VENTURA COUNTY
HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

POLICY: Increlex® (mecasermin [rDNA origin] for subcutaneous injection – Ipsen Biopharmaceuticals/Hospira)

DATE REVIEWED: 10/10/2018

OVERVIEW

Increlex is indicated for the long-term treatment of growth failure in children with severe primary insulin-like growth factor-1 (IGF-1) deficiency (Primary IGFD) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH.[1] Severe Primary IGFD is defined by:

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

Increlex is given by subcutaneous (SC) injection twice daily, shortly before or after a meal or snack. It is a limitation of use that Increlex is not a substitute for GH for approved GH indications. Increlex is not indicated in secondary forms of IGF-1 deficiency, such as GH deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids and is not a substitute for GH (somatropin) therapy.[1] Thyroid and nutritional deficiencies should be corrected before initiating Increlex treatment.

Disease Overview

IGF-1 is the principal hormonal mediator of growth hormone action.[3] Under normal circumstances, GH 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, which is homologous to the insulin 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 IGFD is a group of disorders characterized by decreased IGF production with normal or increased GH secretion.[2] Three distinct molecular abnormalities have been identified as causes of primary IGFD: 1) mutations or gene deletions of the GH receptor gene; 2) mutations affecting the post- GH receptor (GHR) 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 GH deficient, and do not respond adequately to exogenous GH treatment.[1-2] Once a diagnosis of severe primary IGFD 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 IGFD.[1] 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 for change from pre-Tx*		<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 1 year in duration unless otherwise 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 (Primary IGFD) 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 less than 1 Year. Approve for 1 year if the patient meets ALL of the following conditions (i, ii, iii, and iv):
     - **i.** Height standard deviation score is ≤ -3.0 at baseline; AND
       Note: An online tool to assess height SDS is available at: http://www.increlex.com/hcp-growth-tracking-tool.asp
     - **ii.** 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.
     - **iii.** Growth hormone concentration is normal or increased at baseline; AND
     - **iv.** Increlex is prescribed by or in consultation with a pediatric endocrinologist.
   - **B)** Patient has been receiving Increlex for at least 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 (Note: Patients are reviewed annually for growth rate.); AND

ii. The epiphyses are open.

Increlex is indicated for growth failure in children with severe primary IGFD, defined by height standard deviation score ≤ -3.0 and basal IGF-1 standard deviation score ≤ -3.0 and normal or elevated growth hormone.[1] However, the reporting laboratory may not report the SDS for IGF-1; therefore SDS is required to be below the limit of normal but is not required to be ≤ -3 SDS. Studies have evaluated the efficacy of Increlex in patients with severe Primary IGFD.[1] Over the course of 8 years in studies evaluating patients treated with Increlex, mean height velocity (SD) ranged from 8.0 (2.2) cm/year to 4.3 (1.1) cm/year. Treatment should continue until the epiphyses fuse indicating full growth potential has been achieved.[3] In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

2. **Growth Hormone (GH) Gene Deletion in a Child who has Developed Neutralizing Antibodies to GH.** 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 less than 1 Year. Approve if Increlex is prescribed by or in consultation with a pediatric endocrinologist.
   - **B)** Patient has been receiving Increlex for at least 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 (Note: Patients are reviewed annually for growth rate.); AND
     - **ii.** The epiphyses are open.

   Over the course of 8 years in studies evaluating patients treated with Increlex, mean height velocity (SD) ranged from 8.0 (2.2) cm/year to 4.3 (1.1) cm/year.[1] In these studies, 11% of the patients (n = 7) had GH gene deletion. Treatment should continue until the epiphyses fuse indicating full growth potential has been achieved.[3] In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Increlex has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

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: Ipses Biopharmaceuticals/Hospira; May 2016.
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.

OTHER REFERENCES UTILIZED

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- Collett-Solberg PF, Misra M; Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. The role of recombinant human insulin-like growth factor-I in treating children with short stature. *J Clin Endocrinol Metab.* 2008;93:10-18.
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- Chernausek SD, Backeljauw PF, Frane J, et al. Long-term treatment with recombinant IGF-I in children with severe IGF-I deficiency due to growth hormone insensitivity. *J Clin Endocrinol Metab.* 2007;92:902-910.
- Khwaja OS, Ho E, Barnes KV, et al. Safety, pharmacokinetics, and preliminary assessment of efficacy of mecasermin (recombinant human IGF-1) for the treatment of Rett syndrome. *Proc Natl Acad Sci U S A.* 2014;111(12):4596-4601.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Annual revision	No changes to the criteria.	09/16/2015
Annual revision	No changes to the criteria.	09/28/2016
Annual revision	No changes to the criteria.	10/11/2017
Annual revision	No changes to the criteria.	10/10/2018

* For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx; TAC – Therapeutic Assessment Committee.