



## Therapeutic Class Review<sup>SM</sup>

### Hormones – Insulin-like Growth Factor Products Mecasermin rinfabate (IPLEX<sup>®</sup>)

December 2006

**New Product for Review:**

Mecasermin rinfabate (IPLEX<sup>®</sup>)

[also known as: recombinant human insulin growth factor- 1 (rhIGF-1)/rhIGFBP-3]

**Dossier Provided by Manufacturer:** yes

**Dossier Evaluation:** 2 - all components present, except pharmacoeconomic model

#### Executive Summary

- The FDA approved both mecasermin (Increlex) and mecasermin rinfabate (IPLEX) as orphan drugs for the treatment of extreme short stature in children with severe primary IGF-1 deficiency or growth hormone resistance.
- Similar to mecasermin (Increlex), mecasermin rinfabate (IPLEX) has minimal utilization because of the narrow patient population for which it is currently indicated.
- The target population for which mecasermin (Increlex) and mecasermin rinfabate (IPLEX) is intended is small.
  - Approximately 60,000 children world-wide have IGF-1 deficiency.
  - Less than 12,000 of these children have a severe deficiency.
- Both Tercica and Insmed (manufacturers of mecasermin [Increlex] and mecasermin rinfabate [IPLEX]) compete in the same market as the two treatment options for IGF-1 deficiency.
  - This market is estimated to be a:
    - \$200 million marketing opportunity in treatment of the severe form of this condition.
    - \$1 billion world-wide market with potential expansion of product labeling to a broader pediatric population with milder IGF-1 deficiency and short stature.
  - Mecasermin rinfabate (IPLEX) is marketed as having characteristics that are uniquely different from mecasermin (Increlex). Mecasermin rinfabate (IPLEX):
    - Is a protein complex of mecasermin and IGFBP-3.

- Has a longer duration of action and convenient once-daily administration.
- Does not require administration with a meal or snack.
- Has potentially less hypoglycemia than mecasermin (Increlex).
- Claims that differentiate mecasermin (IPLEX) from mecasermin (Increlex) are outweighed by its need for freezer storage, product stability after thawing, inflexible dosing form, and large potential for waste.
- Both mecasermin (Increlex) and mecasermin rinfabate (IPLEX) have the potential for off-label use in conditions other than primary IGF-1 deficiency.

**Evidence:**

- The FDA approved mecasermin (Increlex) and mecasermin/IGFBP-3 (IPLEX) based on small open-label trials with no control groups in recognition that:
  - Primary IGF-1 deficiency is a rare condition.
  - Large scale trials with robust study designs are unlikely.
- There is no useful evidence for either mecasermin (Increlex) or mecasermin rinfabate (IPLEX) in treatment of children with short stature due to IGF-1 deficiency.
  - No comparator to establish if mecasermin (Increlex) or mecasermin rinfabate (IPLEX) is better than no treatment.
  - Trials are designed to measure increases in height.
- Although increases in height with mecasermin (Increlex) and mecasermin rinfabate (IPLEX) may be likely, it is unknown if children treated with mecasermin (Increlex) or mecasermin rinfabate (IPLEX) achieve adult heights that will improve their ability to perform activities of daily living, functioning, cognition, or metabolic status.
- Mecasermin (Increlex) and mecasermin rinfabate (IPLEX) have no proven benefit in:
  - Milder forms of short stature from IGF-1 deficiency
  - Short stature due to unknown cause (idiopathic short stature) or other underlying conditions (such as growth hormone deficiency, Prader Willi, or Turner's syndrome).
  - Amyotrophic lateral sclerosis.
  - Type 1 and Type 2 Diabetes.
  - AIDS-wasting.
  - Cystic fibrosis.

Caution is urged regarding the use of trials with uncertain evidence in making health care decisions.

- The most commonly observed side effects with mecasermin (Increlex) and mecasermin rinfabate (IPLEX) are at least similar:
  - Hypoglycemia (31 - 42%)
  - Injection site reactions (up to 59%)

- Tonsillar hypertrophy (15 - 19%)

- Overall harms data are unreliable to evaluate the long-term risks versus benefit of mecasermin (Increlex) and mecasermin rinfabate (IPLEX).
- Many patients develop antibodies to mecasermin (Increlex) or mecasermin rinfabate (IPLEX); but the clinical significance is unknown.
- Use of mecasermin (Increlex) or mecasermin rinfabate (IPLEX) is limited to treatment in children with open growth plates and who have not completed puberty.
- Neither product should be used in patients with growth hormone deficiency. (Growth hormone stimulation tests are necessary to rule out short stature due to growth hormone deficiency that can cause a secondary IGF-1 deficiency).

### Decision

Mecasermin rinfabate (IPLEX) is non-preferred/non-formulary because:

- It offers no appreciable clinical advantages over mecasermin (Increlex).
- It has storage requirements and a dosage form that increases potential for significant waste.

### Products

Drug Product	FDA approval	FDA approved indications	Usual Dose/Route	Potential Off-label Uses <sup>2,12-14-16</sup>
mecasermin (Increlex)	8/30/05	Long-term treatment of growth failure in children with severe primary IGF-1 deficiency or growth hormone gene deletion with neutralizing antibodies.	0.04 – 0.08mg/kg (40 to 80 mcg/kg) SQ twice daily. (Maximum dose of 0.12mg/kg twice daily.	Amyotrophic lateral sclerosis Diabetes mellitus, Mild-moderate primary IGF-1 deficiency, Short stature; HIV infection.
mecasermin rinfabate (IPLEX)	12/15/2005		0.5 mg/kg, then increased to 1 – 2 mg/kg SQ once daily.	Diabetes mellitus, Severe burn trauma (IV), Osteoporotic hip fracture recovery (IV), Myotonic dystrophy, HIV-associated lipodystrophy, Noonan syndrome, Extreme insulin resistance, and Secondary forms of IGF-1 deficiency, such as growth hormone deficiency, malnutrition, hypothyroidism, or chronic treatment with corticosteroids.

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