Corporate Medical Policy

Treatment for Severe Primary IGF-1 Deficiency

File Name:	treatment_for_severe_IGF-1_deficiency
Origination:	2/2006
Last CAP Review:	6/2019
Next CAP Review:	6/2020
Last Review:	6/2019

Description of Procedure or Service

Insulin-like growth factor-I (IGF-I) deficiency has also been called growth hormone insensitivity syndrome or growth hormone resistance syndrome. IGF-I deficiency was first described in a severe form, due to a block of growth hormone action at the level of the growth hormone receptor. As a consequence of this abnormal growth hormone receptor function, little IGF-I is produced. The ensuing severe IGF-I deficiency causes a type of growth failure that resembles the growth failure seen in patients with severe growth hormone deficiency. However, patients with severe IGF-I deficiency have normal concentrations of growth hormone. This primary form of severe IGF-I deficiency is differentiated from secondary forms of IGF-I deficiency or growth hormone insensitivity, caused by, for example, malnutrition, GH deficiency or hypothyroidism. Children with untreated severe primary IGFD have extremely short stature and may have an increased risk of other metabolic disorders such as lipid abnormalities, decreased bone density, insulin resistance and obesity.

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

- Height standard deviation score less than or equal to -3.0 and
- Basal IGF-1 standard deviation score less than or equal to -3.0 and
- Normal or elevated growth hormone (GH)

The FDA has approved two protein replacements for the IGF-1 deficiency to be used only in children with severe primary insulin-like growth factor deficiency or in children who have growth hormone gene deletion and have developed neutralizing antibodies to growth hormone. These children must have had all secondary causes of insulin-like growth factor deficiency ruled out. Secondary insulin-like growth factor deficiency may be caused by various other conditions such as growth hormone deficiency, malnutrition, hypothyroidism or chronic treatment with anti-inflammatory steroids.

Increlex® (mecasermin, rDNA origin) is a twice a day non-glycosylated human IGF-1 replacement injection that was developed by Tercica Inc. of Brisbane, CA, now Ipsen Biopharmaceuticals Inc. It was approved under the 505b requirements of the FDA in August 2005 for the treatment of severe primary IGF-1 deficiency or growth hormone gene deletion in those who have developed neutralizing antibodies to growth hormone. On April 25, 2013, Ipsen issued a statement that supplies of Increlex® would be interrupted in June 2013, and that re-supply was not expected before the end of 2013. On May 13, 2014, Ipsen announced that a supply of Increlex® will be available in the United States starting June 2, 2014.

IPLEX™ developed by Insmed Inc., Glen Allen VA (formerly called SomatoKine) was approved in December 2005 as the first once a day treatment for severe primary IGF-1 deficiency or growth hormone gene deletion in those who have developed neutralizing antibodies to growth hormone. The generic name for this drug is mecasermin rinfabate and is made of recombinant

insulin-like growth factor I (rhIGF-1) and insulin-like growth factor binding protein-3 (rhIGFBP-3). Insmed Inc. announced in 2012 that drug supplies of IPLEX™ were exhausted and that the company no longer has protein development capability nor the in-house capability to manufacture IPLEX.

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for treatment of Severe Primary IGF-1 Deficiency when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

BCBSNC will provide coverage for treatment of growth hormone gene deletion in children who have developed neutralizing antibodies to growth hormone when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Treatment of Severe Primary IGF-1 Deficiency is covered

Treatment in children with severe primary insulin-like growth factor-1 deficiency or with growth hormone gene deletion who have developed neutralizing antibodies to growth hormone may be considered medically necessary when all the following criteria are met:

- The child's height standard deviation is less than or equal to -3.0 for the child's age and sex (documentation should include sequential growth chart data utilizing clinical growth charts which are consistent with those available through the CDC at http://www.cdc.gov/growthcharts/clinical_charts.htm); and
- The child's basal IGF-1 standard deviation is less than or equal to -3.0; and
- The child has normal or elevated growth hormone (GH) except for children with growth hormone gene deletion; and
- All indications of secondary IGF-1 deficiency have been ruled out such as growth hormone deficiency, malnutrition, and hypothyroidism; and
- The diagnosis has been made by an endocrinologist; and
- The child is not currently taking growth hormone or corticosteroids.

When Treatment of Severe Primary IGF-1 Deficiency is not covered

Treatment of severe primary IGF-1 deficiency is not covered when the criteria stated above are not met; or

- The child's epiphyses (bone growth plates are closed); or

- The child has an active or suspected neoplasia; or
- The child has an allergy to mecasermin (IGF-1) or any of the other ingredients in the medication; or
- The child has growth failure due to other causes; including idiopathic (i.e. of unknown origin) short stature; or
- The child has a chronic illness such as diabetes, cystic fibrosis, etc.; or
- The child is less than 2 years old.

Policy Guidelines

Treatment for insulin-like growth factor-1 deficiency should be administered at approximately the same time every day. It should be scheduled for administration either just before a meal or just after a meal due to its hypoglycemic (low blood sugar) effects.

Dosing should be initiated gradually until the tolerance level can be established. The child's endocrinologist will monitor the child's growth and dosage at least 4 times a year.
Swelling of the tonsils and adenoids has been associated with this treatment and should be reported to the physician as soon as possible.

Patients and caregivers should be instructed in the proper technique of administration, disposal of needles and understand how to recognize the signs and symptoms of any adverse reaction to the therapy.

Treatment should be discontinued once fusion of the epiphysis has occurred. If growth in height velocity does not increase by 2cm in the first year the physician should re-evaluate the cause of growth failure. Response in growth velocity will decrease with time.

Neither Increlex nor IPLEX are intended for use in patients with secondary forms of Insulin Growth-Like Factor 1 Deficiency, such as growth hormone deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of aniti-inflammatory steroids. Thyroid and nutitional deficiencies should be corrected before initiating Increlex treatment. Increlex is not a substitute to growth hormone for approved growth hormone indications.

This drug may require prior approval.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: *J2170*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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FDA Approval Letter for IPLEX. Retrieved 1/9/06 from http://www.fda.gov/cder/foi/appletter/2005/021884ltr.pdf

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Specialty Matched Consultant Advisory Panel - 5/2006

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FDA Approved Package Insert for Increlex. Retrieved 6/14/12 from http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021839s007lbl.pdf

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Cohen, J., Blethen, S., Kuntze, J., Smith, S. L., Lomax, K. G., & Mathew, P. M. (2014). Managing the Child with Severe Primary Insulin-Like Growth Factor-1 Deficiency (IGFD): IGFD Diagnosis and Management. *Drugs in R&D*, *14*(1), 25–29. http://doi.org/10.1007/s40268-014-0039-7

Grimberg A, DiVall S, Polychronakos C, et al. On behalf of the Drug and Therapeutics Committee and Ethics Committee of the Pediatric Endocrine Society. Guidelines for Growth Hormone and Insulin Like Growth Factor-I Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-I Deficiency. Horm Res Paediatr Nov 2016; 86: 361–397.

Ipsen Biopharmaceuticals, Inc. Increlex (mecasermin [rDNAorigin] injection) for subcutaneous use. Prescribing Information. Basking Ridge, NJ:Ipsen; Revised 3/2016. Available at: https://www.ipsenus.com/pdfs/Increlex_Full_Prescribing_Information.pdf. Accessed June 2018.

Specialty Matched Consultant Advisory Panel 6/2018

Specialty Matched Consultant Advisory Panel 6/2019

Policy Implementation/Update Information

02/16/06 New policy implemented. Effective 2/16/2006.

6/19/06 Specialty Matched Consultant Advisory Panel review 5/18/2006. Added additional information to "When Growth Hormone is covered" section under the first bullet to indicate "(documentation should include sequential growth chart data utilizing clinical growth charts which are consistent with those available through the CDC at http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical_charts.htm)". References added.

6/30/08 Specialty Matched Consultant Advisory Panel review 5/29/08. No change to policy statement. References added.

8/25/08 Added HCPCS code J2170 to "Billing/Coding" section. Removed statement indicating; "Physicians will typically submit claims utilizing J3490 or J3590" from "Billing/Coding" section since there is a specific code for this biologic. (btw)

6/22/10 Policy Number(s) removed (amw)

9/28/10 Specialty Matched Consultant Advisory Panel review 8/2010. References updated

8/30/11 Specialty Matched Consultant Advisory Panel review 7/27/11. No change to coverage criteria. Policy accepted as written. (adn)

8/7/12 Specialty Matched Consultant Advisory Panel review 7/18/12. References updated. No change to policy statement. (sk)

7/30/13 Specialty Matched Consultant Advisory Panel review 7/17/13. References updated. Information regarding 2013 interruption of supply added to Description section. No change to policy statement. (sk)

8/12/14 Specialty Matched Consultant Advisory Panel review 7/29/14. References updated. Information regarding 2014 resupply added to Description section. No change to policy statement. (sk)

9/1/15 Specialty Matched Consultant Advisory Panel review 7/29/15. (sk)

8/30/16 Specialty Matched Consultant Advisory Panel review meeting 7/27/2016. No change to policy. (an)

8/11/17 Updated Decription and Policy Guidelines sections. References added. Specialty Matched Consultant Advisory Panel review 7/26/2017. (an)

7/13/18 Minor typographical and grammatical changes made for clarity. Reference added. Specialty Matched Consultant Advisory Panel review 6/27/2018. No change to policy statement. (krc)

7/16/19 Specialty Matched Consultant Advisory Panel review 6/19/2019. No change to policy statements. (krc)