Treatment of IGF-1 Deficiency

Policy # 00209
Original Effective Date: 12/20/2006
Current Effective Date: 05/08/2023

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider replacement therapy with mecasermin (Increlex®)‡ for the treatment of growth failure in children with severe primary insulin-like growth factor-1 (IGF-1) deficiency OR with growth hormone gene deletion who have developed neutralizing antibodies to growth hormone to be **eligible for coverage.****

Severe Primary Insulin-like Growth Factor-1 Deficiency

Patient Selection Criteria

Coverage eligibility for severe primary IGF-1 deficiency with mecasermin (Increlex) will be considered when **ALL** of the following criteria are met:

Initial:

- Patient has a diagnosis of severe primary IGF-1 deficiency; **AND**
- Patient is 2 years of age or older; **AND**
- Patient's height standard deviation is less than or equal to -3.0 at baseline; **AND**
- Patient's basal IGF-1 standard deviation is less than or equal to -3.0; **AND**
- Patient has normal or elevated growth hormone. Normal or elevated growth hormone is defined as greater than 10 nanograms per milliliter (ng/ml) on stimulation or a basal (unstimulated) serum growth hormone level greater than 5 ng/ml; **AND**
- Indications of secondary IGF-1 deficiency, such as growth hormone deficiency, malnutrition, hypothyroidism, and chronic treatment with pharmacological doses of anti-inflammatory steroids have been ruled out. (normal thyroid stimulating hormone [TSH] level is required); **AND**

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- Patient does NOT have closed epiphyses; **AND**
- Patient does NOT have active or suspected neoplasia.

Renewal:

- Patient has a diagnosis of severe primary IGF-1 deficiency; **AND**
- Patient does NOT have closed epiphyses; **AND**
- Patient does NOT have active or suspected neoplasia; **AND**
- Patient's height has increased by ≥ 4 cm/year in the most recent year.
  *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

Growth Hormone Gene Deletion with Neutralizing Antibodies to Growth Hormone

Patient Selection Criteria

Coverage eligibility for growth hormone gene deletion with neutralizing antibodies to growth hormone with mecasermin (Increlex) will be considered for coverage eligibility when **ALL** of the following criteria are met:

Initial:

- Patient is 2 years of age or older; **AND**
- Patient has a growth hormone gene deletion and has developed neutralizing antibodies to growth hormone; **AND**
- Patient does NOT have closed epiphyses; **AND**
- Patient does NOT have active or suspected neoplasia.

Renewal:

- Patient has a growth hormone gene deletion and has developed neutralizing antibodies to growth hormone; **AND**
- Patient does NOT have closed epiphyses; **AND**
- Patient does NOT have active or suspected neoplasia; **AND**
- Patient's height has increased by ≥ 4 cm/year in the most recent year.
  *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

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When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the continued use of mecasermin (Increlex) when the patient's height has NOT increased by ≥ 4 cm/year to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of mecasermin (Increlex) when patient selection criteria are not met (with the exception of those denoted as **not medically necessary****) to be **investigational.***

Background/Overview

Increlex contains human IGF-1 produced by rDNA technology. Insulin-like growth factor-1 is a key hormonal mediator on statural growth. 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, which is homologous to the insulin receptor, is activated by IGF-1, leading to intracellular signaling which stimulates multiple processes resulting in statural 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. Increlex is not intended for use in patients with secondary forms of insulin like growth factor deficiency per the U.S. Food and Drug Administration (FDA) such as growth hormone deficiency, malnutrition, hypothyroidism or chronic treatment with pharmacologic doses of anti-inflammatory steroids. Thyroid and nutritional deficiencies should be corrected before initiating Increlex treatment. Increlex is supplied as a multiple dose glass vial at a concentration of 10 mg per mL (40 mL vial). The recommended dose (to be given subcutaneously) is 0.04 to 0.08 mg/kg twice daily. If well tolerated for at least one week, the dose may be increased by 0.04 mg/kg/dose to the maximum dose of 0.12 mg/kg given twice daily.

Primary IGF-1 deficiency afflicts an estimated 30,000 children evaluated for short stature in the United States. Primary IGF-1 deficiency is a growth hormone-resistant state characterized by lack

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of IGF-1 production in the presence of normal or elevated levels of endogenous growth hormone. Approximately 6,000 children suffer from a more severe form of this condition, called severe primary IGF-1 deficiency. Severe primary IGF-1 deficiency includes persons with mutations in the growth hormone receptor (GHR), post-GHR signaling pathway and IGF-1 gene defects; these persons are not growth hormone deficient, and therefore, they cannot be expected to respond adequately to exogenous growth hormone treatment.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Increlex was approved in 2005 by the FDA for the long-term treatment of growth failure in children with severe primary IGF-1 deficiency or with growth hormone gene deletion who have developed neutralizing antibodies to growth hormone.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The FDA's approval of IGF-1 therapy was based upon the results of five Phase III clinical studies, with subcutaneous doses of IGF-1 generally ranging from 0.06 to 0.12 mg/kg administered twice daily for the treatment of short stature caused by severe primary IGF-1 deficiency (n = 71). Patients were enrolled in the trials on the basis of extreme short stature, slow growth rates, low IGF-1 serum concentrations and normal growth hormone secretion. In clinical studies, normal growth hormone was defined as serum growth hormone level (peak level) of greater than 10 ng/ml (20 mU/liter) after stimulation with insulin, levodopa, arginine, propranolol, clonidine or glucagons, or an unstimulated (basal) serum growth hormone level of greater than 5 ng/ml. Data from these five clinical studies were pooled for global efficacy and safety analysis. Of these children, 61 completed at least one year of rhIGF-1 replacement therapy, which is the generally accepted minimum length of time required to adequately measure growth responses to drug therapy. Data from the study, presented during the 86th Annual Meeting of The Endocrine Society, demonstrated a statistically significant increase ($p < 0.001$) in growth rate over an eight-year period in response to therapy. Compared to pretreatment

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growth patterns, on average, children gained an additional inch per year for each year of therapy over the course of eight years. Patients were treated for an average of 3.9 years, with some patients being treated up to 11.5 years. An analysis of safety in the study concluded that long-term treatment with rhIGF-1 appears to be well tolerated. Side effects were mild to moderate in nature and included hypoglycemia, injection site lipohypertrophy and tonsillar hypertrophy. Intracranial hypertension occurred in three subjects. Funduscopic examination is recommended at the initiation and periodically during the course of IGF-1 therapy. Symptomatic hypoglycemia was generally avoided when a meal or snack was consumed either shortly before or after the administration of IGF-1.

In regards to continuation therapy, according to the package insert studies, the mean height velocity per year with treatment was 8.0 centimeters in the first year and at least 4 centimeters per year thereafter.

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Policy History

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Louisiana

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12/06/2006	Medical Director review
12/20/2006	Medical Policy Committee approval
12/12/2007	Medical Director review
12/19/2007	Medical Policy Committee approval
12/03/2008	Medical Director review
12/17/2008	Medical Policy Committee approval. No change to coverage eligibility.
04/02/2009	Medical Director review.
04/15/2009	Medical Policy Committee approval. Removed criteria bullet, "Diagnosis has been made by an endocrinologist". Added criteria bullet "Child does not have active or suspected neoplasia".
04/08/2010	Medical Policy Committee approval
04/21/2010	Medical Policy Implementation Committee approval. No change to coverage eligibility.
04/07/2011	Medical Policy Committee review
04/13/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/12/2012	Medical Policy Committee review
04/25/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/04/2013	Medical Policy Committee review
04/24/2013	Medical Policy Implementation Committee approval. Added the drug name to the criteria of the policy. Clarified wording in the Patient Selection. Added criteria for the patient not having closed epiphyses (was already being asked on the call tree).
04/03/2014	Medical Policy Committee review
04/23/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/02/2015	Medical Policy Committee review
04/20/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/07/2016	Medical Policy Committee review
04/20/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
04/06/2017	Medical Policy Committee review

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04/19/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/05/2018	Medical Policy Committee review
04/18/2018	Medical Policy Implementation Committee approval. Incorporated renewal criteria. Separated the FDA approved indications.
04/04/2019	Medical Policy Committee review
04/24/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/02/2020	Medical Policy Committee review
04/08/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/01/2021	Medical Policy Committee review
04/14/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/07/2022	Medical Policy Committee review
04/13/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/06/2023	Medical Policy Committee review
04/12/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 04/2024

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J2170
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);

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2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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