Mecasermin; Recombinant Human Insulin-Like Growth Factor-1 (Increlex™)

Number 5.01.519*
Effective Date January 1, 2017
Revision Date(s) 12/13/16; 10/28/16; 05/12/15; 04/14/14; 04/08/13; 04/10/12; 03/08/11; 06/08/10; 07/14/09; 08/12/08
Replaces N/A

*This policy is managed/administered through the Pharmacy benefit.

Policy

Mecasermin may be considered medically necessary for its FDA-approved indication for the treatment of growth failure in children. (See Policy Guidelines for criteria.)

Use of mecasermin to treat all other indications is considered investigational, including but not limited to:

- Less severe forms of IGF-1 deficiency,
- Secondary forms of IGF-1 deficiency (GH deficiency, malnutrition, hypothyroidism, or chronic corticosteroid therapy),
- Growth failure due to other identifiable causes (e.g., Prader-Willi syndrome, Turner syndrome, Noonan syndrome),
- Diabetes mellitus,
- AIDS-associated wasting,
- Women with anorexia nervosa,
- Obesity in postmenopausal women,
- Advanced chronic renal failure,
- Cystic fibrosis,
- Amyotrophic lateral sclerosis (ALS),
- Severe head injury, or
- Use in combination with GH.

The use of Mecasermin for idiopathic short stature is considered not medically necessary.

Note: Policy and guidelines for the use of growth hormone (somatropin) are contained in a separate medical policy. (See Related Policies)

Related Policies

5.01.500 Growth Hormone Therapy
Policy Guidelines

Up to 12 months of coverage may be authorized for patients meeting *ALL* the following criteria:

- Diagnosis of growth failure due to severe primary IGF-1 deficiency (growth hormone receptor mutations [e.g., Laron syndrome], post-growth hormone receptor signaling pathway mutations, or IGF-1 gene defects) OR growth hormone (GH) gene deletion with neutralizing antibodies to GH.
- The patient’s height is below the 3rd percentile on growth charts for their age and gender related height. (i.e., height is greater than 2.25 standard deviations below the mean).
- The patient’s baseline IGF-1 concentration is ≥ 3 SD below normal (based on lab reference range for age and sex).
- The patient’s baseline growth hormone concentration is normal or elevated based on at least one stimulation test.
- Bone age is < 13 years for females or < 15 years for males.

Coverage may be reauthorized for up to 12 months in patients previously receiving mecasermin if *ALL* the following criteria are met:

- Growth velocity is ≥ 2.5 cm / year AND
- Bone age is ≤ 14 years for females or ≤ 16 years for males.

Coding

<table>
<thead>
<tr>
<th>HCPCS</th>
<th>Description</th>
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<tr>
<td>J2170</td>
<td>Injection, Mecasermin (Increlex™), 1 mg</td>
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Description

Mecasermin is produced by recombinant DNA technology and has an identical amino acid sequence to endogenous human insulin-like growth factor-1 (IGF-1). Mecasermin is approved for the treatment of growth failure in children with severe primary IGF-1 deficiency (growth hormone receptor mutations, post-growth hormone receptor signaling pathway mutations, or IGF-1 gene defects) and in those with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH. It is estimated that 30,000 to 60,000 children in the US and Western Europe have primary IGF-1 deficiency. Of these individuals, approximately 20%, or 6,000 to 12,000, have severe primary IGF-1 deficiency.

The current somatomedin hypothesis of statural growth involves GH release by the anterior pituitary that is controlled in a stimulatory fashion by GH-releasing hormone and in an inhibitory fashion by somatostatin. Circulating GH then binds to GH receptors in the liver resulting in production of IGF-1, IGF binding proteins, and acid labile subunit. Virtually all circulating IGF-1 is bound to IGF binding proteins and acid labile subunit. This tertiary complex reduces extravascular passage and increases the half-life of IGF-1. Circulating IGF-1 then stimulates multiple processes leading to statural growth and metabolic changes that support this growth. GH also stimulates prechondrocyte differentiation and local production of IGF-1 (autocrine and paracrine) that in turn stimulate clonal expansion, maturation of chondrocytes, and growth. Approximately 15% to 20% of growth is thought to be the result of this local effect of GH versus that resulting from circulating hepatic IGF-1.

Mecasermin is not a substitute for GH treatment and is not indicated for the treatment of secondary IGF deficiency resulting from GH deficiency, malnutrition, hypothyroidism or chronic corticosteroid therapy.

Scope

Medical policies are systematically developed guidelines that serve as a resource for Company staff when
determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

**Benefit Application**

Enrollees receiving mecasermin should be reviewed on at least an annual basis to assure proper application of benefits.

Mecasermin may be covered under the drug or medical benefit.

**Rationale**

Severe primary IGF-1 deficiency or GH gene deletion with neutralizing antibodies to GH are rare disorders currently without therapeutic alternatives. A small quantity of low quality evidence consistently supports the efficacy and safety of mecasermin for the treatment of children with these conditions to increase statural growth. According to the FDA review report for mecasermin, approval was granted based on four small (n= 6 to 23) and one long-term clinical studies (4 open-label and 1 double-blind placebo-controlled). Because of the rarity of severe primary IGF-1 deficiency, the patients and data from the 4 smaller studies were “rolled into” the larger long-term study.

Chernausek et al. reported long-term efficacy and safety results from a multicenter, open-label, uncontrolled study in 76 children with severe IGF-1 deficiency associated with growth hormone insensitivity. It should be noted that the inclusion criteria used for the study were less stringent than defined by the FDA for identification of patients with severe deficiency. A total of 76 patients initially received mecasermin 0.04-0.08 mg/kg SC twice daily, and if the dose was tolerated for at least a week without hypoglycemic episodes it was titrated by 0.04 mg/kg/dose to 0.12 mg/kg twice daily. The primary study endpoint was change from baseline in height velocity. During the first year of treatment, height velocity increased from a mean baseline of 2.8 cm/yr to 8.0 cm/yr, in 59 evaluable patients (P<0.0001). Height velocity was lower in subsequent years, but remained above baseline for up to 8 years. Height velocity was dose dependent or fastest in those receiving the maximal dose (0.012 mg/kg twice daily). Bone age increased modestly an average of 5.8 yrs over 5.1 years (P=0.01).

A smaller (n=8) open-label uncontrolled study in which patients with severe primary IGF-1 deficiency were treated with mecasermin 0.08-0.12 mg/kg twice daily as tolerated for up to 7.5 years showed similar results. During the first year of treatment, height velocity increased from a mean baseline of 4.0 cm/yr to 9.3 cm/yr (mean height velocity SDS +3.8) and 6.2 cm/yr (mean height velocity SDS +0.5) in the second year of treatment. Mean change in height velocity SDS was +1.4 after 6-7 years of therapy.

The most commonly reported adverse events reported with use of mecasermin at recommended doses in children with severe primary IGF-1 deficiency were hypoglycemia, lymphoid tissue hypertrophy, and injection-site lipohypertrophy. Hypoglycemia was minimized by consumption of a meal or a snack within 20 minutes of administration of the drug, and lipohypertrophy was minimized by rotation of the injection site with each dose. Rarely, intracranial hypertension was also reported.

Labeled contraindications include closed epiphyses, suspected or active neoplasia, intravenous (IV) administration, and hypersensitivity to any component. Labeled warnings and precautions include that the product contains benzyl alcohol as a preservative, which has been associated with neurological toxicity in neonates; sensitivity reactions have been reported; treatment should be directed by physicians experienced in the diagnosis and management of patients with growth disorders; mecasermin should be administered shortly (± 20 min) before or after a meal or snack because mecasermin has insulin-like hypoglycemic effects; hypertrophy of lymphoid tissue with complications (e.g., snoring, sleep apnea) has been observed; intracranial hypertension has been reported; rapid growth may cause slipped capital femoral epiphysis or worsen scoliosis; and allergic reactions have been reported.
The recommended starting dose of mecasermin is 0.04-0.08 mg/kg subcutaneously twice daily. If well-tolerated (without hypoglycemia) for at least one week, the dose may be increased in 0.04 mg/kg/dose increments up to the maximum dose of 0.12 mg/kg SC twice daily. Doses greater than 0.12 mg/kg twice daily have not been studied in children with primary IGF-1 deficiency and should not be used to avoid potential hypoglycemia.

2009 Update
A literature search of the MEDLINE database conducted from August 2008 through June 2009 did not identify any additional published studies that would prompt reconsideration of the policy statements.

2010 Update
A literature search of the MEDLINE database conducted from July 2009 through April 2010 did not identify any additional published studies that would prompt reconsideration of the policy statements.

2011 Update
A literature search of the MEDLINE database conducted from May 2010 through January 2011 did not identify any additional published studies that would prompt reconsideration of the policy statements.

2012 Update
A literature search of the MEDLINE database conducted from January 2011 through February 2012 did not identify any additional published studies that would prompt reconsideration of the policy statements.

2013 Update
A literature search of the MEDLINE database conducted from January through December 2012 did not identify any additional published studies that would prompt reconsideration of the policy statements.

2014 Update
A literature search conducted from January 2013 through February 2014 found no new evidence that would change this policy.

2015 Update
A literature search conducted from January 2014 through March 2015 found no new evidence that would change this policy.

2016 Update
A literature search conducted from July 1, 2015 through December 5, 2016 found no new evidence that would change this policy.

References


Appendix

N/A

History

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<th>Date</th>
<th>Reason</th>
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<tbody>
<tr>
<td>08/12/08</td>
<td>Add to Prescription Drug Section - New PR Policy.</td>
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<tr>
<td>07/14/09</td>
<td>Replace Policy - Policy updated with literature search, no change to the policy statement.</td>
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<tr>
<td>06/08/10</td>
<td>Replace Policy - Policy updated with literature search, no change to the policy statement.</td>
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<tr>
<td>03/08/11</td>
<td>Replace Policy - Policy updated with literature review; no change in policy statement. Policy guidelines updated for improved clarity and administrative simplicity.</td>
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<tr>
<td>04/25/12</td>
<td>Replace policy. Policy updated with literature review; policy statements unchanged. Reference 15 added.</td>
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<tr>
<td>04/16/13</td>
<td>Replace policy. Policy updated with literature review; policy statements unchanged.</td>
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<tr>
<td>05/05/14</td>
<td>Annual review. Policy updated with literature review; policy statements unchanged.</td>
</tr>
<tr>
<td>05/27/15</td>
<td>Annual Review. Policy updated with literature review, policy statements unchanged. Notation added that this policy is managed and administered through the pharmacy benefit.</td>
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Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA).
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Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaint Portal, available at
200 Independence Avenue SW, Room 509F, HHH Building
U.S. Department of Health and Human Services
Office for Civil Rights
200 Independence Avenue SW, Room 509F, HHH Building
U.S. Department of Health and Human Services
640 Independence Avenue SW, Room 509F, HHH Building
U.S. Department of Health and Human Services

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at
https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
Office for Civil Rights
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

You also need to file your complaint with the Office for Civil Rights within 180 days of our decision about your application or coverage through Premera Blue Cross.

You can file a complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, by calling their toll-free number at
800-368-1019, 800-537-7697 (TDD)

If you believe Premera has taken any action prohibited under the Federal Civil Rights laws, you can file a complaint with Premera Blue Cross.

If you have other questions or concerns about this notice, you can contact Premera Blue Cross at
800-368-1019, 800-537-7697 (TDD)

Helping you get the information and help you need to take action to keep your health coverage.

Applicable Federal Civil Rights Laws:
- Title II of the Americans with Disabilities Act
- Section 504 of the Rehabilitation Act
- Indian Health Care Improvement Act
- Civil Rights Act of 1964
- Civil Rights Act of 1990
- Age Discrimination Act
- Age Discrimination in Employment Act of 1967
- Voting Rights Act of 1965
-2000

Gettting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost.

Call 800-722-1471 (TTY: 800-842-5357).

Chinese (Chinese):
本通知有重要的訊息。本通知可能有關於您透過Premera Blue Cross提交的申請或保險的重要訊息。本通知可能有重要日期，您可能需要在截止日期之前採取行動，以保留您的健康保險或費用補貼。您有權利免費以您的母語得到本訊息和幫助。請拔電話800-722-1471 (TTY: 800-842-5357)。

Italian (Italian):