BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

Treatment of IGF-1 Deficiency

Policy # 00209
Original Effective Date: 12/20/2006
Current Effective Date: 04/23/2014

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 treatment in children with severe primary insulin-like growth factor-1 deficiency (IGFD) OR with growth hormone (GH) gene deletion that have developed neutralizing antibodies to growth hormone (GH) to be **eligible for coverage.**

Patient Selection Criteria
Treatment of IGF-1 deficiency with mecasermin (Increlex) will be considered for coverage eligibility when all of the following criteria are met:

- Child has a diagnosis of severe primary insulin-like growth factor-1 deficiency (IGFD) OR growth factor gene deletion that has developed neutralizing antibodies to growth hormone (GH); and
- Child's height standard deviation is less than or equal to -3.0; and
- Child's basal insulin-like growth factor-1 (IGF-1) standard deviation is less than or equal to -3.0; and
- Child has normal or elevated growth hormone (GH) EXCEPT for children with growth hormone (GH) gene deletion who have developed neutralizing antibodies to growth hormone (GH). Normal or elevated growth hormone (GH) is defined as greater than 10 nanograms per milliliter (ng/ml) on stimulation or basal (unstimulated) serum growth hormone (GH) level greater than 5 ng/ml; and
- Indications of secondary insulin-like growth factor-1 deficiency (IGFD), such as growth hormome (GH) 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
- Child is not currently taking growth hormones (GHs) or corticosteroids; and
- Child does not have closed epiphyses; and
- Child does not have active or suspected neoplasia.

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 replacement therapy with mecasermin (Increlex) when patient selection criteria are not met to be **investigational.***

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Background/Overview

Primary insulin growth factor deficiency (IGFD) afflicts an estimated 30,000 children evaluated for short stature in the United States. Primary IGFD is a GH-resistant state characterized by lack of insulin-like growth factor-1 (IGF-1) production in the presence of normal or elevated levels of endogenous GH. Approximately 6,000 children suffer from a more severe form of this condition, called severe primary IGFD. Severe primary IGFD includes persons with mutations in the growth hormone receptor (GHR), post-GHR signaling pathway and IGF-1 gene defects; these persons are not GH deficient, and therefore, they cannot be expected to respond adequately to exogenous GH treatment.

Increlex (mecasermin [recombinant deoxyribonucleic acid/rDNA origin] injection) contains human IGF-1 produced by rDNA technology. Insulin-like growth factor-1 is a key hormonal mediator on statural growth. 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 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 IGFD per U.S. Food and Drug Administration (FDA) such as GH deficiency, malnutrition, hypothyroidism or chronic treatment with pharmacologic doses of anti-inflammatory steroids. Thyroid and nutritional deficiencies should be corrected before initiating Increlex treatment.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration
Increlex was approved in 2005 and is an aqueous solution for injection containing human insulin-like growth factor-1 (rhIGF-1) produced by recombinant DNA technology. Insulin-like growth factor-1 (IGF-1) consists of 70 amino acids in a single chain with 3 intramolecular disulfide bridges and a molecular weight of 7649 daltons. Increlex is approved by the FDA for the long-term treatment of growth failure in children with severe primary IGD or with GH gene deletion who have developed neutralizing antibodies to GH.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated 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 IGFD (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 GH secretion. In clinical studies, normal GH was defined as serum GH 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 GH 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 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.

Similar results were obtained using a prospective open-label multicenter study conducted to evaluate the safety and efficacy of Iplex. Thirty-six subjects were enrolled on the basis of extreme short stature and low IGF-1 and IGFBP3 serum concentrations and normal GH secretion.

References

1. American Society of Health-System Pharmacists. AHFS Drug Information 2010. Mecasermin.
2. Food and Drug Administration. Labeling of the Drug. Mecasermin. February 2012.www.fda.gov
3. Clark RG. Recombinant human insulin-like growth factor I (IGF- I): Risks and benefits of normalizing blood IGF-I concentrations. Horm Res. 2004; 62 Suppl 1:93-100.
4. Savage MO, Camacho-Hubner C, Dunger DB. Therapeutic applications of the insulin-like growth factors. Growth Horm IGF Res.2004; 14(4):301-308.
5. Ranke MB. Insulin-like growth factor-I treatment of growth disorders, diabetes mellitus and insulin resistance. Trends Endocrinol Metab. 2005; 16(4):190-197.
6. U.S. National Institutes of Health (NIH), National Library of Medicine (NLM). Prepubertal children with growth failure associated with primary insulin-like growth factor-1 (IGF-1) deficiency. Clinical Trials Listing. Bethesda, MD: NIH; July 2005. Available at: http://www.clinicaltrials.gov
7. Tercica Inc. Increlex® (mecasermin) Product Information. Brisbane, CA: Tercica Inc. 2/2011.
8. Iplex (mecasermin rinfabate) Product information. INSMED Inc. 02/2007.

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 2013 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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Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

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-9 Diagnosis	253.3
ICD-9 Procedure	No codes

Policy History

Original Effective Date: 12/20/2006
Current Effective Date: 04/23/2014

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.

Next Scheduled Review Date: 04/2015

*****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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
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: 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.