Information That May be Helpful to Health Plans for Evaluating Approval of Increlex® (mecasermin)

For Your Pediatric Patients With Severe Primary IGF-1 Deficiency (SPIGFD)

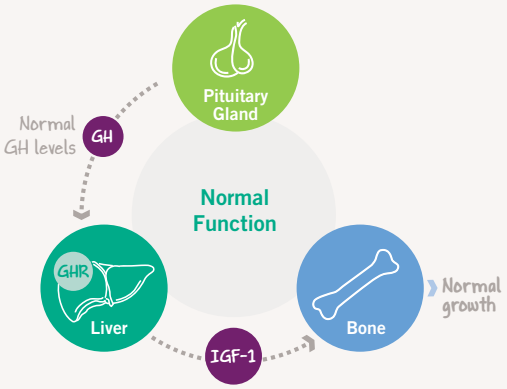
Actual Increlex® patient, Olive.

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

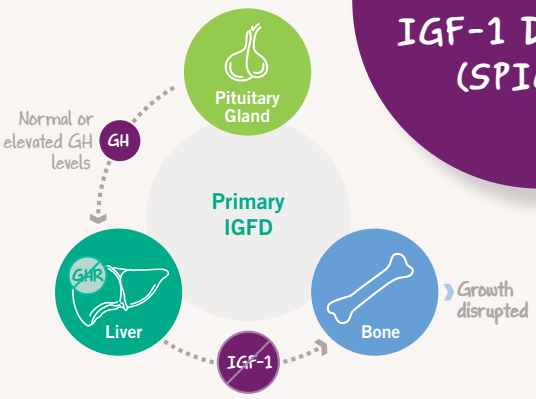
Measure IGF-1 Levels Early in Your Patients With Growth Failure

- 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 GH receptor (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

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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Documentation to Support INCRELEX Approval

Consider Two Pathways

PATHWAY 1: Newly Diagnosed Drug-Naïve Patients
PATHWAY 2: Growth Hormone (GH) Failure

HEALTH PLANS MAY CONSIDER THE FOLLOWING INFORMATION HELPFUL, IF AVAILABLE

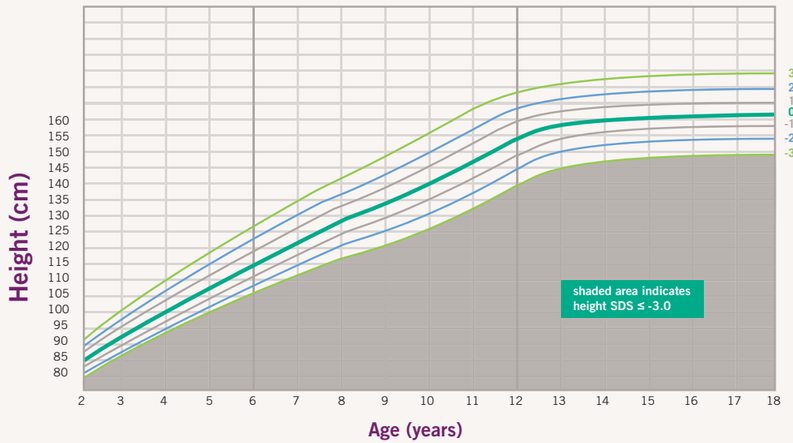
1	2	3	4
Growth chart with mid-parental height and patient's predicted height	IGF-1 blood test results	Bone age x-ray study. Radiological and Pediatric Endocrinologist interpretation	Tanner Scale/Staging results to show onset and progression of pubertal development

5	6	7	8	9
MRI results, if available	GH stimulation test results	Height velocity	Current growth chart following GH treatment	Updated IGF-1 assay/ Pretreatment IGF-1 assay

Causes of secondary IGF-1 deficiency must be excluded including under-nutrition, hepatic disease, and GH deficiency.[5]

It is critical to conduct IGF-1 and GH stimulation tests at time of diagnosis/prior to any therapeutic intervention because GH therapy can increase IGF-1 blood levels[5]

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



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

SPIGF1D is defined by[2]:

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

Additional Information to Consider

1. Identify specific health plan criteria

- Plan-specific guidelines and requirements for treatment authorization, such as letter of Medical Necessity and role of Pediatric Endocrinologist

2. Provide appropriate identification numbers

- Individual provider identification number from insurance card
- Patient's specific identification number from insurance card
- Correct ICD-10 codes
  - Potential ICD-10 diagnosis codes for children with SPIGFD include
    - E34.3: Short stature due to endocrine disease
    - R62.52: Short stature (child)

3. In addition to the documentation discussed on the previous page, include required supporting documents, such as

- INCRELEX prescribing information
- INCRELEX supporting publications
  - Backeljauw PF, Chernausek SD. Treatment of severe IGF-1 deficiency with recombinant human IGF-1 (mecasermin). *Curr Med Lit.* 2009;2(3):69-74.

4. Maintain a communication log

- Store copies of all communications with the health plan

To prepare for a medical necessity review for an appeal, request a peer-to-peer discussion, if possible.

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.

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Guideline Recommended[7]

Guidelines for Growth Hormone and Insulin-Like Growth Factor-I Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-I Deficiency

"We recommend the use of IGF-I therapy to increase height in patients with severe PIGFD. (Strong recommendation)"[7]

IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions (continued)

- **Slipped Capital Femoral Epiphysis:** Carefully evaluate any pediatric patient with the onset of a limp or hip/knee pain during INCRELEX therapy.
- **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.

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-1 deficiency in children with growth factor insensitivity: current and future treatment options. *BioDrugs.* 2009;23:155-163.
3. Increlex [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. van Dijk, Mulder P, Houdjk M, et al. High serum levels of growth hormone (GH) and insulin-like growth factor-I (IGF-I) during high-dose GH treatment in short children born small for gestational age. *J Clin Endocrinol Metabol.* 2006;91:1390-1396.
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. May 30, 2000. Accessed January 2, 2020.
7. Grimberg A, DiValli SA, Polychronakos C, et al. Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: Growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. *Horm Res Paediatr.* 2016;86:361-397.

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