PRIOR AUTHORIZATION POLICY

POLICY: Growth Disorders – Increlex Prior Authorization Policy
- Increlex® (mecasermin [rDNA origin] for subcutaneous injection – Ipsen Biopharmaceuticals/Hospira)

REVIEW DATE: 10/14/2020

OVERVIEW

Increlex, an insulin-like growth factor (IGF-1), is indicated for the treatment of growth failure in pediatric patients ≥ 2 years of age with the following conditions:[1]

- **Primary IGF-1 deficiency**, for patients with severe disease, defined as:
  - Height standard deviation score ≤ -3.0; AND
  - Basal IGF-1 standard deviation score ≤ -3.0; AND
  - Normal or elevated growth hormone level.
- **Growth hormone gene deletion**, in patients who have developed neutralizing antibodies to growth hormone.

Increlex is given by subcutaneous injection twice daily, shortly before or after a meal or snack. Treatment with Increlex should continue until the epiphyses fuse indicating full growth potential has been achieved.[3] It is a limitation of use that Increlex is not a substitute to growth hormone for approved growth hormone indications. Increlex is not indicated in secondary forms of IGF-1 deficiency, such as growth hormone deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory corticosteroids.[1]

Disease Overview

IGF-1 is the principal hormonal mediator of growth hormone action.[3] Under normal circumstances, growth hormone binds to its receptor in the liver and other tissues and stimulates the synthesis/secretion of IGF-1. In target tissues, the Type 1 IGF-1 receptor is activated by IGF-1, leading to intracellular signaling which stimulates multiple processes leading to stature growth. The metabolic actions of IGF-1 are in part directed at stimulating the uptake of glucose, fatty acids, and amino acids so that metabolism supports growing tissues. Primary IGF-1 deficiency is a group of disorders characterized by decreased IGF-1 production with normal or increased growth hormone secretion.[2] Three distinct molecular abnormalities have been identified as causes of primary IGF-1 deficiency: 1) mutations or gene deletions of the GH receptor gene; 2) mutations affecting the post-growth hormone receptor signaling cascade, as observed in a patient homozygous for a point mutation of the gene for signal transducer and activator of transcription (STAT)-5b; and 3) mutations or deletions of the gene for IGF-1. These patients are not growth hormone deficient and do not respond adequately to exogenous growth hormone treatment.[1-2] Once a diagnosis of severe primary IGF-1 deficiency is made, treatment is recommended as soon as possible.[3] Growth rates are highest during the first year of treatment and both first year catch-up growth and long-term outcomes are improved when initiated in younger children.

Clinical Efficacy

The efficacy of Increlex was evaluated in five clinical studies in patients (n = 71) with primary IGF-1 deficiency.[1] In these studies, 11% of the patients (n = 7) had growth hormone gene deletion. Refer to Table 1 for pooled height results from these studies in patients treated for up to 8 years.

Table 1: Annual Height Results by Number of Years Treated with Increlex.[1]

	Pre-Tx	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
Height Velocity (cm/yr)									
n	58	58	48	38	23	21	20	16	13
Mean (SD)	2.8 (1.8)	8.0 (2.2)	5.8 (1.5)	5.5 (1.8)	4.7 (1.6)	4.7 (1.6)	4.8 (1.5)	4.6 (1.5)	4.3 (1.1)
P-value*		<0.0001	<0.0001	<0.0001	0.0045	0.0015	0.0009	0.0897	0.3059
Height SDS									
n	61	61	51	40	24	21	20	16	13
Mean (SD)	-6.7 (1.8)	-5.9 (1.8)	-5.6 (1.8)	-5.4 (1.8)	-5.5 (1.9)	-5.6 (1.8)	-5.4 (1.8)	-5.2 (2.0)	-5.2 (2.0)

Pre-Tx – Pre-treatment; SD – Standard deviation; * P-values for comparison vs. pre-Tx values are computed using paired t-tests; SDS – Standard deviation score.

Most clinical assays used by laboratories in the US report IGF-1 values ± two standard deviations (SD) thereby representing the age-related reference range for the reporting laboratory.[4] Reference ranges for IGF-1 vary among laboratories and are dependent upon patient age, gender, and puberty status. However, some laboratories do not routinely report the SDS for IGF-1.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Increlex. Because of the specialized skills required for evaluation and diagnosis of patients treated with Increlex as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Increlex to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Increlex is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Severe Primary Insulin-Like Growth Factor-1 (IGF-1) Deficiency in a Child.** Approve for 1 year if the patient meets ONE of the following conditions (A or B):
   - **A)** Initial Therapy or Patient has been on Increlex < 1 Year. Approve for 1 year if the patient meets ALL of the following conditions (i, ii, iii, iv, and v):
     - **i.** Patient is ≥ 2 years of age; AND
     - **ii.** Height standard deviation score is ≤ -3.0 at baseline; AND
     - **iii.** Patient has a basal IGF-1 level below the lower limits of the normal reference range for the reporting laboratory; AND
       Note: Reference ranges for IGF-1 vary among laboratories and are dependent upon age, gender, and puberty status.
     - **iv.** Growth hormone concentration is normal or increased at baseline; AND
     - **v.** Increlex is prescribed by or in consultation with a pediatric endocrinologist.
   - **B)** Patient has been receiving Increlex for ≥ 1 Year. Approve for continuation of therapy if the patient meets the following conditions (i and ii):
     - **i.** The patient's height has increased by ≥ 4 cm/year in the most recent year; AND
       Note: Patients are reviewed annually for growth rate.
     - **ii.** The epiphyses are open.

2. **Growth Hormone Gene Deletion in a Child who has Developed Neutralizing Antibodies to Growth Hormone.** Approve for 1 year if the patient meets ONE of the following conditions (A or B):
   - **A)** Initial Therapy or Patient has been on Increlex < 1 Year. Patient meets both of the following (i and ii):
     - **i.** Patient is ≥ 2 years of age; AND
     - **ii.** Increlex is prescribed by or in consultation with a pediatric endocrinologist.
   - **B)** Patient has been receiving Increlex for ≥ 1 Year. Approve for continuation of therapy if the patient meets BOTH of the following conditions (i and ii):
     - **i.** The patient's height has increased by ≥ 4 cm/year in the most recent year; AND
       Note: Patients are reviewed annually for growth rate.
     - **ii.** The epiphyses are open.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Increlex is not recommended in the following situations:

1. **Idiopathic Short Stature, Growth Hormone Deficiency.** A Phase II open-label study evaluated somatropin in combination with Increlex in children with short stature associated with IGF-1 deficiency.[6] This study includes prepubertal children with IGF-1 SDS of ≤ -1 for age and gender, height SDS ≤ -2 for age and gender, and GH sufficiency demonstrated by a maximal stimulated GH response of ≥ 10 ng/mL; however, results are not yet available. Somatropin monotherapy is indicated for idiopathic short stature.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Increlex® injection [prescribing information]. Basking Ridge, NJ: Ipsen Biopharmaceuticals/Hospira; December 2019.
2. Rosenfeld RG. The IGF system: new developments relevant to pediatric practice. *Endocr Dev*. 2005;9:1-10.
3. Cohen J, Blethen S, Kuntze J, et al. 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.
4. Elmlinger MW, Kühnel W, Weber MM, Ranke MB. Reference ranges for two automated chemiluminescent assays for serum insulin-like growth factor I (IGF-I) and IGF-binding protein 3 (IGFBP-3). *Clin Chem Lab Med*. 2004;42(6):654-664.
5. Rosenbloom AL. Is there a role for recombinant insulin-like growth factor-I in the treatment of idiopathic short stature? *Lancet*. 2006;368:612-616.