Introduction

Insulin-like growth factor-1 (IGF-1) acts a bit like a go-between in the growth process. It is a hormone that’s naturally produced in the liver and certain other tissues. The pituitary gland, located in the brain, stimulates the production of growth hormone, which is then released into the blood. When growth hormone reaches the liver, it causes the liver to create IGF-1. Then, IGF-1 acts as the link between growth hormone that’s in the blood and the growth processes inside cells. The levels of IGF-1 increase during childhood, peak during puberty, and then decline. Children whose bodies don’t create enough IGF-1 are very short for their age. IGF-1 that made in a lab may be used to help children grow when other causes of slow growth have been ruled out. This policy describes when IGF-1 may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider can also be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increlex® (mecasermin)</td>
<td>Increlex® (mecasermin) may be considered medically necessary for its FDA-approved indication for the treatment of growth failure in children. (See Authorization Criteria below.) The use of Increlex® (mecasermin) for idiopathic short stature is considered not medically necessary.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Investigational</th>
</tr>
</thead>
</table>
| Increlex® (mecasermin) | Use of Increlex® (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 (eg, 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  
  - Use in combination with GH |

**Authorization Criteria**

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 [eg, 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. (ie, 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
Authorization Criteria

- 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 \( \geq 2.5 \) cm / year
  AND
- Bone age is \( \leq 14 \) years for females or \( \leq 16 \) years for males

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

Coding

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

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

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.
Evidence Review

Description

Increlex® (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.

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 Increlex® (mecasermin) for the treatment of children with these conditions to increase statural growth. According to the FDA review report
for mecausermin, 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 mecausermin 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 mecausermin 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 mecausermin 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; mecausermin should be administered shortly (± 20 min) before or after a meal or snack because mecausermin has insulin-like hypoglycemic effects; hypertrophy of lymphoid tissue with complications (eg, 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 mecamsermin 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 no new evidence found that would change this policy.

2015 Update

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

2016 Update

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

2017 Update

A literature search conducted from October 1, 2016, through November 1, 2017, no new evidence found that would change this policy.

References


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>08/12/08</td>
<td>Add to Prescription Drug Section - New PR Policy.</td>
</tr>
<tr>
<td>07/14/09</td>
<td>Replace Policy - Policy updated with literature search, no change to the policy statement.</td>
</tr>
<tr>
<td>06/08/10</td>
<td>Replace Policy - Policy updated with literature search, no change to the policy statement.</td>
</tr>
<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>
</tr>
<tr>
<td>04/25/12</td>
<td>Replace policy. Policy updated with literature review; policy statements unchanged. Reference 15 added.</td>
</tr>
<tr>
<td>04/16/13</td>
<td>Replace policy. Policy updated with literature review; policy statements unchanged.</td>
</tr>
<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>
</tr>
<tr>
<td>10/28/16</td>
<td>Formatting update. Coding table reformatted and moved to Policy Guidelines section.</td>
</tr>
<tr>
<td>01/01/17</td>
<td>Annual Review, approved December 13, 2016. Policy updated with literature review, policy statements unchanged.</td>
</tr>
<tr>
<td>12/01/17</td>
<td>Annual Review, approved November 21, 2017. No new evidence was found, and policy statements unchanged.</td>
</tr>
</tbody>
</table>

**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). ©2017 Premera All Rights Reserved.

**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.
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 - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5952. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

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:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at

Getting 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).

Arabic (Amharic):
لا يوجد هذا الإشعار محتويات دامية. قد يحتوي هذا الإشعار معلومات مهمة يفضل منك الاتصال بالخط التحذيري. يحتوي هذا الإشعار على ترتيبات خاصة للحفاظ على معلوماتك الصحية والمساعدة في ذكرك الأكلي. يحمل كل المعلومات على هذه المعلومات والمساعدة بكل تكلفة. العمر

0-800-722-1471 (TTY: 800-842-5357) /العربية

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。請接電話 800-722-1471 (TTY: 800-842-5357).

Oromoo (Cushite):
Portugês (Portuguese):
Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde e ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e em custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

Română (Romanian):

Русский (Russian):
Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Español (Spanish):
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Français (French):

Український (Ukrainian):
Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про ваше звернення щодо страхувального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам троби буде здійснити ніжки круги у конкретні кінцівки строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дозвоніться за номером телефону 800-722-1471 (TTY: 800-842-5357).