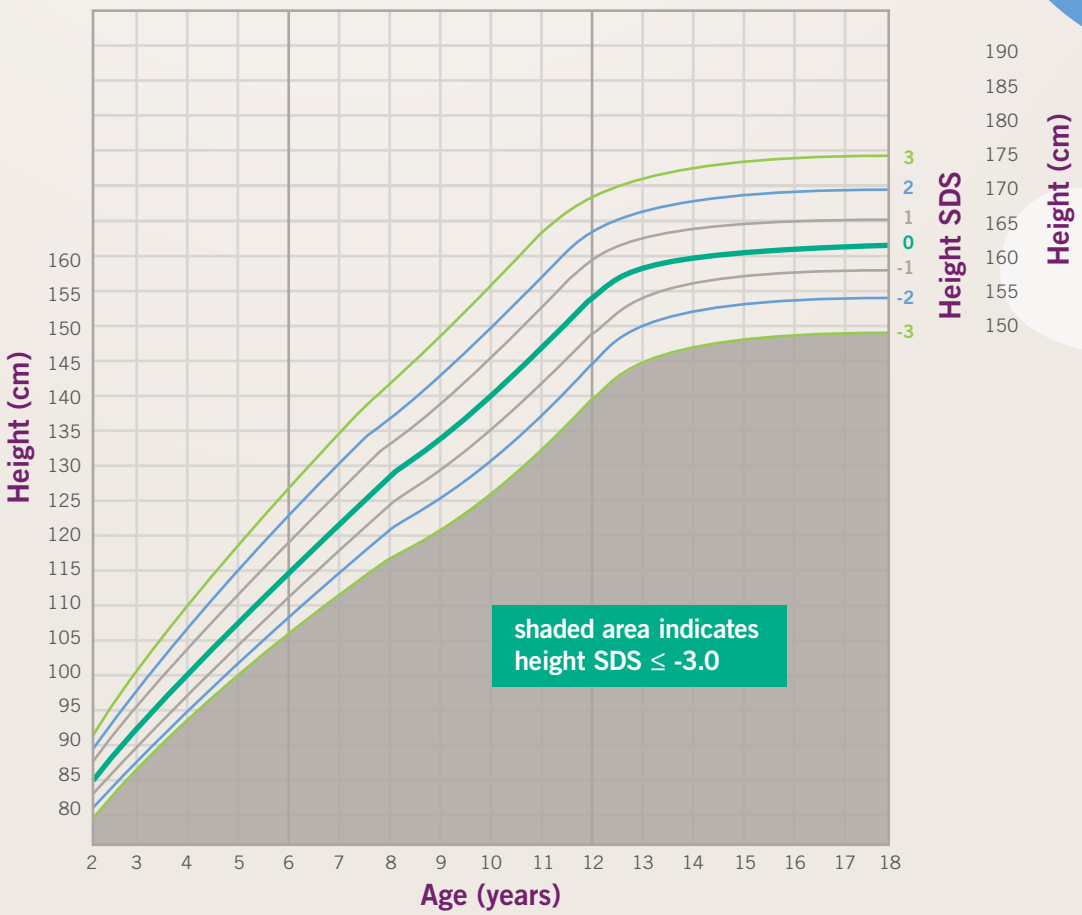
- These children have a limited time to reach full growth potential with treatment before epiphyseal fusion[3,5]
- Proper diagnosis allows you to treat the condition from the start[5]

GH therapy may not help these children because patients with Primary IGFD have normal levels of GH[1,3]

Severe Primary IGF-1 Deficiency is defined by[3]:

- Height SDS ≤ -3.0
- IGF-1 concentration SDS ≤ -3.0
- GH is normal or elevated

SEVERE PRIMARY IGFD PATIENTS HAVE HEIGHT STANDARD DEVIATION SCORE (SDS) ≤ -3.0[3]:



Data and formula from Centers for Disease Control and Prevention.[6]

Consider reevaluating your patients who are not responding adequately to GH therapy and determine if they meet the criteria for Severe Primary IGFD

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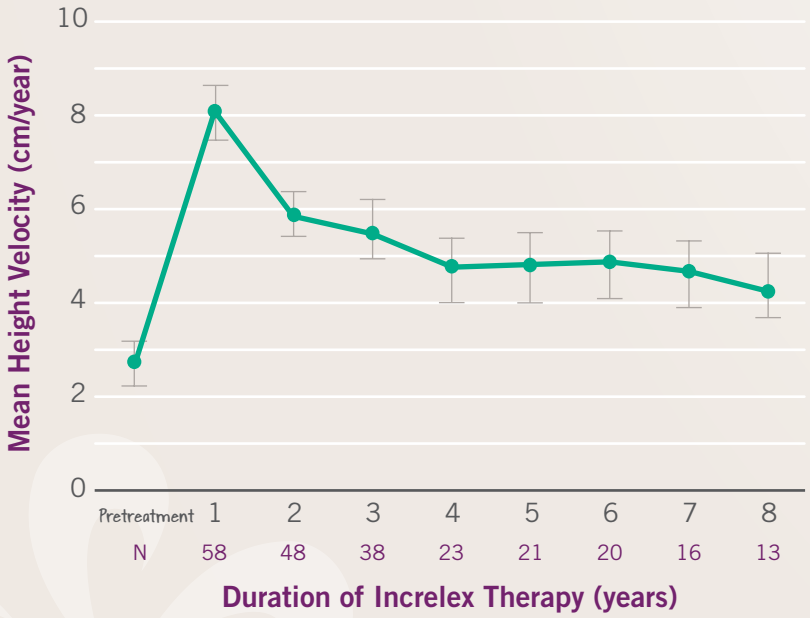
Improve Growth Rates in Children With Severe Primary IGF-1 Deficiency

Olive's growth rate increased to 3.2 inches/year with Increlex from 1.6 inches/year before treatment.[7]

In clinical trials, Increlex improved statural growth in patients diagnosed with Severe Primary IGFD[3]

GROWTH RATE WITH INCRELEX® OVER 8 YEARS[3]*



Data shown are from individuals treated continually in 5 integrated clinical studies (4 open-label and 1 double-blind, placebo-controlled) conducted in 71 pediatric subjects with Severe Primary IGFD. Pretreatment height velocity was available for 58 subjects.[3]

*95% confidence intervals are shown.

Results[3]

- Mean height velocity nearly tripled over baseline in the first year ($P<0.0001$)
  - Mean height velocity increased to 8 cm/year in the first year, on average, from a baseline of 2.8 cm/year ($P<0.0001$)
- Mean height velocity was sustained at approximately 5 cm/year in years 2 through 6 of treatment
- Change in bone age progressed in accord with advancing chronological age†

†Forty-nine subjects were included in an analysis of the effects of Increlex on bone age advancement. The mean ± SD change in chronological age was 4.9 ± 3.4 years and the mean ± SD change in bone age was 5.3 ± 3.4 years.[3]

IMPORTANT SAFETY INFORMATION (continued)

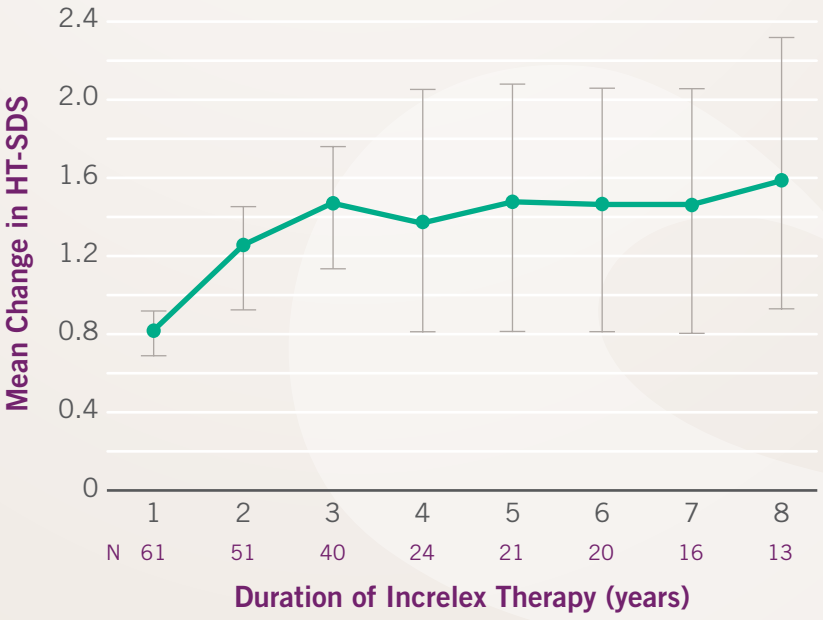
Warnings and Precautions

- **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.

Please see Important Safety Information throughout and Full Prescribing Information.

Increasing Height SDS

CHANGE IN HEIGHT SDS WITH INCRELEX OVER 8 YEARS[3‡]



Data shown are from individuals treated in 5 integrated clinical studies (4 open-label and 1 double-blind, placebo-controlled) conducted in 71 pediatric subjects with Severe Primary IGFD. The average height SDS was -6.7 at baseline for the 61 subjects in the efficacy analysis.[3]

‡95% confidence intervals are shown.

Results[3]

- Average height SDS had increased from start of treatment by +0.8 at year 1 and +1.2 at year 2

He got his favorite book from the top shelf

Actor portrayal is for illustrative purposes only.

Growth rates are highest during the first year of treatment with Increlex[3]

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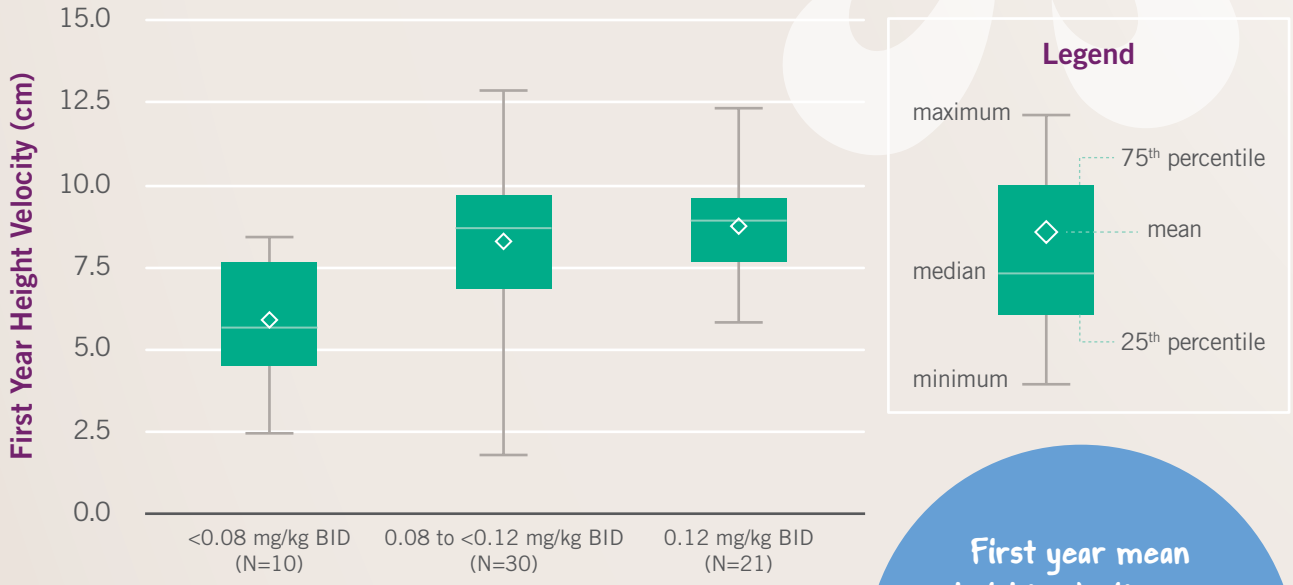
Post Hoc Analysis of Dose and Height Velocity in the First Year

FIRST YEAR HEIGHT VELOCITY IN 3 DIFFERENT INCRELEX® DOSE GROUPS (AVERAGE DOSE DURING THE YEAR)[8]



Data consolidated from all individual patients treated with Increlex in 5 clinical studies: four open-label and one double-blind placebo-controlled, included a total of 71 pediatric subjects with Severe Primary IGFD. The efficacy analysis above included a total of 61 subjects. Ten subjects who received Increlex for less than one year or had prior IGF-1 therapy were excluded.[8]

Doses greater than 0.12 mg/kg given twice daily should not be administered due to potential hypoglycemic effects.[3]

First year mean height velocity was 5.9 cm/year with <0.08 mg/kg BID and 8.8 cm/year with 0.12 mg/kg BID[8]

Analysis Limitations: This analysis should not be used to draw conclusions about differences in efficacy between doses. The post hoc nature of the analysis and the retrospective grouping of the dose groups preclude any statistical testing of the data.

SELECTED SAFETY INFORMATION: WARNING & PRECAUTION FOR HYPOGLYCEMIA

- Because Increlex has insulin-like hypoglycemic effects it should be administered shortly before or after (± 20 minutes) a meal or snack.
- Glucose monitoring and Increlex dose titration are recommended until a well-tolerated dose is established and subsequently as medically indicated.
- Special attention should be paid to small children because their oral intake may not be consistent.
- Patients should avoid engaging in any high-risk activities (e.g. driving, exercise, etc.) within 2 to 3 hours after dosing, particularly during the initiation of Increlex treatment until tolerability and a stable dose have been established.
- Increlex should not be administered when the meal or snack is omitted.
- The dose of Increlex should never be increased to make up for one or more omitted doses.

Please see Important Safety Information throughout and Full Prescribing Information.

Adjust Dosing With 3 Simple Steps

Patients start Increlex on an individualized, weight-based dose within the recommended starting dose range of 0.04 mg/kg BID to 0.08 mg/kg BID[3]

- Preprandial glucose monitoring is recommended at treatment initiation and until a well-tolerated dose is established[3]*

Increlex dose may be increased to the maximum recommended dose of 0.12 mg/kg BID[3]

Step 1 | **START**	Step 2 | **TITRATE**	Step 3 | **ADJUST**
0.04 mg/kg BID to 0.08 mg/kg BID	If Increlex is well tolerated for at least 1 week, the dose may be increased by 0.04 mg/kg per dose, to the maximum dose of 0.12 mg/kg given twice daily†	The dose should be adjusted based on tolerability and weight. If a child's weight changes, the dose should be adjusted to maintain a consistent mg/kg dosage

If a child's weight changes, the dose should be adjusted to maintain a consistent mg/kg dosage. This means that if a child continues to grow, the unit dose will need to be increased. Dosage may be increased by 0.04 mg/kg per injection (if well tolerated), until a maximum recommended dose of 0.12 mg/kg BID is reached[3]

*If frequent symptoms of hypoglycemia or severe hypoglycemia occur, preprandial glucose monitoring should continue.

†Doses greater than 0.12 mg/kg given twice daily have not been evaluated in children with Primary IGFD and, due to potential hypoglycemic effects, should not be used.

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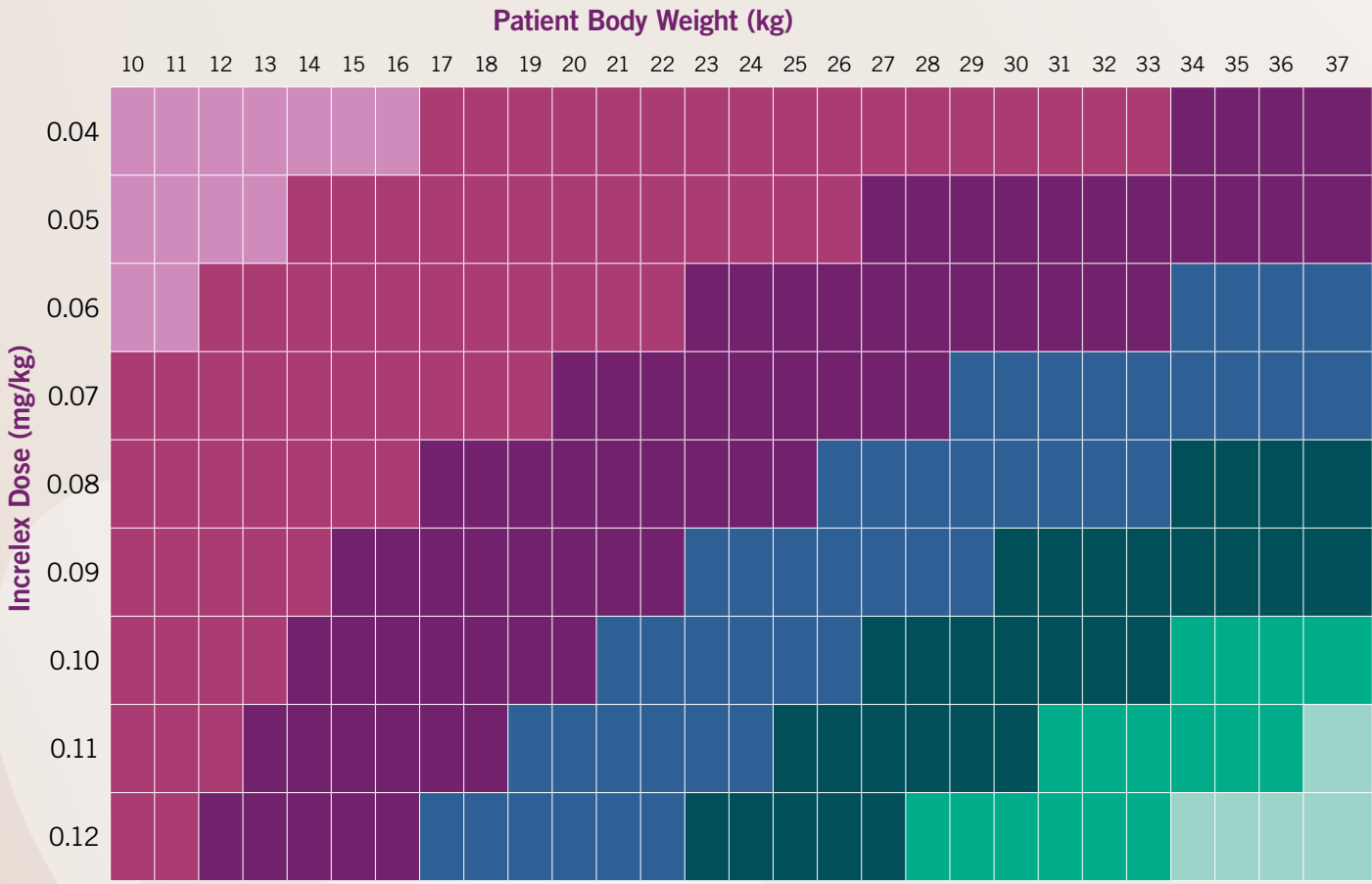
Prescribe the Correct Number of Vials

When prescribing a 30-day supply of Increlex®, your patients will need a specific number of Increlex vials depending on body weight and dosage regimen

- Increlex is supplied as a 10 mg per mL sterile solution in multiple dose glass vials (40 mg per 4 mL vial)[3]

NUMBER OF INCRELEX VIALS TO PRESCRIBE FOR A 30-DAY SUPPLY[8]*



*The following formula was used to determine the number of vials per month: patient body weight [kg] x single dose of Increlex [mg/kg] x 2 doses per day x 30 days per month/40 [mg/vial] = vials/month.

If using syringes that measure dose in units, doses in mg/kg must be converted to units using the following formula: patient body weight [kg] x single dose of Increlex [mg/kg] x 1 mL/10 mg x 100 units/1 mL = units/injection.[3]

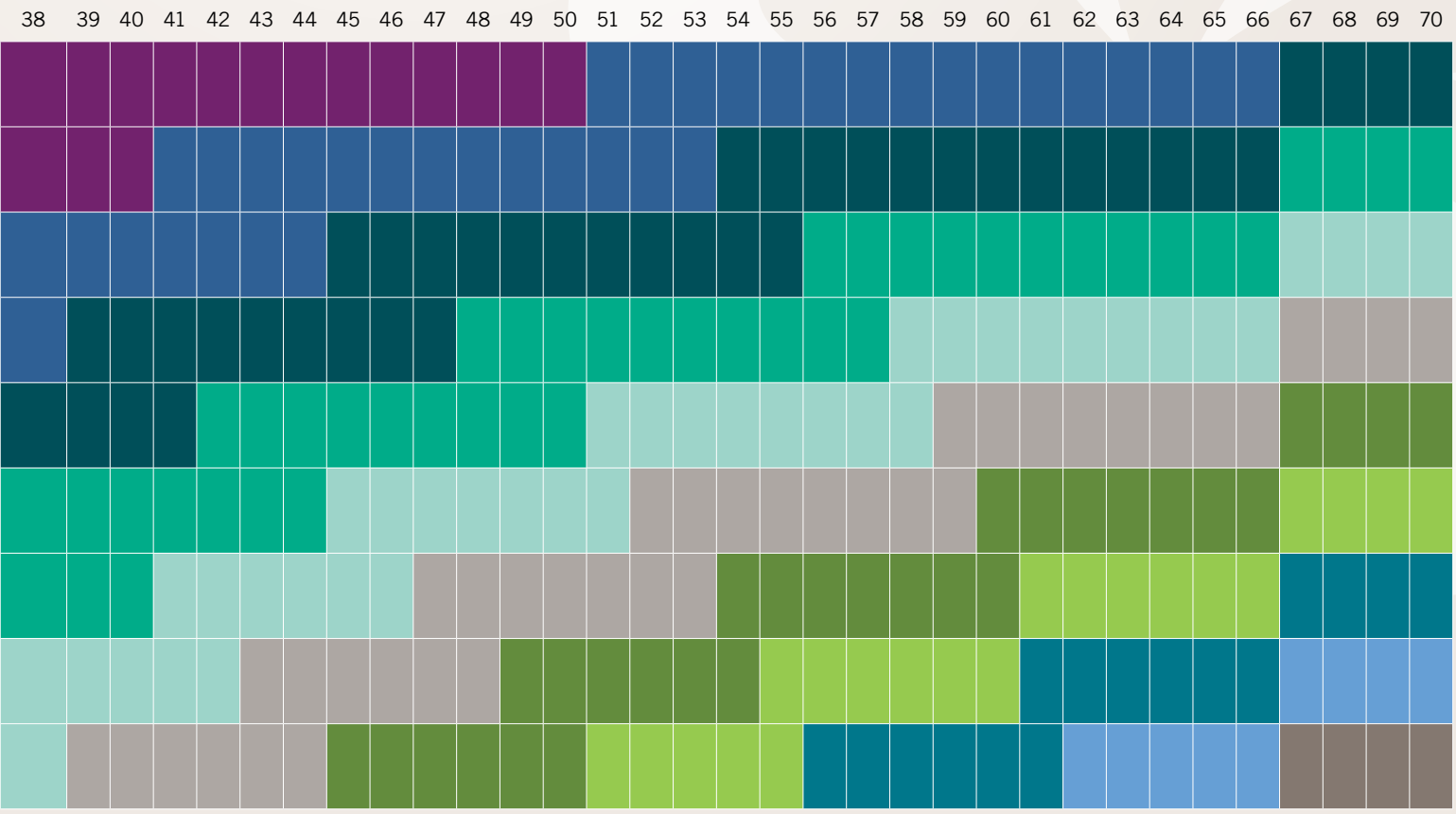
IMPORTANT SAFETY INFORMATION (continued)

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.

Please see Important Safety Information throughout and Full Prescribing Information.

To arrive at the correct number of vials of Increlex to prescribe your patient, simply locate where your patient's body weight and dosing regimen align in the figure



Legend

- 1 vial
- 2 vials
- 3 vials
- 4 vials
- 5 vials
- 6 vials
- 7 vials
- 8 vials
- 9 vials
- 10 vials
- 11 vials
- 12 vials
- 13 vials

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Established Safety Profile With Increlex®

Adverse reactions occurring with Increlex in ≥5% of patients in clinical studies* included[3]:

- Hypoglycemia, lipohypertrophy, bruising, otitis media, serous otitis media, snoring, tonsillar hypertrophy, headache, dizziness, convulsions, vomiting, hypoacusis, fluid in middle ear, ear pain, abnormal tympanometry, cardiac murmur, arthralgia, pain in extremity, thymus hypertrophy, ear tube insertion

Hypoglycemia was reported by 30 patients (42%) at least once during their course of therapy[3]

- Most cases of hypoglycemia were mild or moderate in severity
- Five subjects had severe hypoglycemia (requiring assistance and treatment) on one or more occasions and 4 subjects experienced hypoglycemic seizures/loss of consciousness on one or more occasions
- 14 of the 30 patients (47%) reporting hypoglycemia had a history of hypoglycemia prior to treatment
- The frequency of hypoglycemia was highest in the first month of treatment and episodes were more frequent in younger children

*In clinical studies of 71 patients with Primary IGFD treated for a mean duration of 3.9 years and representing 274 patient years.[3]

No patients withdrew from any clinical study because of adverse reactions[3]

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.

Adverse Reactions

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

Please see Important Safety Information throughout and Full Prescribing Information.

IPSEN CARES®—Helping patients get access to medications and services they need

The IPSEN CARES® Patient Access Specialists are fully dedicated to providing information and support for the interactions between your office, the patient, and the insurance company:

Benefits Verification—verifies patients' coverage, restrictions (if applicable), and copayment/co-insurance amounts

Referrals to Specialty Pharmacy Network—Increlex® is a limited distribution product. We will triage the prescription to the appropriate specialty pharmacy based on the insurance requirements. We will follow up after the referral is triaged to confirm receipt and shipment date

Prior Authorization (PA) Information and Appeals Information—provides information on required documentation for PA appeals processes, and recommendations for next steps based on payor policy

Injection Training—processes requests for injection training for HCPs and caregivers, and we follow up to confirm injection training and shipment date

Copayment Assistance for Eligible* Patients—facilitates eligibility determination and provides information about the Copay Assistance program. This could include referrals to the commercial copay program or to an independent nonprofit organization

Billing and Coding Information—provides information regarding billing and coding and answers questions from those calling the IPSEN CARES® program

Patient Assistance Program (PAP)† Determination—determines patients' eligibility for PAP and dispenses free product to eligible* patients

Communication With Providers and Patients—conducts calls to both healthcare providers and patients with status updates about patients' IPSEN CARES® enrollment, benefits verification results, coverage status, dispense date, etc

*Patient Eligibility & Terms and Conditions: Patients are not eligible for copay assistance through IPSEN CARES® if they are enrolled in any state or federally funded programs, including, but not limited to, Medicare Part B, Medicare Part D, Medicaid, Medigap, VA, DoD, or TRICARE (collectively, "Government Programs"), or where prohibited by law. Patients residing in Massachusetts, Minnesota, Michigan, or Rhode Island can only receive assistance with the cost of Ipsen products but not the cost of related medical services (injection). Patients receiving free starter therapy through the IPSEN CARES® program are not eligible for the copay assistance program while they are waiting for insurance prescription coverage to begin. Patients receiving assistance through another assistance program or foundation, free trial, or other similar offer or program, also are not eligible for the copay assistance program during the current enrollment year.

Cash-pay patients are eligible to participate. "Cash-pay" patients are defined for purposes of this program as patients without insurance coverage or who have commercial insurance that does not cover Increlex®. Medicare Part D enrollees who are in the prescription drug coverage gap ("donut hole") are not considered cash-pay patients and are not eligible for copay assistance through IPSEN CARES®. For patients with commercial insurance that are not considered to be cash-pay patients, the maximum copay benefit amount per prescription is an amount equal to the difference between the annual maximum copay benefit of $12,000 and the total amount of copay benefit provided to the patient in the Increlex® Copay Program. For cash-pay patients, the maximum copay benefit amount per prescription is $1,000, subject to the annual maximum of $12,000 in total. Patient pays any amount greater than the maximum copay savings amount per prescription.

Patient or guardian is responsible for reporting receipt of copay savings benefit to any insurer, health plan, or other third party who pays for or reimburses any part of the prescription filled through the program, as may be required. Additionally, patients may not submit any benefit provided by this program for reimbursement through a Flexible Spending Account, Health Savings Account, or Health Reimbursement Account. Ipsen reserves the right to rescind, revoke, or amend these offers without notice at any time. Ipsen and/or RxCrossroads by McKesson are not responsible for any transactions processed under this program where Medicaid, Medicare, or Medigap payment in part or full has been applied. Data related to patient participation may be collected, analyzed, and shared with Ipsen, for market research and other purposes related to assessing the program. Data shared with Ipsen will be de-identified, meaning it will not identify the patient. Void outside of the United States and its territories or where prohibited by law, taxed, or restricted. This program is not health insurance. No other purchase is necessary.

†Uninsured patients may be eligible for free medication through our Patient Assistance Program. To qualify, patients must: 1) be uninsured, 2) have an on-label diagnosis, 3) be US residents, and 4) meet income criteria. Parents/caregivers may enroll their child through IPSEN CARES®. If eligible, they may receive free medication from Ipsen.

Eligible patients can enroll by calling (866) 435-5677 between 8:00 AM and 8:00 PM ET Monday through Friday. www.IpsenCares.com

IPSENCARES™
Coverage, Access, Reimbursement & Education Support

Each Patient Is Unique

Measure IGF-1 Levels Early in Your Patients With Growth Failure

The ONLY treatment for Severe Primary IGF-1 Deficiency (SPIGFD)

He crossed the monkey bars

She was able to write on the board

Actor portrayals are for illustrative purposes only.

- Testing for insulin-like growth factor-1 (IGF-1) deficiency prior to starting treatment may help ensure proper diagnosis
- If Increlex® is well tolerated for at least 1 week, the dose may be increased by 0.04 mg/kg per dose, to the maximum dose of 0.12 mg/kg given twice daily[3]*
- The dose should be adjusted based on tolerability and weight. If a child's weight changes, the dose should be adjusted to maintain a consistent mg/kg dosage[3]
- IPSEN CARES® provides support for your office and patients

*Doses greater than 0.12 mg/kg given twice daily have not been evaluated in children with Primary IGFD and, due to potential hypoglycemic effects, should not be used.

IMPORTANT SAFETY INFORMATION

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Please see Important Safety Information throughout and Full Prescribing Information.

Please visit www.increlex.com for more information

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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.** 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. **3.** Increlex full Prescribing Information. Cambridge, MA: Ipsen Biopharmaceuticals, Inc; 2019. **4.** Le Roith D, Scavo L, Butler A. What is the role of circulating IGF-I? *Trends Endocrinol Metab*. 2001;12(2):48-52. **5.** 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. **6.** 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. Updated August 4, 2009. Accessed September 18, 2018. **7.** Vairamani K, Merjaneh L, Casano-Sancho P, et al. Novel dominant-negative GH receptor mutations expands the spectrum of GHI and IGF-I deficiency. *J Endocr Soc*. 2017;1(4):345-358. **8.** Data on file. September 2018. Ipsen Biopharmaceuticals, Inc.

IPSEN Innovation for patient care