



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Effective Date 5/15/2011
Next Review Date.....5/15/2012
Coverage Policy Number 6107

Subject **Mecasermin (Increlex®)**

Table of Contents

Coverage Policy	1
General Background	2
Coding/Billing Information	3
References	3
Policy History	4

Hyperlink to Related Coverage Policies

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

CIGNA covers mecasermin (Increlex®) as medically necessary for the treatment of growth failure in children with severe primary insulin-like growth factor-1 (IGF-1) deficiency OR with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH and all of the following:

- height is three standard deviations (SD) or more below normal
- basal IGF-1 level is three standard deviations (SD) or more below normal
- normal or elevated growth hormone (GH)

CIGNA does not cover mecasermin (Increlex®) for treatment of secondary forms of IGF-1 deficiency due to ANY of the following because it is considered experimental, investigational or unproven (this list may not be all-inclusive):

- GH deficiency
- malnutrition
- hypothyroidism

- chronic treatment with pharmacologic doses of anti-inflammatory drugs

Note: Severe primary IGF-1 deficiency includes patients with mutations in the GH receptor (GHR), post-GHR signaling pathway, and IGF-1 gene defects.

Coverage for continuation of therapy requires meeting current initial use criteria and evidence of a beneficial response as shown by growth curve chart.

When coverage is available and medically necessary, the dosage, frequency, site of administration, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to mecasermin (Increlex[®]) therapy.

FDA Approved Indications

Severe Primary IGF-1 Deficiency (Primary IGFD)

Increlex is indicated for the treatment of growth failure in children with severe primary IGF-1 deficiency or growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH.

FDA Recommended Dosing

Preprandial glucose monitoring is recommended at treatment initiation and until a well tolerated dose is established. If frequent symptoms of hypoglycemia or severe hypoglycemia occur, preprandial glucose monitoring should continue. The dosage of Increlex should be individualized for each patient. The recommended starting dose of Increlex is 0.04 to 0.08 mg/kg (40 to 80 micrograms/kg) twice daily by subcutaneous injection. If well-tolerated for at least one week, the dose may be increased by 0.04 mg/kg per dose, to the maximum dose of 0.12 mg/kg given twice daily. Doses greater than 0.12 mg/kg given twice daily have not been evaluated in children with Primary IGFD and, due to potential hypoglycemic effects, should not be used. If hypoglycemia occurs with recommended doses despite adequate food intake, the dose should be reduced. Subsequent doses of Increlex should never be increased to make up for one or more omitted dose.

Drug Availability

Increlex is supplied as a 10 mg per mL sterile solution in multiple dose glass vials (40 mg per vial). After opening, vials of Increlex are stable for 30 days after initial vial entry when stored at 2° to 8°C (35° to 46°F). Protect from direct light.

General Background

Pharmacology

Mecasermin contains recombinant deoxyribonucleic acid (DNA)-engineered human insulin-like growth factor-1 (rhIGF-1). It is designed to replace natural IGF-1 in pediatric patients who are deficient, promoting normalized statural growth. Patients with severe primary IGF-1 deficiency (Primary IGFD) fail to produce adequate levels of IGF-1, due to disruption of the growth hormone (GH) pathway used to promote IGF-1 release (possible GH pathway disruptions include mutations in the GH receptor [GHR], post-GHR signaling pathway, and IGF-1 gene defects). The active ingredient of mecasermin is identical to the natural hormone IGF-1, which the body normally produces in response to stimulation by GH. IGF-1 is the direct mediator of growth hormone's effect on statural growth and must be present in order for children's bones, cartilage and organs to grow normally. Without adequate IGF-1, children cannot achieve a height within the normal range.

Severe Primary IGF-1 deficiency (IGFD) is defined by the following:

- height standard deviation score ≤ -3.0 and
- basal IGF-1 standard deviation score ≤ -3.0 and
- normal or elevated growth hormone (GH)

Severe Primary IGFD can lead to a range of other metabolic disorders, including lipid abnormalities, decreased bone density, obesity, and insulin resistance.

Mecasermin is the first product based on the IGF-1 protein approved by the FDA specifically indicated for the long-term treatment of growth failure in pediatric patients with Primary IGFD or with GH gene deletion who have developed neutralizing antibodies to GH. Mecasermin is not indicated to treat secondary IGFD resulting from GH deficiency, malnutrition, hypothyroidism or chronic treatment with pharmacologic doses of anti-inflammatory steroids. Thyroid and nutritional deficiencies should be corrected before initiating mecasermin treatment. Mecasermin is not a substitute for GH treatment. Mecasermin was approved as part of the FDA's orphan drug program, in which drugs designed to treat rare conditions or those with few available therapies are given expedited approval.

In blood, IGF-1 is bound to six IGF binding proteins, with > 80% bound as a complex with IGFBP-3 and an acid-labile subunit. At dose of 0.045 mg/kg, the total IGF-1 volume of distribution after subcutaneous administration in subjects with severe primary IGFD is estimated to be 0.257 (\pm 0.073) L/kg, and it is estimated to increase as the dose of mecasermin increases. IGF-1 is metabolized by both the liver and the kidney. The mean half-life after single subcutaneous administration of 0.12 mg/kg mecasermin in pediatric subjects with severe Primary IGFD is estimated to be 5.8 hours.

Clinical Efficacy

Approval of mecasermin was based on five clinical trials of the drug: four were open-label studies, and one was double-blind and placebo-controlled. The studies enrolled a total of 71 children suffering from extreme short stature; all children exhibited symptoms of Primary IGFD, including slow growth rates, low IGF-1 serum concentrations, and normal growth hormone secretion. Data from these five clinical studies were presented during the 86th Annual Meeting of The Endocrine Society (June, 2004). A total of 61 children 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. Results 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 4.4 years, with some patients being treated up to 11.5 years. An analysis of safety showed that long-term treatment with mecasermin has an acceptable safety profile and appears to be well tolerated. Side effects were mild to moderate in nature and included hypoglycemia (42%), injection site lipohypertrophy, and tonsillar hypertrophy (15%). Funduscopic examination is recommended at the initiation and periodically during the course of Increlex therapy.

Adverse Reactions / Contraindications

The most common adverse events of mecasermin reported are hypoglycemia, lipohypertrophy and tonsillar hypertrophy. Mecasermin is contraindicated in patients with closed epiphyses, active or suspected neoplasia and allergy to mecasermin (IGF-1) or any of the inactive ingredients in this product. Intravenous administration of mecasermin is also contraindicated.

Coding/Billing Information

Note: This section is not in use.

References

1. Clark RG. Recombinant human insulin-like growth factor I (IGF-I): risks and benefits of normalizing blood IGF-I concentrations. *Frontiers of Hormone Research* 2004; 62 Suppl 1:93-100.

2. Guevara-Aguirre J, Vasconez O, Martinez V, et al. A randomized, double blind, placebocontrolled trial on safety and efficacy of recombinant human insulin-like growth factor-I in children with growth hormone receptor deficiency. *J Clin Endocrinol Metab.* 1995;80(4):1393-1398.
3. McEvoy GK, ed. *AHFS 2011 Drug Information.* Bethesda, MD: American Society of Health-Systems Pharmacists, Inc; 2011.
4. Rosenfeld RG, Rosenbloom AL, Guevara-Aguirre J. Growth hormone (GH) insensitivity due to primary GH receptor deficiency. *Endocr.* 1994;15(3):369-390.
5. Tercica, Inc. *Increlex® (mecasermin) package insert.* Brisbane, CA: Tercica, Inc. Feb 2011.
6. U.S. National Institutes of Health. *Clinical Trials. Prepubertal Children with Growth Failure Associated with Primary Insulin-Like Growth Factor-1 (IGF-1) Deficiency.* Available at: <http://www.clinicaltrials.gov/ct/gui/show/NCT00125164>. Accessed December 9, 2005.

Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	3/15/2008	6107	Mecasermin (Increlex®)
Great-West Healthcare	12/2007	P06.100.1	Increlex

“CIGNA”, “CIGNA HealthCare” and the “Tree of Life” logo are registered service marks of CIGNA Intellectual Property, Inc., licensed for use by CIGNA Corporation and its operating subsidiaries. All products and services are provided by such operating subsidiaries and not by CIGNA Corporation. Such operating subsidiaries include Connecticut General Life Insurance Company, CIGNA Health and Life Insurance Company, CIGNA Behavioral Health, Inc., CIGNA Health Management, Inc., and HMO or service company subsidiaries of CIGNA Health Corporation and CIGNA Dental Health, Inc. In Arizona, HMO plans are offered by CIGNA HealthCare of Arizona, Inc. In

California, HMO plans are offered by CIGNA HealthCare of California, Inc. In Connecticut, HMO plans are offered by CIGNA HealthCare of Connecticut, Inc. In North Carolina, HMO plans are offered by CIGNA HealthCare of North Carolina, Inc. In Virginia, HMO plans are offered by CIGNA HealthCare Mid-Atlantic, Inc. All other medical plans in these states are insured or administered by Connecticut General Life Insurance Company or CIGNA Health and Life Insurance Company.