UnitedHealthcare Pharmacy
Clinical Pharmacy Programs

<table>
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<tr>
<th>Program Number</th>
<th>2016 P 1039-6</th>
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<tr>
<td>Program</td>
<td>Prior Authorization/Notification – Human Growth Hormone, Growth Stimulating Products</td>
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</table>
| Medication     | Human Growth Hormone: Somatropin (Genotropin®, Humatrope®, Norditropin®, NordiFlex®, Nutropin AQ®, Nutropin AQ® NuSpin™, Omnitrope®, Saizen®, Zomacton®, Zorbtive®, and Serostim®)
Growth Stimulating Products: Mecasermin (Increlex®) |
| Effective Date | 3/1/2017; Oxford: N/A |

1. **Background:**
Somatropin is indicated for the treatment of growth hormone deficiency, short stature associated with Turner syndrome or Noonan syndrome, short-stature homeobox (SHOX) gene deficiency, growth failure due to Prader-Willi syndrome, short stature in children born small for gestational age, growth failure in children with chronic renal insufficiency up to the time of transplant, short bowel syndrome in patients receiving specialized nutritional support, and HIV-associated wasting. Somatropin is also indicated for replacement of endogenous growth hormone in adults with confirmed growth hormone deficiency.

Mecasermin is indicated for the treatment of growth failure in children with severe primary insulin-like growth factor-1 (IGF-1) deficiency or with growth hormone gene deletion that have developed neutralizing antibodies to growth hormone.

**Coverage Information**
Since short stature in the absence of defined pathology is not a sickness or injury, growth hormone is not a covered health service for these indications. The standard UnitedHealthcare Pharmacy Rider explicitly excludes coverage of growth hormone for short stature caused by heredity and not by a diagnosed medical condition.

Coverage for somatropin (Genotropin, Humatrope, Norditropin, NordiFlex, Nutropin, Nutropin AQ, Nutropin AQ NuSpin, Omnitrope, Saizen, and Zomacton) and mecasermin (Increlex) will be provided for members who meet the following criteria:
2. Coverage Criteria:

A. Pediatric Growth Hormone Deficiency (GHD)

Note: Includes children who have undergone brain radiation. If patient is a Transition Phase Adolescent or Adult who had childhood onset GH deficiency, utilize criteria for Transition Phase Adolescent or Adult GH Deficiency.

1. Initial Therapy

   a. Somatropin will be approved based on one of the following criteria:

      (1) One of the following:

         (a) Both of the following:

            i. Infant is < 4 months of age
            ii. Infant has growth deficiency

            -OR-

         (b) History of neonatal hypoglycemia associated with pituitary disease

         -OR-

         (c) Diagnosis of panhypopituitarism

         -OR-

      (2) All of the following:

         (a) Diagnosis of pediatric GH deficiency as confirmed by one of the following:

            i. Projected height (as determined by extrapolating pre-treatment growth trajectory along current channel to 18-20 year mark) is >2.0 standard deviations [SD] below midparental height utilizing age and gender growth charts related to height

            -OR-

            ii. Height is > 2.25 SD below population mean (below the 1.2
percentile for age and gender) utilizing age and gender growth charts related to height

-OR-

iii. Growth velocity is > 2 SD below mean for age and gender

-OR-

iv. Delayed skeletal maturation of > 2 SD below mean for age and gender (e.g., delayed > 2 years compared with chronological age)

-AND-

(b) One of the following:

i. Both of the following:

▪ Patient is male
▪ Bone age < 16 years

-OR-

ii. Both of the following:

▪ Patient is female
▪ Bone age < 14 years

-AND-

(c) One of the following:

i. Both of the following:

▪ Patient has undergone two of the following provocative GH stimulation tests:
  - Arginine
  - Clonidine
  - Glucagon
  - Insulin
  - Levodopa
  - Growth hormone releasing hormone

-AND-
Both GH response values are < 10 mcg/L

-OR-

ii. Both of the following:

- Patient is < 1 year of age

-AND-

- One of the following is below the age and gender adjusted normal range as provided by the physician’s lab:
  - Insulin-like Growth Factor 1 (IGF-1/Somatomedin-C)
  - Insulin Growth Factor Binding Protein-3 (IGFBP-3)

Authorization will be issued for 12 months.

Note: Documentation of previous height, current height and goal expected adult height will be required for renewal.

2. Reauthorization

a. Somatropin will be approved based on both of the following criteria:

(1) Height increase of at least 2 cm/year over the previous year of treatment as documented by both of the following:

(a) Previous height and date obtained
(b) Current height and date obtained

-AND-

(2) Both of the following:

(a) Expected adult height not attained
(b) Documentation of expected adult height goal

Authorization will be issued for 12 months.

B. Prader-Willi Syndrome
1. **Initial Therapy**

   a. **Somatropin** will be approved based on the following criterion:

   (1) Diagnosis of Prader-Willi Syndrome

   **Authorization will be issued for 12 months.**

2. **Reauthorization**

   a. **Somatropin** will be approved based on **one** of the following criteria:

   (1) Evidence of positive response to therapy (eg, increase in total lean body mass, decrease in fat mass)

   -OR-

   (2) **Both** of the following:

   (a) Height increase of at least 2 cm/year over the previous year of treatment as documented by **both** of the following:

   i. Previous height and date obtained
   ii. Current height and date obtained

   -AND-

   (b) **Both** of the following:

   i. Expected adult height not attained
   ii. Documentation of expected adult height goal

   **Authorization will be issued for 12 months.**

C. **Growth Failure in Children Small for Gestational Age (SGA)**

1. **Initial Therapy**

   a. **Somatropin** will be approved based on **both** of the following criteria:

   (1) Diagnosis of SGA based on demonstration of catch up growth failure in the first 24 months of life using a 0-36 month growth chart as confirmed by the following criterion:

   (a) **One** of the following is below the 2\textsuperscript{nd} percentile for
gestational age (more than 2 SD below population mean):

   i. Birth weight
   ii. Birth length

   -AND-

(2) Height remains ≤ 3rd percentile (more than 2 SD below population mean)

Authorization will be issued for 12 months.

Note: Documentation of previous height, current height and goal expected adult height will be required for renewal.

2. Reauthorization
   
a. Somatropin will be approved based on both of the following criteria:

      (1) Height increase of at least 2 cm/year over the previous year of treatment as documented by both of the following:

         (a) Previous height and date obtained
         (b) Current height and date obtained

      -AND-

      (2) Both of the following:

         (a) Expected adult height not attained
         (b) Documentation of expected adult height goal

Authorization will be issued for 12 months.

D. Turner Syndrome or Noonan Syndrome

1. Initial Therapy
   
a. Somatropin will be approved based on both of the following criteria:

      (1) Diagnosis of pediatric growth failure associated with one of the following:

         (a) Both of the following:
i. Turner Syndrome (Gonadal Dysgenesis)

-AND-

ii. Documentation of both of the following:

- Patient is female
- Bone age < 14 years

-OR-

(b) Both of the following:

i. Noonan Syndrome

-AND-

ii. Documentation of one of the following:

- Both of the following:
  - Patient is male
  - Bone age < 16 years

-OR-

- Both of the following:
  - Patient is female
  - Bone age < 14 years

-AND-

(2) Height is below the 5th percentile on growth charts for age and gender

Authorization will be issued for 12 months.

Note: Documentation of previous height, current height and goal expected adult height will be required for renewal.

2. Reauthorization

a. Somatropin will be approved based on both of the following criteria:

(1) Height increase of at least 2 cm/year over the previous year of
treatment as documented by both of the following:

(a) Previous height and date obtained
(b) Current height and date obtained

-AND-

(2) Both of the following:

(a) Expected adult height not attained
(b) Documentation of expected adult height goal

Authorization will be issued for 12 months.

E. Short-Stature Homeobox (SHOX) Gene Deficiency

1. Initial Therapy

   a. Somatropin will be approved based on both of the following criteria:

      (1) Diagnosis of pediatric growth failure with short-stature homeobox (SHOX) gene deficiency as confirmed by genetic testing

           -AND-

      (2) Documentation of one of the following:

           (a) Both of the following:

                   i. Patient is male
                   ii. Bone age < 16 years

                   -OR-

           (b) Both of the following:

                   i. Patient is female
                   ii. Bone age < 14 years

Authorization will be issued for 12 months.

Note: Documentation of previous height, current height and goal expected adult height will be required for renewal.

2. Reauthorization
a. Somatropin will be approved based on both of the following criteria:

(1) Height increase of at least 2 cm/year over the previous year of treatment as documented by both of the following:

(a) Previous height and date obtained
(b) Current height and date obtained

-AND-

(2) Both of the following:

(a) Expected adult height not attained
(b) Documentation of expected adult height goal

Authorization will be issued for 12 months.

F. Growth Failure associated with Chronic Renal Insufficiency

1. Initial Therapy

   a. Somatropin will be approved based on both of the following criteria:

   (1) Diagnosis of pediatric growth failure associated with chronic renal insufficiency

   -AND-

   (2) Documentation of one of the following:
   (a) Both of the following:
       i. Patient is male
       ii. Bone age < 16 years

   -OR-

   (b) Both of the following:
       i. Patient is female
       ii. Bone age < 14 years

   Authorization will be issued for 12 months.

Note: Documentation of previous height, current height and goal
expected adult height will be required for renewal.

2. **Reauthorization**

   a. **Somatropin** will be approved based on **both** of the following criteria.

      (1) Height increase of at least 2 cm/year over the previous year of treatment as documented by **both** of the following:

         (a) Previous height and date obtained
         (b) Current height and date obtained

         *-AND-*

      (2) **Both** of the following:

         (a) Expected adult height not attained
         (b) Documentation of expected adult height goal

   **Authorization will be issued for 12 months.**

G. **Adult Growth Hormone Deficiency**

1. **Initial Therapy**

   a. **Somatropin** will be approved based on **all** of the following criteria:

      (1) Diagnosis of adult GH deficiency as a result of **one** of the following:

         (a) Clinical records supporting a diagnosis of childhood-onset GHD

         *-OR-*

         (b) **Both** of the following:

            i. Adult-onset GHD

            *-AND-*

            ii. Clinical records documenting that hormone deficiency is a result of hypothalamic-pituitary disease from organic or known causes (e.g., damage from surgery, cranial irradiation, head trauma, or subarachnoid hemorrhage)
(2) **One** of the following:

(a) **Both** of the following:

   i. Patient has undergone **one** of the following GH stimulation tests to confirm adult GH deficiency:

      - Insulin tolerance test (ITT)
      - Arginine & GHRH (GHRH+ARG)
      - Glucagon
      - Arginine (ARG)

   -AND-

   ii. **One** of the following peak GH values:

      - ITT $\leq 5$ µg/L
      - GHRH+ARG ($\leq 11$ µg/L if body mass index [BMI] < 25 kg/m$^2$; $\leq 8$ µg/L if BMI $\geq 25$ and < 30 kg/m$^2$; $\leq 4$ µg/L if BMI $\geq 30$ kg/m$^2$)
      - Glucagon $\leq 3$ µg/L
      - ARG $\leq 0.4$ µg/L

   -OR-

(b) **Both** of the following:

   i. Documented deficiency of **three** of the following anterior pituitary hormones:

      - Prolactin
      - ACTH
      - TSH
      - FSH/LH

   -AND-

   ii. IGF-1/Somatomedin-C level is below the age and gender adjusted normal range as provided by the physician's lab

   -AND-

(3) **One** of the following:
(a) Diagnosis of panhypopituitarism

-OR-

(b) Other diagnosis and not used in combination with the following:

i. Aromatase inhibitors [e.g., Arimidex (anastrozole), Femara (letrozole)]

ii. Androgens [e.g., Delatestryl (testosterone enanthate), Depo-Testosterone (testosterone cypionate)]

Authorization will be issued for 12 months.

2. Reauthorization

a. Somatropin will be approved based on all of the following criteria:

(1) Evidence of ongoing monitoring as demonstrated by documentation within the past 12 months of an IGF-1/Somatomedin C level

-AND-

(2) One of the following:

i. Diagnosis of panhypopituitarism

-OR-

ii. Other diagnosis and not used in combination with the following:

- Aromatase inhibitors [e.g., Arimidex (anastrozole), Femara (letrozole)]
- Androgens [e.g., Delatestryl (testosterone enanthate), Depo-Testosterone (testosterone cypionate)]

Authorization will be issued for 12 months.

H. Transition Phase Adolescent Patients

1. Initial Therapy

a. Somatropin will be approved based on all of the following criteria:
(1) **One** of the following:
   
   (a) Attained expected adult height  
   (b) Closed epiphyses on bone radiograph  
   
   **-AND-**

(2) **One** of the following:

   (a) **Both** of the following:

   i. Documentation of high risk of GH deficiency due to GH deficiency in childhood from **one** of the following:

      ○ Embryopathic/congenital defects  
      ○ Genetic mutations  
      ○ Irreversible structural hypothalamic-pituitary disease  
      ○ Panhypopituitarism  
      ○ Deficiency of **three** of the following anterior pituitary hormones:

         ▪ ACTH  
         ▪ TSH  
         ▪ Prolactin  
         ▪ FSH/LH

   **-AND-**

   ii. **One** of the following:

      ○ IGF-1/Somatomedin-C level is below the age and gender adjusted normal range as provided by the physician’s lab

   **-OR-**

      ○ **All** of the following:

         ▪ Patient does not have a low IGF-1/Somatomedin C level

   **-AND-**

      ▪ Discontinued GH therapy for at least 1 month

   **-AND-**
• Patient has undergone a **one** of the following GH stimulation tests after discontinuation of therapy for at least 1 month:
  
  - ITT
  - GHRH+ARG
  - ARG
  - Glucagon

-AND-

• **One** of the following peak GH values:
  
  - ITT ≤ 5 µg/L
  - GHRH+ARG (≤ 11 µg/L if body mass index [BMI] < 25 kg/m²; ≤ 8 µg/L if BMI ≥ 25 and < 30 kg/m²; ≤ 4 µg/L if BMI ≥ 30 kg/m²)
  - Glucagon ≤ 3 µg/L
  - ARG ≤ 0.4 µg/L

OR-

(b) **All** of the following:

i. At low risk of severe GH deficiency (e.g., due to isolated and/or idiopathic GH deficiency)

-AND-

ii. Discontinued GH therapy for at least 1 month

-AND-

iii. **Both** of the following:

  ○ Patient has undergone **one** of the following GH stimulation tests after discontinuation of therapy for at least 1 month:

    - ITT
    - GHRH+ARG
    - ARG
    - Glucagon

-AND-
○ **One** of the following peak GH values:

- ITT ≤ 5 µg/L
- GHRH+ARG (≤ 11 µg/L if body mass index [BMI] < 25 kg/m²; ≤ 8 µg/L if BMI ≥ 25 and < 30 kg/m²; ≤ 4 µg/L if BMI ≥ 30 kg/m²)
- Glucagon ≤ 3 µg/L
- ARG ≤ 0.4 µg/L

Authorization will be issued for 12 months.

2. **Reauthorization**

   a. **Somatropin** will be approved based on the following criterion:

   (1) Evidence of positive response to therapy (e.g., increase in total lean body mass, exercise capacity or IGF-1 and IGFBP-3 levels)

   Authorization will be issued for 12 months.

I. **Human Immunodeficiency Virus (HIV)-Associated Cachexia (Serostim only)**

1. **Initial Therapy**

   a. Serostim will be approved based on **all** of the following criteria:

      (1) Diagnosis of HIV-associated wasting syndrome or cachexia

      -AND-

      (2) **One** of the following:

         (a) Unintentional weight loss of > 10% over the last 12 months
         (b) Unintentional weight loss of > 7.5% over the last 6 months
         (c) Loss of 5% body cell mass (BCM) within 6 months
         (d) Body mass index (BMI) < 20 kg/m²
         (e) **One** of the following:

            i. **All** of the following

               - Patient is male
               - BCM < 35% of total body weight
               - BMI < 27 kg/m²
ii. All of the following:

- Patient is female
- BCM < 23% of total body weight
- BMI < 27 kg/m²

-AND-

(3) Nutritional evaluation since onset of wasting first occurred

-AND-

(4) Patient has not had weight loss as a result of other underlying treatable conditions (e.g., depression, mycobacterium avium complex, chronic infectious diarrhea, or malignancy with the exception of Kaposi’s sarcoma limited to skin or mucous membranes)

-AND-

(5) Anti-retroviral therapy has been optimized to decrease the viral load

Authorization will be issued for 3 months.

2. Reauthorization

a. Serostim will be approved based on both of the following criteria:

(1) Evidence of positive response to therapy (i.e., ≥ 2% increase in body weight and/or BCM)

-AND-

(2) One of the following targets or goals has not been achieved:

(a) Weight
(b) BCM
(c) BMI

Authorization will be issued for 6 months.

J. Short Bowel Syndrome (Zorbtive only)
1. **Zorbative** will be approved based on **all** of the following criteria:

   a. Diagnosis of Short Bowel Syndrome

   -AND-

   b. Patient is currently receiving specialized nutritional support (e.g., intravenous parenteral nutrition, fluid, and micronutrient supplements

   -AND-

   c. Patient has not previously received 4 weeks of treatment with Zorbative

Authorization will be issued for 4 weeks.

Note: Treatment with Zorbative will not be authorized beyond 4 weeks. Administration for more than 4 weeks has not been adequately studied.

K. **Idiopathic Short Stature (for the state of Maryland only)**

1. **Initial Therapy**

   a. **Somatropin** will be approved based on **all** of the following criteria:

      (1) Diagnosis of idiopathic short stature

      -AND-

      (2) Diagnostic evaluation has excluded other causes associated with short stature (e.g., growth-hormone deficiency, chronic renal insufficiency, etc.)

      -AND-

      (3) Documentation of height $\leq -2.25$ SD score (SDS) below the corresponding mean height for age and gender

      -AND-

      (4) Documentation of growth velocity less than 25th percentile for bone age

      -AND-
(5) Documentation of **one** of the following:

(a) **Both** of the following:

   i. Patient is male  
   ii. Bone age < 16 years

-OR-

(b) **Both** of the following:

   i. Patient is female  
   ii. Bone age < 14 years

**Authorization will be issued for 12 months.**

**Note:** Documentation of previous height, current height and goal expected adult height will be required for renewal.

2. **Reauthorization**

   a. **Somatropin** will be approved based on **both** of the following criteria:

   (1) Height increase at least 2 cm/year over the previous year of treatment as documented by **both** of the following:

   (a) Previous height and date obtained  
   (b) Current height and date obtained

   -AND-

   (2) **Both** of the following:

   (a) Expected adult height not attained  
   (b) Documentation of expected adult height goal

**Authorization will be issued for 12 months.**

**I. Severe Primary IGF-1 Deficiency / Growth Hormone Gene Deletion (Increlex only)**

1. **Initial Therapy**

   a. **Increlex** will be approved based on **one** of the following criteria:
(1) **All** of the following:

(a) Diagnosis of severe primary IGF-1 deficiency

-AND-

(b) Height standard deviation score ≤ -3.0

-AND-

(c) Basal IGF-1 standard deviation score ≤ -3.0

-AND-

(d) Normal or elevated growth hormone levels

-AND-

(e) Documentation of open epiphyses on last bone radiograph

-AND-

(f) The patient will not be treated with concurrent growth hormone therapy

-OR-

b. **All** of the following:

(1) Diagnosis of growth hormone gene deletion and has developed neutralizing antibodies to growth hormone

-AND-

(2) Documentation of open epiphyses on last bone radiograph

-AND-

(3) The patient will not be treated with concurrent growth hormone therapy

Authorization will be issued for 12 months.

**Note:** Documentation of previous height, current height and goal expected adult height will be required for renewal.
2. **Reauthorization**

a. **Inrelex** will be approved based on **both** of the following criteria:

   (1) Height increase of at least 2 cm/year over the previous year of treatment as documented by **both** of the following:
   
   (a) Previous height and date obtained
   (b) Current height and date obtained
   
   -AND-

   (2) **Both** of the following:
   
   (a) Expected adult height not obtained
   (b) Documentation of expected adult height goal
   
   -AND-

   (3) Patient is not treated with concurrent growth hormone therapy

   **Authorization will be issued for 12 months.**

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**Educational Statement:** Documentation of previous height, current height and goal expected adult height will be required for renewal.

**Essential versus Nonessential Use**

The Patient Protection and Affordable Care Act (PPACA) of 2010 includes a mandate that prohibits annual dollar maximum limits for “essential” benefits. A strict definition of “essential” was not provided in PPACA or in federal health care regulations published as of the date this program was revised. UnitedHealthcare defines an “essential” use of growth hormone as therapy to treat a deficiency as part of chronic disease management. Other uses such as replacement therapy in a disorder where a deficiency is not noted are considered “nonessential.”

This information applies to groups with benefit caps in place for growth hormone therapy. If the diagnosis is considered an essential use of the medication, the cap will not apply. For these cases, an override for the cap amount will be entered at the same time the authorization (if criteria met) is entered for the medication. If the diagnosis is a nonessential use of the medication, then only the authorization for the medication will be entered.

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<th>Diagnosis</th>
<th>Essential/Nonessential</th>
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<td>Pediatric growth hormone deficiency</td>
<td>Essential</td>
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<tr>
<td>Growth failure in children small for gestational age</td>
<td>Nonessential</td>
</tr>
<tr>
<td>Growth failure due to chronic renal insufficiency</td>
<td>Nonessential</td>
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<table>
<thead>
<tr>
<th>Condition</th>
<th>Essential/Nonessential</th>
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<tr>
<td>Growth failure due to Turner Syndrome</td>
<td>Nonessential</td>
</tr>
<tr>
<td>Growth failure due to Noonan Syndrome</td>
<td>Nonessential</td>
</tr>
<tr>
<td>Growth failure due to short-stature homeobox (SHOX) gene deficiency</td>
<td>Nonessential</td>
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<tr>
<td>Prader-Willi Syndrome</td>
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<td>Adult growth hormone deficiency</td>
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<td>Transition phase adolescent patients</td>
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<td>HIV-associated wasting syndrome/cachexia</td>
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<td>Short bowel syndrome</td>
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<tr>
<td>Severe primary IGF-1 deficiency</td>
<td>Essential</td>
</tr>
<tr>
<td>Idiopathic short stature (not currently covered per criteria)</td>
<td>Nonessential</td>
</tr>
</tbody>
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3. **Additional Clinical Rules:**

- Supply limits may be in place.
- Genotropin, Humatrope, Norditropin, NordiFlex, Omnitrope, Saizen and Zomacton are excluded for lines of business with therapeutic equivalent exclusions.

4. **References:**


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<th>Program</th>
<th>Prior Authorization/Notification – Human Growth Hormone, Growth Stimulating Products</th>
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<tbody>
<tr>
<td><strong>Change Control</strong></td>
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<tr>
<td>8/2013</td>
<td>Annual review with clarification of transitional phase adolescent and SGA criteria. Updated formatting and references.</td>
</tr>
<tr>
<td>2/2014</td>
<td>Modified bone age and height requirement to align with Lawson-Wilkins pediatric guidelines. Added correct dosing to be utilized per PI to both adult and children. Added not to be used in combination with androgens and aromatase inhibitors to adult criteria.</td>
</tr>
<tr>
<td>8/2014</td>
<td>Added concomitant use requirement to Increlex reauthorization criteria.</td>
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<tr>
<td>8/2015</td>
<td>Added requirement for SL dosing maximum to pediatric GHD, adult GHD, transitional, and ISS. Removed Tev-Tropin and added Zomacton.</td>
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<tr>
<td>12/2016</td>
<td>Updated criteria for diagnosis of pediatric GH deficiency. Updated references.</td>
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