



Therapeutic Class ReviewSM

Hormones – Insulin-like Growth Factor Products Mecasermin rinfabate (IPLEX[®])

December 2006

New Product for Review:

Mecasermin rinfabate (IPLEX[®])

[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

Available Therapeutic Alternatives:

Preferred/Formulary	Non-preferred/non-formulary
Mecasermin (Increlex) [Tercica] [also known as recombinant human insulin growth factor- 1 (rhIGF-1)] Approved: August 30, 2005 Market Availability: January 2006	Mecasermin rinfabate (IPLEX [®]) [Insmed] Approved: December 15, 2005 Market availability: June 2006

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).
- Considerations in Subpopulations:
 - **Pediatrics:** Children younger than two years of age for mecasermin (Increlex) and three years of age for mecasermin rinfabate (IPLEX) have not been studied.
 - **Geriatrics:** Safety and efficacy in adults and the elderly has not been established.
 - **Race/Ethnicity/Gender:** No specific considerations.

Conclusion

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	Cost ^a	Potential Off-label Uses ^{2,12-14-16}
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.	\$1,350 - \$4,050	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.	\$2,700 – \$5,400	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.

^a Cost estimate based on AWP (average wholesale price) listed in First Data Bank as of September 2006 for a 30 days supply for a 40 kg child.

References

1. Increlex (mecasermin) prescribing information. Tercica, Inc., Brisbane, CA. August 2005.
2. FDA Center for Drug Evaluation and Research. Approval package for application number [NDA 21-839](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm). <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm> (assessed December 10, 2005).
3. Mitchell JD, Wokke JHJ, Borasio GD. Recombinant human insulin-like growth factor (rhIGF-I) for amyotrophic lateral sclerosis/motor neuron disease. The Cochrane Database of Systematic Reviews 2002, Issue 3. Art No.: CD002064. DOI:10.1002/14651858.CD002064.
4. Bucuvalas JC, Chernausk SD, Alfaro MP, Krug SK, Ritschel W, Wilmott RW. Effect of insulin-like growth factor-1 treatment in children with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 2001;33:576-81.
5. Acerini CL, Patton CM, Savage MO, Kernell A, Westphal O, Dunger DB. Randomised placebo-controlled trial of human recombinant insulin-like growth factor I plus intensive insulin therapy in adolescents with insulin-dependent diabetes mellitus. *Lancet* 1997;350:1199-204.

6. Waters D, Danska J, Hardy K, Koster F, Oualls C, Nickell D, et al. Recombinant human growth hormone, insulin-like growth factor 1, and combination therapy in AIDS-associated wasting. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1996;125:865-72.
7. Lee PDK, Pivarnik JM, Bukar JG, Muurahainen N, Berry PS, Skolnik PR et al. A randomized, placebo-controlled trial insulin-like growth factor I and low dose growth therapy for wasting associated with human immunodeficiency virus infection. *J Clin Endocrinol Metab* 1996;81:2968-75.
8. Quattrin T, Thrailkill K, Baker L, Kuntze J, Compton P, Martha P; rhIGF-I in IDDM Study Group. Improvement of hba1c without increased hypoglycemia in adolescents and young adults with type 1 diabetes mellitus treated with recombinant human insulin-like growth factor-I and insulin. rhIGF-I in IDDM Study Group. *J Pediatr Endocrinol Metab* 2001;14:267-77.
9. Thrailkill KM, Quattrin T, Baker L, Kuntze Je, Compton PG, Martha PM. Cotherapy with recombinant human insulin-like growth factor I and insulin improves glycemic control in type 1 diabetes. RhIGF-I in IDDM Study Group. *Diabetes Care* 1999;22:585-92.
10. Ranke MB, Savage MO, Chatelain PG, Preece MA, Rosenfeld RG, Blum WF et al. Insulin-like growth factor I improves height in growth hormone insensitivity: two years results. *Horm Res* 1995;44:253-64.
11. Kinger B and Laron Z. Three year IGF-1 treatment of children with Laron syndrome . *J Pediatr Endocrinol Metab* 1995;8:149-58.
12. Guevara-Aguire J, Vasconez O, Martinez V, Martinez AL, Rosenbloom AL, Diamond FB et al. A randomized , double blind, placebo-controlled trial on safety and efficacy of recombinant human insulin-like growth factor-I in children with growth hormone receptor deficiency. *J Clin Endocrinol Metab* 1995;80:1393-8.
13. Center for Disease Control. National Center for Health Statistics. <http://www.cdc.gov/growthcharts/>. (accessed December 28, 2005).
14. Backeljaw PF, Underwood LE and the Growth Hormone Insensitivity Syndrome Collaborative Group. Prolonged treatment with recombinant insulin-like growth factor-I in children with growth hormone insensitivity syndrome- a clinical research center study. *J Clin Endocrinol Metab* 1996;81:3312-7.
15. Backeljaw PE, Underwood LE and the Growth Hormone Insensitivity Syndrome Collaborative Group. Therapy for 6.5-7.5 years with recombinant insulin-like growth factor I in children with growth hormone insensitivity syndrome: a clinical research center study. *J Clin Endocrinol Metab* 2001;86:1504-10.
16. Ranke MB, Savage MO, Chatlain PG, Preece MA, Rosenfeld RG, Wilton P. Long-term treatment of growth hormone insensitivity syndrome with IGF-1. Results of the european multicenter study. *Horm Res* 1999;51:128-34.
17. American Association for Clinical Chemistry. IGF-1 Insulin-Like Growth Factor 1. December 6, 2004. <http://www.labtestsonline.org/understanding/analytes/igf1/test.html> (accessed December 28, 2005).
18. ALS CNTF treatment study phase I – II Group. Abstract, *Neurology* 1993;43:A417.
19. Cedarbaum JM, Wittes J, Brittain E. Correlation between rates of change in functional rating scales and muscle strength measures in amyotrophic lateral sclerosis (ALS) patients. Abstract, *Neurology* 1994;44 (supple 2):A256.
20. FDA Center for Drug Evaluation and Research. Approval package for application number [NDA 21-884](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm). <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm> (assessed September 6, 2006).

21. Rogol AD, Jacoson W, Smith A, Hernandez, R, Dunn F, Allan G, Sommer A. A double-blind, randomized, placebo-controlled study to determine the dose response profile of rhIGF-I/rhIGFBP-3 in subjects with type 2 diabetes mellitus requiring insulin therapy. American Diabetes Association 62nd Scientific Sessions, San Francisco, CA, June 2002.