

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-839

Administrative/Correspondence Reviews

1.3.5.1 Patent Information

FEB 24 2005

Department of Health and Human Services Food and Drug Administration	Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/06 See OMB Statement on Page 3.
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>	NDA NUMBER 21839
	NAME OF APPLICANT / NDA HOLDER Tercica, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME) INCRELEX™	
ACTIVE INGREDIENT(S) Recombinant human Insulin-like Growth Factor-1 (rhIGF-1)	STRENGTH(S) 10 mg/ml

DOSAGE FORM
 Sterile, aqueous solution intended for subcutaneous injection.

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL		
a. United States Patent Number 5,681,814	b. Issue Date of Patent 10/28/1997	c. Expiration Date of Patent 10/28/2014
d. Name of Patent Owner Genentech, Inc.	Address (of Patent Owner) 1 DNA Way	
	City/State South San Francisco	
	ZIP Code 94080	FAX Number (if available)
	Telephone Number (650) 225-1000	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		

1.3.5.1 Patent Information

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

1.3.5.1 Patent Information

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



11/4/04

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Stephen N. Rosenfield

Address

Tercica, Inc.
651 Gateway Boulevard, Suite 950

City/State

South San Francisco, CA 94080

ZIP Code

94080

Telephone Number

(650) 624-4994

FAX Number (if available)

(650) 624-4940

E-Mail Address (if available)

stephen.rosenfield@tercica.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.



US005681814A

United States Patent [19]
Clark et al.

[11] **Patent Number:** **5,681,814**
 [45] **Date of Patent:** **Oct. 28, 1997**

[54] **FORMULATED IGF-I COMPOSITION**

[75] **Inventors:** Ross G. Clark, Pacifica; Douglas A. Yeung, Fremont; James Q. Oeswein, Moss Beach, all of Calif.

[73] **Assignee:** Genentech, Inc., South San Francisco, Calif.

[21] **Appl. No.:** 71,819

[22] **Filed:** Jun. 4, 1993

Related U.S. Application Data

[60] Continuation-in-part of Ser. No. 806,748, Dec. 13, 1991, abandoned, which is a division of Ser. No. 535,005, Jun. 7, 1990, Pat. No. 5,126,324.

[51] **Int. Cl.⁶** A61K 38/00; A01N 37/18

[52] **U.S. Cl.** 514/12; 514/2; 514/21

[58] **Field of Search** 514/2, 12, 21

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,609,640	9/1986	Morishita et al.	514/12
4,857,505	8/1989	Arendt	514/12
4,988,675	1/1991	Froesch	514/4
5,126,324	6/1992	Clark	514/12
5,187,151	2/1993	Clark et al.	

FOREIGN PATENT DOCUMENTS

123228	10/1984	European Pat. Off.
123304	10/1984	European Pat. Off.
128733	12/1984	European Pat. Off.
193372	9/1986	European Pat. Off.
193917	9/1986	European Pat. Off.
230869	8/1987	European Pat. Off.
261599	3/1988	European Pat. Off.
267015	5/1988	European Pat. Off.
288451	10/1988	European Pat. Off.
308238	3/1989	European Pat. Off.
312208	4/1989	European Pat. Off.
327503	8/1989	European Pat. Off.
58/224687	12/1983	Japan
57/026625	2/1992	Japan
2193891	2/1988	United Kingdom
2160528	3/1988	United Kingdom
WO 87/01038	2/1987	WIPO
WO 89/05822	6/1989	WIPO
WO 91/03253	3/1991	WIPO
WO 93/23071	11/1993	WIPO

OTHER PUBLICATIONS

The Merck Index, 11th edition, ed. Susan Budavari (Merck & Co., Inc., Rahway, NJ 1989), p. 49.

Merck Index, 11th ed. p. 1207.

J. Zapf et al., *J. Clin. Inv.*, 77, 1768-1775 (1986).

Guler et al., "S.C. Infusion of Recombinant Human Insulin-like Growth Factor I (rhIGF I) Stimulates Growth of Hypophysectomized Rats Continuously During 18 Days", *1st European Congress of Endocrinology*, Copenhagen, Jensen & Christiansen, eds., 103:12-390, (Jun. 21-25, 1987).

Guler et al. "Effects of recombinant insulin-like growth factor I on insulin secretion and renal function in normal human subjects", *Proc. Natl. Acad. Sci. USA*, 86: 2868-2872 (1989).

Schoenle et al., "Comparison of in vivo effects of insulin-like growth factors I and II and of growth hormone in hypophysectomized rats", *Acta Endocrin.*, 108: 167-174 (1985).

Skottner et al., "Recombinant human insulin-like growth factor: testing the somatomedin hypothesis in hypophysectomized rats", *J. Endocr.*, 112: 123-132 (1987).

Skottner et al., "Growth Responses in a Mutant Dwarf Rat to Human Growth Hormone and Recombinant Human Insulin-Like Growth Factor I", *Endocrinology*, 124(5): 2519-2526 (1989).

Tanner et al., "Comparative rapidity of response of height, limb muscle, and limb fat to treatment with human growth hormone in patients with and without growth hormone deficiency", *Acta Endocrinol.*, 84: 681-696 (1977).

Uihne et al., "Effects of Human Somatomedin Preparations on Membrane Transport and Protein Synthesis in the Isolated Rat Diaphragm", *J. Clin. Endocrinol. Metab.*, 39: 548-554 (1974).

Guler et al., "Short-term metabolic effects of recombinant human insulin-like growth factor I in healthy adults", *N. Engl. J. Med.*, 317(3): 137-140 (1987).

Guler et al., "IGF I and II and recombinant human (RH) IGF I are hypoglycemic in the rat, mini-pig and men", *The Endocrine Society, 68th Annual Mtg.*, #394, (1986).

Guler et al., "Recombinant human insulin-like growth factor I stimulates growth and has distinct effects on organ size in hypophysectomized rats", *Proc. Natl. Acad. Sci. USA*, 85: 4889-4893 (1988).

Froesch et al., "IGF I and II: in vitro and in vivo effects", *Endocrinology, Intl. Congress Series 655*, Labrie and Proulx, eds. Amsterdam: Excerpta Medica, 475-479 (1984).

Scheiwiller et al., "Growth restoration of insulin-deficient diabetic rats by recombinant human insulin-like growth factor I", *Nature*, 323: 169-171 (1986).

van Buul-Offers et al., "Biosynthetic Somatomedin C(SM-C/IGF-I) Increases the Length and Weight of Snell Dwarf Mice", *Pediatr. Res.*, 20(9): 825-827 (1986).

Niall, "Revised Primary Structure for Human Growth Hormone", *Nature, New Biology*, 230(11): 90-91 (1971).

Moore et al., "Equivalent potency and pharmacokinetics of recombinant human growth hormones with or without an N-terminal methionine", *Endocrinology*, 122(6): 2920-2926 (1988).

(List continued on next page.)

Primary Examiner—Toni R. Scheiner
Assistant Examiner—Sheela J. Huff
Attorney, Agent, or Firm—Janet E. Hasak

[57] **ABSTRACT**

A formulation for IGF-I is disclosed that is useful in treating hyperglycemic disorders and, in combination with growth hormone, in enhancing growth of a mammal. Also disclosed is a process for preparing a formulation of growth hormone and IGF-I from the IGF-I formulation. The IGF-I formulation comprises about 2-20 mg/ml of IGF-I, about 2-50 mg/ml of an osmolyte, about 1-15 mg/ml of a stabilizer, and a buffered solution at about pH 5-5.5, optionally with a surfactant.

8 Claims, 25 Drawing Sheets

OTHER PUBLICATIONS

- Kaplan, *Growth Disorders in Children and Adolescents* 47-69, 131-139, 165-169 (Springfield, IL: Charles C. Thomas, 1964).
- Salmon and Daughaday, "A Hormonally Controlled Serum Factor Which Stimulates Sulfate Incorporation by Cartilage In Vitro", *J. Lab. Clin. Med.*, 49(6): 825-836 (1957).
- Phillips & Vassilopoulou-Sellin, "Somatomedins", (First of Two Parts), *N. Engl. J. Med.*, 302(7): 371-380 (Feb. 14, 1980).
- Phillips & Vassilopoulou-Sellin, "Somatomedins", (Second of Two Parts), *N. Engl. J. Med.*, 302(8): 438-446 (Feb. 21, 1980).
- Vetter et al., "Human Fetal and Adult Chondrocytes: Effects of insulinlike growth factors I and II, insulin and growth hormone on clonal growth", *J. Clin. Invest.*, 7: 1903-1908 (1986).
- Cook et al., "Mitogenic Effects of Growth Hormone in Cultured Human Fibroblasts", *J. Clin. Invest.*, 81: 206-212 (1988).
- Isgaard et al., "Pulsatile intravenous growth hormone (GH) infusion to hypophysectomized rats increases insulin-like growth factor I messenger ribonucleic acid in skeletal tissues more effectively than continuous GH infusion", *Endocrinology*, 123(6): 2605-2610 (1988).
- Isaksson et al., "Growth hormone stimulates longitudinal bone growth directly", *Science*, 216: 1237-1239 (1982).
- Russell and Spencer, "Local injections of human or rat growth hormone or of purified human somatomedin-C stimulate unilateral tibial epiphyseal growth in hypophysectomized rats", *Endocrinology*, 116(6): 2563-2567 (1985).
- Schlechter et al., "A direct growth effect of growth hormone in rat hindlimb shown by arterial infusion", *Am. J. Physiol.*, 250: E231-235 (1986).
- Madsen et al., "Growth hormone stimulates the proliferation of cultured chondrocytes from rabbit ear and rat rib growth cartilage", *Nature*, 304: 545-547 (1983).
- Schlechter et al., "Evidence suggesting that the direct growth-promoting effect of growth hormone on cartilage in vivo is mediated by local production of somatomedin", *Proc. Natl. Acad. Sci. USA*, 83: 7932-7934 (1986).
- Nilsson et al., "Effects of unilateral arterial infusion of GH and IGF-I on tibial longitudinal bone growth in hypophysectomized rats", *Calcif. Tissue Int.*, 40: 91-96 (1987).
- Otonkoski et al., "Effects of growth hormone and insulin-like growth factor I on endocrine function of human fetal islet-like cell clusters during long-term tissue culture", *Diabetes*, 37: 1678-1683 (1988).
- Green et al., "A dual effector theory of growth-hormone action", *Differentiation*, 29: 195-198 (1985).
- Zeulak and Green, "The Generation of Insulin-Like Growth Factor-1-Sensitive Cells by Growth Hormone Action", *Science*, 233: 551-553 (1986).
- Young et al., "Growth hormone and testosterone can independently stimulate the growth of hypophysectomized prepubertal lambs without any alteration in circulating concentrations of insulin-like growth factors", *J. Endocrin.*, 121: 563-570 (1989).
- Orlowski and Chernauek, "Discordance of Serum and Tissue Somatomedin Levels in Growth Hormone-Stimulated Growth in the Rat", *Endocrinol.*, 123(1): 44-49 (1988).
- Trippel et al., "Effect of Somatomedin-C/Insulin-Like Growth Factor I and Growth Hormone on Cultured Growth Plate and Articular Chondrocytes", *Pediatr. Res.*, 25(1): 76-82 (1989).
- Isgaard et al., "Effects of local administration of GH and IGF-1 on longitudinal bone growth in rats", *Am. J. Physiol.*, 250: E367-E372 (1986).
- Robinson and Clark, "Growth Promoting Activity of IGF-1 in the Rat", *Acta Paediatr. Scand. Supp.*, 347: 93-103 (1988).
- Ernst and Froesch, "Growth hormone dependent stimulation of osteoblast-like cells in serum-free cultures via local synthesis of insulin-like growth factor I", *Biochem. Biophys. Res. Commun.*, 151(1): 142-147 (1988).
- Smith et al., "Growth Hormone Stimulates Insulin-like Growth Factor I Actions on Adult Articular Chondrocytes", *J. Orthop. Res.*, 7: 198-207 (1989).
- Merchav et al., "Enhancement of Human Granulopoiesis In Vitro by Biosynthetic Insulin-like Growth Factor I/Somatostatin C and Human Growth Hormone", *J. Clin. Invest.*, 81: 791-797 (1988).
- Lobie et al., "Growth Hormone Receptor Expression in the Rat Gastrointestinal Tract", *Endocrinol.*, 126: 299-306 (1990).
- Lindahl et al., "Growth hormone in vivo potentiates the stimulatory effect of insulin-like growth factor-1 on colony in vitro on colony formation of epiphyseal chondrocytes isolated from hypophysectomized rats", *Endocrinol.*, 121(3): 1070-075 (1987).
- van Neste et al., "Cellular distribution of somatogenic receptors and insulin-like growth factor-I mRNA in the rat liver", *J. Endocr.*, 199: 69-74 (1988).
- Namba et al., "Insulin-Like Growth Factor-I Action on Growth Hormone Secretion and Messenger Ribonucleic Acid Levels: Interaction with Somatostatin", *Endocrinol.*, 124(4): 1794-1799 (1989).
- Yamashita et al., "Regulation of Human Growth Hormone Gene Expression by Insulin-like Growth Factor I in Transfected Cells", *J. Biol. Chem.*, 262(27): 13254-13257 (1987).
- Schwartz et al., "Growth hormone and insulin-like growth factors I and II produce distinct alterations in glucose metabolism in 3T3-F442A adipocytes", *Proc. Natl. Acad. Sci. USA*, 82: 8724-8728 (1985).
- Horikawa et al., "Growth hormone and insulin-like growth factor I stimulate Leydig cell steroidogenesis", *Eur. J. Pharmacol.*, 166: 87-94 (1989).
- Rosselot et al., "Effect of Growth Hormone and Insulin-Like Growth Factor I on Cell Proliferation and Metabolic Activity of Cultured Chondrocytes", *The Endocrine Society 72nd Annual Meeting*, abstract 202, p. 75, of Program and Abstracts released prior to the meeting in Atlanta, GA on Jun. 20, 23, 1990.
- Watanabe et al., "Characterization of a specific insulin-like growth factor-1/somatostatin-C receptor on high density, primary monolayer cultures of bovine articular chondrocytes: regulation of receptor concentration by somatomedin insulin and growth hormone", *J. Endocr.*, 107: 275-283 (1985).
- Ikkos et al., "The Effect of Human Growth Hormone in Man", *Acta Endocrinol.* (Copenhagen), 32: 341-361 (1959).
- Biglieri et al., "Sodium Retention with Human Growth Hormone and its Subfractions", *J. Clin. Endocrinol. Metab.*, 21(4): 361-370 (1961).

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/06 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 21839	
		NAME OF APPLICANT / NDA HOLDER Tercica, Inc.	
<p align="center">The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</p>			
TRADE NAME (OR PROPOSED TRADE NAME) INCRELEX™			
ACTIVE INGREDIENT(S) Recombinant human Insulin-like Growth Factor-1 (rhIGF-1)		STRENGTH(S) 10 mg/ml	
DOSAGE FORM Sterile, aqueous solution intended for subcutaneous injection.			
<p>This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.</p>			
<p>For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.</p>			
<p>FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.</p>			
<p>For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.</p>			
1. GENERAL			
a. United States Patent Number 5,824,642	b. Issue Date of Patent 10/20/1998	c. Expiration Date of Patent 10/20/2015	
d. Name of Patent Owner Genentech, Inc.	Address (of Patent Owner) 1 DNA Way		
	City/State South San Francisco		
	ZIP Code 94080	FAX Number (if available)	
	Telephone Number (650) 225-1000	E-Mail Address (if available)	
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)		
	City/State		
	ZIP Code	FAX Number (if available)	
	Telephone Number	E-Mail Address (if available)	
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	

1.3.5.1 Patent Information

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) 8, 9, 10, 11, 12 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
 INCRELEX™ replacement therapy is indicated for patients with primary IGF-1 deficiency 1

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

1.3.5.1 Patent Information

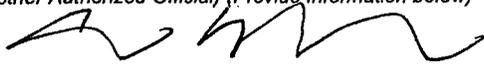
6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



11/4/04

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Stephen N. Rosenfield

Address

Tercica, Inc.
651 Gateway Boulevard, Suite 950

City/State

South San Francisco, CA 94080

ZIP Code

94080

Telephone Number

(650) 624-4994

FAX Number (if available)

(650) 624-4940

E-Mail Address (if available)

stephen.rosenfield@tercica.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.



US005824642A

United States Patent [19]
Attie et al.

[11] **Patent Number:** **5,824,642**
[45] **Date of Patent:** **Oct. 20, 1998**

- [54] **TREATMENT OF PARTIAL GROWTH HORMONE INSENSITIVITY SYNDROME**
- [75] Inventors: **Kenneth Attie**, San Francisco, Calif.; **Lena M. S. Carlsson**, Goteborg, Sweden; **Neil Gesundheit**, Los Altos; **Audrey Goddard**, San Francisco, both of Calif.
- [73] Assignee: **Genentech, Inc.**, South San Francisco, Calif.
- [21] Appl. No.: **468,580**
- [22] Filed: **Jun. 6, 1995**

Related U.S. Application Data

- [63] Continuation of Ser. No. 410,452, Mar. 24, 1995, abandoned, which is a continuation-in-part of Ser. No. 224,982, Apr. 7, 1994, Pat. No. 5,646,113.
- [51] **Int. Cl.**⁶ **C07K 13/00; A61K 38/00; A61K 38/28**
- [52] **U.S. Cl.** **514/12; 514/12; 530/303; 530/311; 530/399**
- [58] **Field of Search** **514/12, 21; 530/303, 530/311, 399**

References Cited

U.S. PATENT DOCUMENTS

- 5,126,324 6/1992 Clark et al. 514/12
- 5,187,151 2/1993 Clark et al. 514/3

FOREIGN PATENT DOCUMENTS

WO 91/18621 12/1991 WIPO .

OTHER PUBLICATIONS

Shimasaki and Ling, Progress in Growth Factor Research, vol. 3 pp. 243-266, 1991.
Pediatric and Adolescent Endocrinology: Lessons from Laron Syndrome (LS) 1966-1992, Laron et al., Basel:Karger vol. 24:1-367 (1992).
 Aguirre et al., "High-Affinity Serum Growth-Hormone-Binding Protein, Absent in Laron-Type Dwarfism, is Diminished in Heterozygous Parents" *Horm. Res.* 34:4-8 (1990).
 Albertson-Wikland, "Growth Hormone Treatment in Short Children—Short-Term and Long-Term Effects on Growth" *Acta Paediatr Scand Suppl.* 343:77-84 (1988).
 Albertsson-Wikland et al., "Analyses of 24-Hour Growth Hormone Profiles in Children: Relation to Growth" *J. Clin. Endocrin. and Metabol.* 67(3):493-500 (1988).
 Amselem et al., "Laron Dwarfism and Mutations of the Growth Hormone-Receptor Gene" *New England J. of Med.* 321(15):989-995 (1989).
 Amselem et al., "Molecular Basis of Laron Dwarfism" *TEM*, Elsevier Science Publishing Co., Inc. pp. 35-40 (1991).
 Amselem et al., "Molecular Defects in the Growth Hormone Receptor" *Acta Paediatr Scand [Suppl]* 377:81-86 (1991).
 Amselem et al., "Spectrum of Growth Hormone Receptor Mutations and Associated Haplotypes in Laron Syndrome" *Human Molecular Genetics* 2(4) :355-359 (1993).

Attie et al., "Evidence for Partial Growth Hormone (GH) Insensitivity among Idiopathic Short Stature (ISS) Patients Treated with Growth Hormone" *4th Joint LWPESESPE Meeting* (San Francisco) (1993).
 Attie et al., "Evidence for partial growth hormone insensitivity among patients with idiopathic short stature" *J. Pediatrics* 127:244-250 (Aug. 1995).
 August et al., "Growth Hormone Treatment in the United States: Demographic and Diagnostic Features of 2331 Children" *J. Pediatr.* 116(6) :899-903 (1990).
 Bäckeljauw et al., "Effects of Prolonged IGF-I Treatment in Children with Growth Hormone Insensitivity Syndrome (GHIS)" *Pediatr. Res.* 33:S56, 5 Suppl., #314 (1993).
 Baumann et al., "Absence of the Plasma Growth Hormone-Binding Protein in Laron-Type Dwarfism" *J. Clin. Endocrin. and Metabol.* 65(4) :814-816 (1987).
 Baumann et al., "Circulating Molecular Variants of Growth Hormone in Childhood" *Pediatr. Res.* 22(1) :21-22 (1987).
 Baumann et al., "Short Stature and Decreased Serum Growth Hormone-Binding Protein in the Mountain Ok People of Papua New Guinea" *J. Clin. Endocrin. and Metabol.* 72(6) :1346-1349 (1991).
 Baumbach et al., "the Growth Hormone-Binding Protein in Rat Serum is an Alternatively Spliced Form of the Rat Growth Hormone Receptor" *Gene & Development* 3:1199-1205 (1989).
 Baumgartner et al., "The Role of the WSXWS Equivalent Motif in Growth Hormone Receptor Function" *J. Biol. Chemistry* 269(46) :290494-29101 (1994).
 Bierich et al., "Die Spontansekretion des Wachstumshormons bei der konstitutionellen Entwicklungsverzögerung und der fruehnormalen Pubertat" *Monatsschrift fur Kinderheilkunde* (English abstract) 127:561-565 (1979).

(List continued on next page.)

Primary Examiner—Cecilia J. Tsang
Assistant Examiner—P. Lynn Touzeau
Attorney, Agent, or Firm—Flehr Hohbach Test Albritton & Herbert LLP; Walter H. Dreger

[57] **ABSTRACT**

Methods for increasing the growth rate of a human patient having partial growth hormone insensitivity syndrome, but not Laron syndrome, are described. One such method comprises administering an effective dose of growth hormone, preferably growth hormone with a native human sequence, with or without an N-terminal methionine, to the patient. The patient is characterized as having a height of less than about -2 standard deviations below normal for age and sex, a serum level of high-affinity growth hormone binding protein that is at least 2 standard deviations below normal levels, a serum level of IGF-I that is below normal mean levels, and a serum level of growth hormone that is at least normal. In another such method, the same patient population is treated with an effective amount of IGF-I, given alone or in combination with an amount of growth hormone that is effective in combination with the IGF-I.

16 Claims, 12 Drawing Sheets

1.3.5.1 Patent Information

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/06 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 21839	
		NAME OF APPLICANT / NDA HOLDER Tercica, Inc.	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) INCRELEX™			
ACTIVE INGREDIENT(S) Recombinant human Insulin-like Growth Factor-1 (rhIGF-1)		STRENGTH(S) 10 mg/ml	
DOSAGE FORM Sterile, aqueous solution intended for subcutaneous injection.			
<p>This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.</p>			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number 6,207,640		b. Issue Date of Patent 03/27/2001	c. Expiration Date of Patent 10/20/2015
d. Name of Patent Owner Genentech, Inc.		Address (of Patent Owner) 1 DNA Way	
		City/State South San Francisco	
		ZIP Code 94080	FAX Number (if available)
		Telephone Number (650) 225-1000	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No

1.3.5.1 Patent Information

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) 15, 16, 17	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
--	--	---

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) INCRELEX™ replacement therapy is indicated for patients with primary IGF-1 deficiency
---	---

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

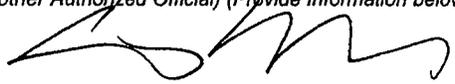
1.3.5.1 Patent Information

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)



Date Signed

11/4/04

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Stephen N. Rosenfield

Address

Tercica, Inc.
651 Gateway Boulevard, Suite 950

City/State

South San Francisco, CA 94080

ZIP Code

94080

Telephone Number

(650) 624-4994

FAX Number (if available)

(650) 624-4940

E-Mail Address (if available)

stephen.rosenfield@tercica.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.



US006207640B1

(12) **United States Patent**
Attie et al.

(10) **Patent No.:** US 6,207,640 B1
(45) **Date of Patent:** *Mar. 27, 2001

(54) **TREATMENT OF PARTIAL GROWTH HORMONE INSENSITIVITY SYNDROME**

(75) **Inventors:** Kenneth M. Attie, San Francisco, CA (US); Lena M. S. Carlsson, Gothenburg (SE); Neil Gesundheit, Los Altos; Audrey Goddard, San Francisco, both of CA (US)

(73) **Assignee:** Genentech, Inc., South San Francisco, CA (US)

(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) **Appl. No.:** 08/643,212

(22) **Filed:** May 3, 1996

Related U.S. Application Data

(63) Continuation of application No. 08/410,452, filed on Mar. 24, 1995, now abandoned, and a continuation of application No. 08/224,982, filed on Apr. 7, 1994, now Pat. No. 5,646,113.

(51) **Int. Cl.⁷** A61K 38/00

(52) **U.S. Cl.** 514/12; 514/21; 514/3; 530/303; 530/311; 530/399

(58) **Field of Search** 514/12, 21, 3; 530/303, 311, 399

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,187,151 * 2/1993 Clark et al. 514/3
5,646,113 * 7/1997 Attie et al. 514/12
5,824,642 * 10/1998 Attie et al. 514/12

FOREIGN PATENT DOCUMENTS

95/27495 10/1995 (WO) .

OTHER PUBLICATIONS

Mauras et al., "IGF-K Deficiency and Growth Failure: Association with Mutations in the Intracellular Domain of the Growth Hormone Receptor Gene," Joint Meeting of the American Pediatric Society and the Society for Pediatric Research, Washington, DC, (May 6-10, 1996) *Pediatric Research* 39(4 Part 2):93A Abstract No. 541 (1996).

Shimasaki et al., *Progress in Growth Factor Res.*, vol. 3, pp 243-66 (1991).*

* cited by examiner

Primary Examiner—Dwayne C. Jones

Assistant Examiner—C. Delacroix-Muirheid

(74) *Attorney, Agent, or Firm*—Knobbe, Martens, Olson & Bear, LLP

(57) **ABSTRACT**

Methods for increasing the growth rate of a human patient having partial growth hormone insensitivity syndrome, but not Laron syndrome, are described. One such method comprises administering an effective dose of growth hormone, preferably growth hormone with a native human sequence, with or without an N-terminal methionine, to the patient. The patient is characterized as having a height of less than about -2 standard deviations below normal for age and sex, a serum level of high-affinity growth hormone binding protein that is at least 2 standard deviations below normal levels, a serum level of IGF-I that is below normal mean levels, and a serum level of growth hormone that is at least normal. In another such method, the same patient population is treated with an effective amount of IGF-I, given alone or in combination with an amount of growth hormone that is effective in combination with the IGF-I.

21 Claims, 38 Drawing Sheets

OTHER PUBLICATIONS

- Bjarnason et al., "Seasonal Variation in Growth Hormone Binding Protein (GHBP) Levels in Prepubertal Normal Growing Healthy Children" *The Endocrine Society 77th Annual Meeting* (Abstract P3-137) p. 500 (Jun. 1995).
- Blum et al., "Clinical Studies of IGFBP-2 by Radioimmunoassay" *Growth Regulations* 3:100-104 (1993).
- Blum et al., "Growth Hormone Insensitivity Syndromes: A Preliminary Report On Changes in Insulin-Like Growth Factors and Their Binding Proteins During Treatment with Recombinant Insulin-Like Growth Factor I" *Acta Paediatr Suppl* 391:15-19 (1993).
- Blum et al., "Improvement of Diagnostic Criteria in Growth Hormone Insensitivity Syndrome: Solutions and Pitfalls" *Acta Paediatr. Suppl.*, B. Lippe et al., Lisbon, Portugal vol. 399:117-124 (Presented Oct. 1993).
- Bramswig et al., "Adult Height in Boys and Girls with Untreated Short Stature and Constitutional Delay of Growth-And Puberty: Accuracy of Five Different Methods of Height Prediction" *J. Pediatr.* 117:886-891 (1990).
- Buchanan et al., "Laron-Type Dwarfism with Apparently Normal High Affinity Serum Growth Hormone-Binding Protein" *Clinical Endocrinology* 35:179-185 (1991).
- Carlsson et al., "Analysis of 24-Hour Plasma Profiles of Growth Hormone (GH)-Binding Protein, GH/GH-Binding Protein-Complex, and GH in Healthy Children" *J. Clin. Endocrin. and Metabol.* 77(2):356-361 (1993).
- Carlsson et al., "Decreased Growth Hormone (GH)-Binding Protein and Normal Endogenous GH Secretion in Children with Idiopathic Short Stature" (The Amer. Pediatric Society/The Society for Pediatric Research) (1992).
- Carlsson et al., "Ligand-Mediated Immunofunctional Assay for Quantitation of Growth Hormone-Binding Protein in Human Blood" *J. Clin. Endocrin. and Metabol.* 73(6):1216-1223 (1991).
- Carlsson et al., "Reduced Concentration of Serum Growth Hormone-Binding Protein in Children with Idiopathic Short Stature" *J. Clin. Endocrin. and Metabol.* 78(6):1325-1330 (1994).
- Chan et al., "Expression of Insulin-Like Growth Factor-1 in Uremic Rats: Growth Hormone Resistance and Nutritional Intake" *Kidney International* 43:790-795 (1993).
- Chanoine et al., "Growth Hormone (GH) Treatment in Short Normal Children: Absence of Influence of Time of Injection and Resistance to GH Autofeedback" *J. Clin. Endocrin. and Metabol.* 73(6):1269-1275 (1991).
- Clackson et al., "A Hot Spot of Binding Energy in a Hormone-Receptor Interface" *Science* 267:383-386 (1995).
- Clemons et al., "Laron Dwarfism: Growth and Immunoreactive Insulin Following Treatment with Human Growth Hormone" *J. Pediatr.*, 88(3):427-433 (1976).
- Costantino et al., "Insulin-Resistant MDA-MB231 Human Breast Cancer Cells Contain a Tyrosine Kinase Inhibiting Activity" *Molecular Endocrinology* 7(12):1667-1676 (1993).
- Cotterill et al., "The Effect of Recombinant Human Insulin-Like Growth Factor-I Treatment on Growth Hormone Secretion in Two Subjects with Growth Hormone Insensitivity (Laron Syndrome)" *Clin. Endocrin.* 39:119-122 (1993).
- Cowell et al., "Effects of Growth Hormone in Short, Slowly Growing Children Without Growth Hormone Deficiency" *Acta Paediatr Scand Suppl.* 366:29-30 (1990).
- Crowne et al., "Final Height in Boys with Untreated Constitutional Delay in Growth and Puberty" *Archives of Disease in Childhood* 65:1109-1112 (1990).
- Cunningham et al., "Growth Hormone Binding Protein Enhances the Growth Promoting Activity of GH in the Rat" *The Endocrine Society-Program and Abstracts* (73rd Annual Meeting) 1611:433 (1991).
- Daughaday et al., "Absence of Serum Growth Hormone Binding Protein in Patients with Growth Hormone Receptor Deficiency (Laron Dwarfism)" *Proc. Natl. Acad. Sci. USA* 84:4636-4640 (1987).
- De Vos et al., "Human Growth Hormone and Extracellular Domain of its Receptor: Crystal Structure of the Complex" *Science* 255:306-312 (1992).
- Diamond et al., "Hormonal, Metabolic and Pharmacokinetic Changes in Adults with Growth Hormone Receptor Deficiency Treated with Recombinant Human Insulin-Like Growth Factor I" *Acta Paediatr Suppl.* 383:148 (1992).
- Eshet et al., "Defect of Human Growth Hormone Receptors in the Liver of Two Patients with Laron-Type Dwarfism" *Is. J. Med. Sci.* 20:8-11 (1984).
- Fielder et al., "Expression of Serum Insulin-Like Growth Factors, Insulin-Like Growth Factor-Binding Proteins, and the Growth Hormone-Binding Protein in Heterozygote Relatives of Equadorian Growth Hormone Receptor Deficient Patients" *J. Clin. Endocrin. and Metabol.* 74:743-750 (1992).
- Fielder et al., "Serum Profiles of Insulin-Like Growth Factors and Their Binding Proteins in Adults with Growth Hormone Receptor Deficiency Treated with Insulin-Like Growth Factor I" *Acta Paediatr Suppl.* 388:40-43 (1993).
- Fine et al., "Growth After Recombinant Human Growth Hormone Treatment in Children with Chronic Renal Failure: Report of a Multicenter Randomized Double-Blind Placebo-Controlled Study" *J. Pediatr.* 124(3):374-382 (Mar. 1994).
- Fontoura et al., "Effect of growth hormone on the low level of growth hormone binding protein in idiopathic short stature" *Clin. Endocrin.* 37:249-253 (1992).
- Frasier et al., "Clinical Review 11: The Rational Use of Growth Hormone During Childhood" *J. Clin. Endocrin. and Metabol.* 71:269-273 (1990).
- Gargosky et al., "The Composition and Distribution of Insulin-Like Growth Factors (IGFs) and IGF-Binding Proteins (IGFBPs) in the Serum of Growth Hormone Receptor-Deficient Patients: Effects of IGF-I Therapy on IGFBP-3" *J. Clin. Endocrin. and Metabol.* 77:1683-1689 (1993).
- Genentech, Inc., "Response to Growth Hormone in Children with Idiopathic Short Stature" *Acta Paediatr Scand* (Suppl.) 366:24-26 (1990).
- Gillespie et al., "Enhanced Potency of Truncated Insulin-Like Growth Factor-I (des (1-3) IGF-I) Relative to IGF-I in lit/lit mice" *J. Endocrin.* 127:401-405 (1990).
- Gluckman et al., "Therapeutic use of insulin-like growth factor I: lessons from in vivo animal studies" *Acta Paediatr* (Suppl.) 383:134-136 (1992).
- Goddard et al., "Growth Hormone (GH) Receptor Defects are Present in Selected Children with Non-GH-Deficient Short Stature: A Molecular Basis for Partial GH-Insensitivity" *Proc. 76th Ann. Meeting of Endocrine Society* p. 204 (Jun. 1994).

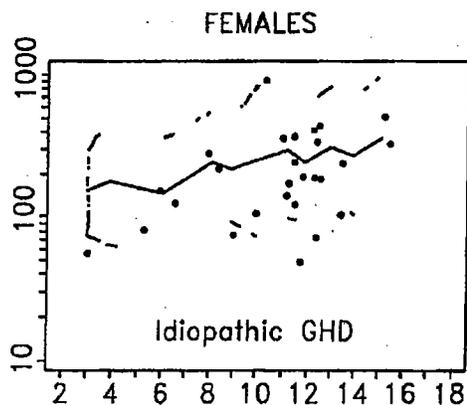


FIG. 1A

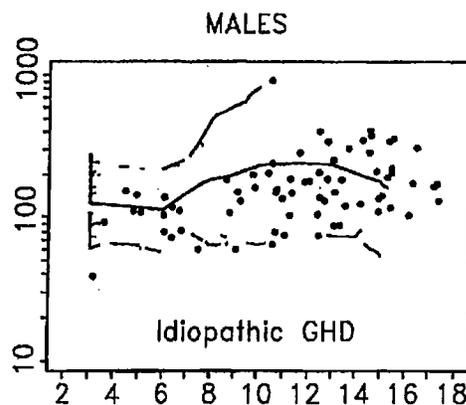


FIG. 1B

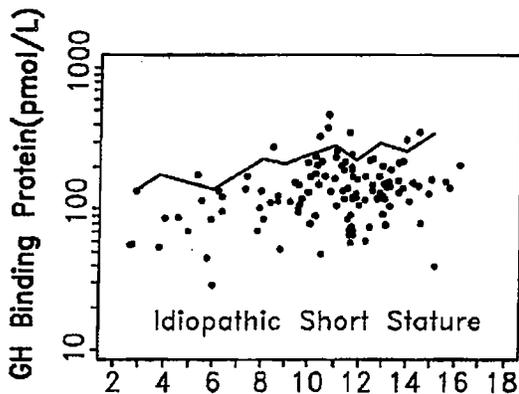


FIG. 1C

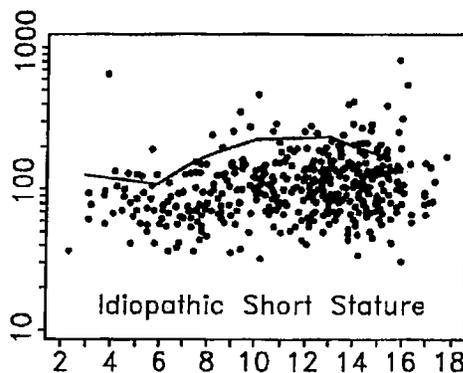


FIG. 1D

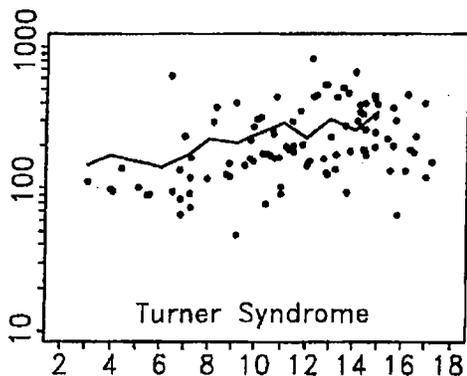


FIG. 1E AGE(yr)

8/5/05

EXCLUSIVITY SUMMARY

NDA # 21-839

SUPPL #

HFD # 510

Trade Name INCRELEX

Generic Name mecasermin (rDNA origin) injection, 10 mg/mL

Applicant Name Tercica, Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement? YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1) original NDA

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.") YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

7 - orphan exclusivity

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

Investigation #2

!

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Enid Galliers
Title: CPMS, DMEDP
Date: 8/4/05

Name of Office/Division Director signing form: David G. Orloff, MD
Title: Director, DMEDP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Enid Galliers
8/5/05 11:52:17 AM

David Orloff
8/5/05 12:10:45 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-839 Supplement Type (e.g. SE5): _____ Supplement Number: n/a

Stamp Date: 2/28/05 Action Date: no later than 8/31/05

HFD-510 Trade and generic names/dosage form: INCRELEX (mecasermin [rDNA origin] injection) 10 mg/mL

Applicant: TERCICA, INC. Therapeutic Class: 1 P, V DESIGNATED ORPHAN

Indication(s) previously approved: None.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application: 1

Indication #1: Treat growth failure in pediatric patients with severe primary IGF-1 deficiency or with growth hormone gene deletion who have developed neutralizing antibodies to growth hormone.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min x kg _____ mo. 0 yr. _____ Tanner Stage _____

Max x kg _____ mo. _____ yr. 2 Tanner Stage _____

Reason(s) for partial waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Adult studies ready for approval

Formulation needed

Other: Condition is usually not diagnosed before this age.

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. 2 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 18 Tanner Stage _____

Comments: This drug should not be used in patients after their epiphyses have closed.

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by: Enid Galliers

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-839
HFD-960/ Grace Carmouze

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.
(revised 12-22-03)**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Enid Galliers
8/8/05 06:16:36 PM

1.3.3 Debarment Certification

FEB 24 2005

DEBARMENT CERTIFICATION

In accordance with the certification provision of the Generic Drug Enforcement Act of 1992, Tercica, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Ira Wallis, Ph.D
Vice President, Regulatory Affairs

Date



eSign Approval Form

As per 21CFR, Part 11 regulations, your electronic signature is a legally binding equivalent of your handwritten signature, and it indicates you have read, understood, and approved the attached document.

UserName: Ira Wallis (iwallis)

Title:

Date: Wednesday, 22 September 2004, 02:34 PM Pacific Standard Time

Meaning: Document Approval

Galliers, Enid M

From: Shawn McLaughlin [Shawn.McLaughlin@tercica.com]
Date: Thursday, August 25, 2005 6:39 PM
To: galliers@cder.fda.gov
Subject: Final Increlex PI and PPI
Importance: High

Dear Enid,

Attached are the final Package Insert and Patient Package Insert, as agreed upon at today's conference call.

We will also be submitting these items to the eCTD, as requested.

Please confirm receipt of this e-mail.

Regards,
Shawn

Shawn D. McLaughlin, MBA
Associate Director, Regulatory Affairs
Tercica Inc.
2000 Sierra Point Parkway, Suite 400
Brisbane, CA 94005
Direct: 650.624.4993
FAX: 650.624.4989

This communication is intended solely for the use of the addressee and may contain information that is legally privileged, confidential or exempt from disclosure. If you are not the intended recipient, please note that any dissemination, distribution, or copying of this communication is strictly prohibited. Anyone who receives this message in error should notify the sender immediately and delete it from his or her computer.

Galliers, Enid M

From: Shawn McLaughlin [Shawn.McLaughlin@tercica.com]
Date: Friday, August 26, 2005 5:12 PM
To: Galliers, Enid M
Subject: RE: PI.Tercica. 8-25-05.doc Agreed upon changes as dicussed this aft ernoon
Importance: High

Dear Enid,

We have incorporated the requested changes and I have attached the revised final PI.

We are also able to get the eCTD submission out today, so it should arrive in the EDR tomorrow.

Regards,
Shawn

Shawn D. McLaughlin, MBA
Associate Director, Regulatory Affairs
Tercica Inc.
2000 Sierra Point Parkway, Suite 400
Brisbane, CA 94005
Direct: 650.624.4993
FAX: 650.624.4989

This communication is intended solely for the use of the addressee and may contain information that is legally privileged, confidential or exempt from disclosure. If you are not the intended recipient, please note that any dissemination, distribution, or copying of this communication is strictly prohibited. Anyone who receives this message in error should notify the sender immediately and delete it from his or her computer.

-----Original Message-----

From: Galliers, Enid M [mailto:GALLIERS@cder.fda.gov]
Sent: Friday, August 26, 2005 1:44 PM
To: Shawn McLaughlin
Subject: PI.Tercica. 8-25-05.doc Agreed upon changes as dicussed this aft ernoon

9 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

ADRA Rev #1 of Action Package for NDA 21-839, Increlex (mescasermin injection)

Reviewer: Lee Ripper, HFD-102

Date received: 8/12/05

Date of review: 8/15/05

Date original NDA received: 2/28/05

UF goal date: 8/31/05

Proposed Indication: Long-term Tx of growth failure in children with severe primary IGF-1 deficiency (primary IGDF) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to growth hormone.

Action type: AP

RPM: Enid Galliers, x7-6429

Drug Classification: 1PV
505(b)(1) application

Patent Info on form FDA 3542a: Yes

Debarment Certification: AC

Safety Update: MOR pp 123-27

Clinical Inspection Summary: No DSI audits were performed.

ODS/DMETS Review of Proprietary Name: AC 8/20/04, 6/24/05

ODS/DMETS Review of Labels: 7/27/05

DSRCS Review of PPI: 7/25/05

DDMAC Review: 8/17/05

Risk Management Plan: Per 7/26/05 PSC/WU mtg, an RMP is not needed. Dr. Orloff to check with OCC on issues of abuse with mescasermin.

EA: Categorical exclusion granted.

EER: AC 8/2/05

Financial Disclosure: AC

PSC/WU Mtg: Minutes of 7/26/05 mtg are in pkg

CMC section to Eric Duffy, 8/16/05; review completed 8/24/05

P/T section to Ken Hastings, 8/16/05; review completed 8/24/05

1. Statistical review has not been finalized. Draft in package. *CM 8/23/05*
2. No division director memo. *Dr. Orloff will not write a review. Dr. Meyer's office director memo will suffice.*
3. DDMAC labeling review pending. *CM 8/17/05.*
4. Comments on letter to Dr. Meyer and Enid Galliers.
5. *Comments on PI and PPI to Dr. Meyer 8/24/05.*

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Leah Ripper
8/30/2005 01:42:01 PM
CSO

8/4/05

NDA REGULATORY FILING REVIEW (Including Memo of Filing Meeting)

NDA # 21-839 Supplement # N/A SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: INCRELEX
Generic Name: (mecasermin [rDNA origin] injection
Strengths: 10 mg/mL

Applicant: TERCICA, INC.

Date of Application: 24-FEB-2005
Date of Receipt: 28-FEB-2005
Date clock started after UN: N/A
Date of Filing Meeting: 20-APR-2005
Filing Date: 29-APR-2005
Action Goal Date (optional): N/A User Fee Goal Date: 31-AUG-2005

Indication(s) requested: "Long-term treatment of growth failure in children with primary IGF-1 deficiency (primary IGFD)"

Type of Original NDA: (b)(1) (b)(2) _____
OR
Type of Supplement: (b)(1) _____ (b)(2) _____

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:
_____ NDA is a (b)(1) application OR _____ NDA is a (b)(2) application

Therapeutic Classification: S: _____ P:
Resubmission after withdrawal? n/a Resubmission after refuse to file? n/a
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.) V

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid _____ Exempt (**orphan**, government)
Waived (e.g., small business, public health) _____

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx to OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the

product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO ✓

If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES NO ✓

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO ✓

If yes, explain.

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES ✓ NO

- Was form 356h included with an authorized signature? YES ✓ NO

If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ✓ NO

If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ✓ YES NO

If an electronic NDA, all certifications must be in paper and require a signature.

Which parts of the application were submitted in electronic format?

Additional comments:

- If in Common Technical Document format, does it follow the guidance? N/A ✓ YES NO

- Is it an electronic CTD? N/A YES ✓ NO

(If an electronic CTD, all certifications must be in paper and require a signature.) This eCTD properly contains electronic signatures.

Which parts of the application were submitted in electronic format?

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, _____ years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
However, the applicant referred to its orphan designation and included copies of relevant orphan designation letters.
- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.
NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"
- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES NO
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
- List referenced IND numbers: 139,679;
- End-of-Phase 2 Meeting(s)? Date(s) 3/5/03(Guidance) NO
 If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 5/27/04 NO
 If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 20, 2005

BACKGROUND: This product is a new molecular entity, mecasermin (recombinant human IGF-1) and is being proposed for the orphan indication, long-term treatment of pediatric patients with growth hormone deficiency. The worldwide population with Laron Syndrome, a subset of the GHIS population may only number 250 – 350 individuals. The drug product is a solution for subcutaneous injection that will be packaged in multiple dose vials.

Mecasermin was approved in Japan as SOMAZON for a different sponsor.

ATTENDEES:

Drs. Ahn, El Hage, L. Green, Roman, Sahlroot, Shen, & Yim; Mr. Fritsch, Ms. Slavin, Ms. Galliers

ASSIGNED REVIEWERS:

Dragos Roman, Xavier Ysern, Shen Xiao, Sang Chung, Todd Sahlroot, Vinayak Pawar

<u>Discipline</u>	<u>Reviewer</u>
Medical:	D. Roman
Secondary Medical:	-
Statistical:	T. Sahlroot
Pharmacology:	S. Xiao
Statistical Pharmacology:	?
Chemistry:	X. Ysern
Environmental Assessment (if needed):	n/a (categorical exclusion request)
Biopharmaceutical:	S. Chung
Microbiology, sterility:	V. Pawar
Microbiology, clinical (for antimicrobial products only):	n/a
DSI:	A. Slavin
Regulatory Project Management:	E. Galliers
Other Consults:	Carol Pamer, ODS safety evaluator Sandy Birdsong, ODS PM Diane Smith, DMETS, Debi Tran, DDMAC Jeanine Best, DSRCS - PPI

Per reviewers, are all parts in English or English translation? YES NO
 If no, explain:

CLINICAL FILE REFUSE TO FILE _____

- Clinical site inspection needed: YES NO
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A YES NO

The sponsor did not submit a risk management plan (RMP), but clinical reviewers did not think it necessary. Dr. Orloff decided that this NDA should have Priority review status (with a six-month review clock).

CLINICAL MICROBIOLOGY	NA <input checked="" type="checkbox"/>	FILE _____	REFUSE TO FILE _____
STATISTICS		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE _____
BIOPHARMACEUTICS		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE _____
	• Biopharm. inspection needed:		YES NO <input checked="" type="checkbox"/>
PHARMACOLOGY	NA _____	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE _____
	• GLP inspection needed:		YES NO <input checked="" type="checkbox"/>
CHEMISTRY		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE _____
	• Establishment(s) ready for inspection? (Contract mfr.'s do not make this drug continuously)		YES <input checked="" type="checkbox"/> NO
	• Microbiology		YES <input checked="" type="checkbox"/> NO

ELECTRONIC SUBMISSION: This is an eCTD, and all reviewers have been scheduled for training. The firm has established secure email w/ CDER.

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

- _____ The application is unsuitable for filing. Explain why:
- _____ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.
- _____ No filing issues have been identified.
- _____ Filing issues to be communicated by Day 74. List (optional):
- Although not a refuse to file issue, the biopharmaceutics reviewer could not locate raw data for the clinical pharmacology studies and an electronic submission of those data was requested and made.
 - The reviewers needed clarification on how various formulations in different studies relate to the to-be-marketed formulation.
 - The original orphan designation letter (for Genentech) was requested and received.

ACTION ITEMS:

Document filing issues/no filing issues must be conveyed to applicant by Day 74, May 13, 2005. An "FN" letter issued May 4, 2005.

_____ *{See appended electronic signature page.}*
 Enid Galliers, Supervisory Project Manager, HFD-510

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Appears This Way
On Original**

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES NO

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES NO

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO

10. Are there certifications for each of the patents listed for the listed drug(s)? YES NO

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

_____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

_____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

_____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

_____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

*IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

_____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

_____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

_____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

_____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

	YES	NO
--	-----	----

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

	YES	NO
--	-----	----

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

	N/A	YES	NO
--	-----	-----	----

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

	N/A	YES	NO
--	-----	-----	----

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

	YES	NO
--	-----	----

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

	YES	NO
--	-----	----

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.		IND # _____	NO
OR			
A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?			
	YES	NO	

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

	YES	NO
--	-----	----

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Enid Galliers
8/4/05 12:51:37 AM
CSO

8/2/05

Galliers, Enid M

From: Galliers, Enid M
Sent: Tuesday, August 02, 2005 6:03 PM
To: 'Shawn McLaughlin'
Subject: Requested changes to the vial and carton labels

Dear Shawn:

We are requesting the following changes to the vial and carton labels based on consult reviews just completed by two divisions in the Office of Drug Safety as well as this division's review. Please contact me as soon as possible regarding your decision on these changes.

A. VIAL LABEL

1. Assure that the established name is at least as high as half the height of the proprietary name (see 21 CFR 201.10(g)(2).)
2. The "weight" of the established name is very light and it is quite difficult to read. This should be remedied.
3. The strength statements must be relocated directly below the established name and be stated as shown below:

40 mg/4 mL
(10 mg/mL)

4. The net quantity statement ("40 mg") should remain on the principal panel, but it should be less prominent in font weight. We also suggest adding a clarifying descriptor such as "Net wt. 40 mg" and relocating it to a less prominent position and font weight.)
5. "For subcutaneous use only" should be moved to the principal display panel.
6. The large pinwheel logo obscures the text; it should be removed. The small pinwheel logo used to dot the "i" is acceptable.
7. Modify the storage condition statement to "Protect from freezing and direct light."

CARTON LABEL:

1. See A1-A7.
2. Follow the instruction to "Protect from freezing and direct light" with another sentence, "Keep refrigerated and use within 30 days of vial entry" on the same display panel. (Moving the distributor information to another panel (not the principal one) should make this feasible.
3. The statement [] should be changed to "One multi-use vial," and it might allow room for other required information if that statement appeared on only one or two panels.

Clean copies of the PI and PPI agreed to last Friday, July 29, are enclosed in MS Word. I've accepted the changes we agreed to but the items which require your input (e.g., the structure of the compound, information for Table 1, figure labeling in Instructions for Use, etc.) have been marked up (as changes) in red. Also, minor typing errors were corrected but are not marked in red. It would be helpful to use a labeling identifier number for the package insert, patient package insert, carton label, and vial label to be able to distinguish among versions of approved labeling in the future. Please consider adding ID numbers to labeling pieces. An issuance date (for the initial approved label) and a "Revised" date for subsequent approved labeling is required for the PI and PPI. Finally, we discovered that the name "INCRELEX" needed to be replaced with "IGF-1" in another part of the DESCRIPTION section, and it is marked in red. Please notify me if we have different understandings about anything in the PI or PPI.

Best regards,



PI.NDA PPI.agreed07-2
9.080205.doc (marked up.0802

Enid

11 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

MEMORANDUM OF TELECON

DATE: 29 July 2005

APPLICATION NUMBER: NDA 21-839
INCRELEX (mecasermin [rDNA origin] injection)

BETWEEN:

Thorsten Von Stein, MD, PhD	Sr. Vice President-Clinical & Regulatory, Chief Medical Officer
George Bright, MD	Vice President and Medical Director, Endocrinology
Ira Wallis, PhD	Vice President – Regulatory Affairs
Ross Clark, PhD	Chief Technical Officer
James Frane, PhD	Acting Director – Biostatistics
Shawn McLaughlin, MBA	Associate Director – Regulatory Affairs
Christine Kubik, RAC	Manager – Regulatory Affairs

Phone: Conference Call-in Number

Representing: Tercica, Inc.

AND

FDA:

David Orloff, MD, Director, Division of Metabolic and Endocrine Drug Products (DMEDP)
Dragos Roman, MD, Medical Officer, DMEDP
Enid Galliers, CPMS, DMEDP

SUBJECT: Discussion of changes to Package Insert (PI) and Patient Package Insert (PPI)

BACKGROUND: On July 22, 2005, FDA sent (by secure email) labeling changes to Tercica that had been requested by the preclinical, clinical pharmacology and chemistry disciplines. Tercica responded with acceptance or suggestions that were subsequently accepted. Those changes were incorporated in the February 24, 2005, Tercica proposed labeling. That revised labeling was then modified with FDA-proposed clinical changes and sent to Tercica by secure email on July 25, 2005.

DISCUSSION:

On July 27, 2005, FDA and Tercica discussed the proposed changes. At the conclusion of the telecon, both groups appeared to be in agreement. FDA reminded the firm that review by the Office Director had not yet occurred, so additional labeling change requests might still be made.

Tercica agreed to incorporate the changes discussed in that telecon in the PI and PPI and to send them to FDA by secure email as soon as they were available. In the case of the PPI, Tercica needed to have a contractor produce some additional illustrations. Because of the possibility of additional changes, FDA requested the firm not to submit the revised labeling to the eCTD.

POSTMEETING NOTE:

Tercica emailed revised PI on August 2, 2005, with a few minor changes. The revised PPI was emailed to FDA on August 8, 2005. The FDA chemist accepted the chemical structure that had

July 29, 2005, Telecon – NDA 21-839

Page 2

been inserted at his request. The medical officer found the labeling generally acceptable but wants to propose a few minor changes.

On the date this memo is completed, the labeling needs to be reviewed by the FDA statistician (Table 1 in the PI only) and have a final check by the Division Director. Attached to this memo is a copy of the most recent labeling submitted by the firm with Tercica's changes accepted and FDA's latest comments added. Since not all FDA changes are clearly indicated, a summary of the comments and changes precedes the labeling.

{See appended signature page.}

Enid Galliers
CPMS, DMEDP

ATTACHMENTS:

August 10 FDA Comments, Change Requests

August 10, 2005, PI (w/ FDA mark-ups)

August 10, 2005, PPI (w/ FDA mark-ups)

August 10, 2005, FDA Division Comments on PI & PPI – INCRELEX, NDA 21-839

Package Insert (PI)-

1. [
- 2.
- 3.
- 4.
- 5.

J

Patient Package Insert (PPI) –

1. [
2. -----
- 3.
- 4.

J

Appears This Way
On Original

13 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

27 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

7/27/05

MEMO

To: David Orloff, MD
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

From: Kristina C. Arnwine, PharmD
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Through: Linda Kim-Jung, PharmD, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Date: July 25, 2005

Re: ODS Consult 04-0186-2, Increlex [Mecasermin (rDNA origin) Injection],
40 mg; NDA 21-839

This memorandum is in response to a June 29, 2005 request from your Division for a review of the container label and carton labeling of Increlex. The proposed proprietary name was found acceptable by DMETS initially on August 20, 2004 (see ODS Consult 04-0186) and then again on June 24, 2005 (see ODS Consult 04-0186-1). Although the package insert was available at the time of the previous reviews, only the text of the container label and carton labeling were available at that time. Thus, DMETS could not fully assess the container labels and carton labeling. This request contains full-color drafts of the container label and carton labeling. In review of the full-color drafts, DMETS has identified the following areas of improvement.

A. GENERAL COMMENTS

1. Per CFR 21 201.10(g)(2), increase the prominence of the established name so that it is at least ½ the size of the proprietary name. Additionally, the low “weight” of the font used for the established name causes the established name to be difficult to read. Revise accordingly.
2. Revise the total drug content statement to include the total volume as well as the number of total milligrams per vial followed by the concentration. For example.

40 mg/4 mL
(10 mg/mL)

3. Relocate the total drug content statement and concentration so that they are presented directly below the established name.
4. Include the route of administration on the principal display panel.
5. Remove the large “pinwheel” graphic, as it is distracting and detracts from the readability of the labels and labeling.

B. CARTON LABELING

Include the statement, “Keep refrigerated and use within 30 days of initial vial entry,” on the carton labeling as well as the container label.

We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Diane Smith, project manager, at 301-827-1998.

**Appears This Way
On Original**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Kristina Arnwine
7/27/05 04:06:26 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
7/27/05 04:08:12 PM
DRUG SAFETY OFFICE REVIEWER
Also signing for Linda Kim-Jung Team Leader

Carol Holquist
7/27/05 04:34:11 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 26, 2005

TIME: 9:00 – 10:00 AM

LOCATION: PKLN 14B-39

APPLICATION: NDA 21-839

DRUG NAME: INCRELEX (mecasermin [rDNA origin] injection), 40 mg/mL

TYPE OF MEETING: Pre-Approval Safety Conference (PASC) & Wrap-Up (WU)

MEETING CHAIR: David G. Orloff, MD

MEETING RECORDER: Enid Galliers

FDA ATTENDEES: (Title and Office/Division)

Rosemary Johann-Liang, MD, Deputy Director, Division of Drug Risk Evaluation, ODS

Lanh Green, PharmD, Team Leader, Safety Evaluators, DDRE, ODS

Carol Pamer, RPh, Safety Evaluator, DDRE, ODS

Sammie Beam, RPh, Regulatory Project Manager, DDRE, ODS

Robert J. Meyer, MD, Director, Office of Drug Evaluation II (ODE II), OND

Lee Ripper, ADRA, ODE II, OND

Jeff Fritsch, Office of Orphan Product Development, OC

David Orloff, MD, Director, Division of Metabolic and Endocrine Drug Products (DMEDP), ODE II

Dragos Roman, MD, Clinical Reviewer, DMEDP

Jeri El Hage, PhD, Supervisory Pharmacologist, DMEDP

Shen Xiao, PhD, Pharmacology Reviewer, DMEDP

Sang Chung, PhD, Biopharmaceutics Reviewer, DPE II, OCPB

Eric Duffy, PhD, Director, Division of New Drug Chemistry II, ONDC

EXTERNAL CONSTITUENT ATTENDEES: None.

BACKGROUND:

INCRELEX is an injectable human recombinant insulin-like growth factor-1 (IGF-1) product that is proposed for the treatment of extreme short stature in pediatric patients who have normal growth hormone secretion but are growth hormone insensitive. The applicant has received an orphan designation for the proposed indication/product. Most of the patients studied have been diagnosed with growth hormone insensitivity syndrome (GHIS) associated with Laron syndrome in which the patients have growth hormone receptor defects.

This drug product was studied – and the proposed labeling recommends – using twice daily dosing via subcutaneous injection. The product is packaged in multi-use vials containing a total of 40 mg mecasermin at a concentration of 10 mg/mL.

MEETING OBJECTIVES:

- **PASC-** To discuss potential serious adverse events (SAEs) that could appear in the postmarketing phase and ways to minimize or manage SAEs observed in the clinical trials.
- **WU -** To provide the signatory authority with an overview of the NDA.

DISCUSSION POINTS:

The progress of the following reviews was described:

- Pharmacology and biopharmaceutics reviews are complete and recommend approval.
- Chemistry review # 2 is in final draft (recommending approval) but awaits submission of two postmarketing commitments and revised specifications by Tercica.
- The sterility assurance review is in final draft and awaits submission of data already provided by secure email. A recommendation to approve is anticipated.
- The drafted clinical review will recommend approval.
- The statistical review is ongoing.

Because of mecaseermin's insulin-like action, hypoglycemia is a likely adverse reaction. Hypoglycemia was observed in 42% of the patients studied in the open-label, historical-controlled trials. However, about 50% of GHIS patients were hypoglycemic before treatment. Most of the hypoglycemia reactions were mild to moderate, but four of the five severe hypoglycemia episodes involved hypoglycemic seizures. A temporal relationship between dosing and hypoglycemic events was observed. The activity of mecaseermin (rhIGF-1) is analogous to treatment with short-acting insulins. Dr. Roman recommended strengthening labeling language to reinforce the need to consume a meal within a short time frame of injecting IGF-1, and the participants concurred. Also, the labeling for patients strongly warns against taking an injection if the patient has not eaten or cannot eat and also includes instructions not to double the dose if one was missed.

Injection site reactions were cited frequently, but they were not deemed serious. The labeling instructs the patient to rotate sites among four areas of the body (eight sites) and illustrates those sites clearly. This was not identified as an area of concern by the participants at the meeting.

Tonsillar hypertrophy can be monitored easily since the symptoms include snoring, sleep apnea, and difficulty breathing or swallowing. These symptoms are described in the patient labeling with advice to notify the patient's physician if the symptoms are bothersome.

Intracranial hypertension can be caused by IGF-1 as well as growth hormone. The patient labeling mentions that the occurrence of headache with vomiting should be reported to the physician

As with growth hormone, IGF-1 is contraindicated in patients with active or suspected neoplasia.

Some metabolic abnormalities including hypercholesterolemia and liver enzyme elevations were observed in the GHIS patients but it is believed likely that they may be associated with the disease itself.

Although rare instances of valvular disease were observed in the studies, there is no plausible mechanism that would implicate IGF-1.

The possibility of diversion by body builders, etc. was discussed. It appears currently that the manufacturer is not ready to make enough of this drug product to supply such a market, and the Division has no special concern about the possibility of diversion. Nonetheless, it was recommended to contact OCC to explore the issue of regulatory prohibition of off-label prescribing similar to that for growth hormone. In addition, it was agreed that the labeling would state that IGF-1 should not be used as a substitute for growth hormone.

DECISIONS (AGREEMENTS) REACHED:

- Anticipated occurrence of hypoglycemia may be reduced by only injecting the drug product within a short (to-be-defined) time before or after the patient consumes a snack or meal. Also, DMEDP is considering adding a labeling recommendation to initiate treatment at a dose lower than the recommended therapeutic dose.
- The expected adverse events can be monitored and managed by the endocrinologist who treats the GHIS patient.
- This NDA does not require a Risk Management Plan.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION: None.

ACTION ITEMS: Consult ORP and OCC regarding the potential for diversion of the drug product by the same population that uses growth hormone off-label.

Cleared by: 8.05.05
David Orloff, MD

Recorded by: 8.10.05
Enid Galliers

HANDOUTS:

Applicant's Original (2/24/05) Proposed Package Insert & Patient Package Insert

Initialed by: R. Meyer/ 8.04.05/ D. Orloff/ 8.05.05/ D. Roman/ 8.08.05/ C. Pamer/ 8.09.05/ L. Green/ 8.09.05/ R. Johann-Liang/ 8.10.05/

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Enid Galliers

8/10/05 04:39:06 PM

7/25/05

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 25, 2005

TO: David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products
HFD-510

VIA: Enid Galliers, Chief, Project Management Staff,
Division of Metabolic and Endocrine Drug Products
HFD-510

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCs Review of the Patient Labeling for Increlex (mecasermin [rDNA origin] injection), NDA 21-839

The attached is the revised patient labeling for Increlex (mecasermin [rDNA origin] injection), NDA 21-839. We have simplified the wording, made it consistent with the PI, and removed unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications). Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. We have also revised the leaflet to direct it to the parent or caregiver, as the product is indicated only in children.

These revisions are based on draft labeling submitted by the sponsor February 24, 2005. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

There are instructions for use at the end of the Patient Information leaflet and we have provided recommendations for minor language changes in the instructions section. Please also refer to the recommendations to improve clarity of instructions provided by the Division of Medication Errors and Technical Support (DMETS) (proprietary name review dated June 24, 2005).

Comments to the review division are bolded, underlined and italicized. We can provide a

3 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Jeanine Best
7/25/05 10:05:53 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
7/25/05 10:10:30 AM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

MEMORANDUM OF TELECON

DATE: 21 July 2005

APPLICATION NUMBER: NDA 21-839
INCRELEX (mecasermin [rDNA origin] injection)

BETWEEN:

Name: Shawn McLaughlin
Phone:
Representing: Tercica, Inc.

AND

Name: Enid Galliers and Xavier Ysern
DMEDP, HFD-510

SUBJECT: Request for agreement to and submission of Chemistry PMCs

BACKGROUND: The sponsor submitted (by email) on June 27, 2005, and to the eCTD on (July 13, 2005) responses to the CMC DR letter dated June 20, 2005, and CMC review #2 has been drafted. The Agency does not agree to certain responses made by the company; however, some of the required information may be submitted subsequent to approval. Also, some of the firm's proposed responses now need to be submitted formally. The firm will be asked to agree to the studies and to amend the pending NDA with the PMCs.

DISCUSSION:

The issues are identified by the item number in the June 20, 2005, DR letter.

Dr. Ysern and I told Mr. McLaughlin that the firm's response to Item 2 in the DR letter was acceptable; the firm proposed to [] and to include [] additional [] test. However, the firm must submit the revised drug substance specifications reflecting the inclusion of the additional test.

For Item 5, we told Mr. McLaughlin that determination of the expiration dating for the formulated drug substance [] could be evaluated after approval but the firm would need to make a Post-Marketing commitment (PMC) to submit the data from three lots of ds with at least [] (or more) stability data as soon after approval as available. (CMC Post-Marketing Commitment # 1)

Mr. McLaughlin asked if the firm could use the ds that had been stored in [] for [] to produce finished drug product if they tested each lot to confirm that it met acceptance criteria. Dr. Ysern told him that the Agency agreed to that proposal. We confirmed that the expiry dating for drug product is 12 months.

For Item 6, Dr. Ysern noted that acceptance criteria are based on the provided stability data of

commercial size batches, and due to the limited stability data currently available, the Agency-recommended modifications (from June 20, 2005) to those criteria; i.e., purity, ζ remain unchanged. Therefore, the firm needs to provide updated Drug Product Specifications that reflect these changes. Dr. Ysern commented that the recommended acceptance criteria could be re-evaluated in the future after submission of more extensive stability data.

For Item 7, Dr. Ysern verified that the Agency accepted the firm's proposal to conduct the antimicrobial efficacy testing with — benzyl alcohol and to submit those results by early August was acceptable.

For Item 8, we told the firm that it would need to characterize the ζ J that are observed by — ' in the stability studies, but that could be done post-approval as a PMC. (*CMC Post-Marketing Commitment # 2*)

Mr. McLaughlin asked what the next steps were, and I told him that the firm should amend the NDA with the updated drug substance specifications for Item 2 and the revised acceptance criteria for Item 6. In addition, they should describe the studies for Items 5 and 8 with estimates for dates to submit the protocols, start the studies, and to submit the final results. I said that the firm did not need to respond immediately, but a submission by the end of next week would be good.

{See appended signature page.}

Enid Galliers
CPMS, DMEDP

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Enid Galliers
7/22/05 01:09:49 PM
CSO



13 July 2005

David Orloff, MD
Director, Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
ATTN: Document Control Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

**RE: NDA 21-839; Amendment 0003
INCRELEX™ (mecasermin [rDNA origin] injection)
Recombinant Human Insulin-Like Growth Factor-1 (rhIGF-1)
Chemistry Information Amendment and Orphan Drug Correspondence**

Dear Dr. Orloff,

Reference is made to our New Drug Application 21-839 for recombinant human Insulin-like Growth Factor-1 (rhIGF-1) for use as replacement therapy in the long-term treatment of growth failure in children with primary IGF-1 deficiency (Primary IGFD). This NDA was submitted in electronic Common Technical Document (eCTD) format on 24 February 2005, and filed on 28 April 2005.

The purpose of this amendment (0003) to the NDA is to provide responses to review questions from the Chemistry Discipline Review letter (Item 1.11.1), received on 20 June 2005 (unchanged from the responses submitted on 27 June 2005 via secure e-mail).

In addition, this amendment contains a revised Section 3.2.P.8.2 Post-Approval Stability Protocol. The only change made in the section is in Table 3.2.P.8.2-3, where [] test had inadvertently been included. As discussed in NDA sections 3.2.P.8.3.1.1.6 and 3.2.P.5.6.3, the [] has been discontinued as a [] test, and is no longer run as part of stability protocols. These sections in the original NDA describe the rationale and justification for discontinuing the use [] because of its qualitative nature, and that two other assays [] performed as part of stability testing provide superior quantitative estimates of the degradation products expected to be seen by [] Its inclusion as a test in the proposed Post-Approval Stability Protocol was an error in the original NDA, so the revised version removes this test in Table 3.2.P.8.2-3.

Finally, as requested by Enid Galliers on 11 July 2005, this amendment provides copies of correspondence related to our Orphan Drug designation (Item 1.11.3).

The enclosed CD-ROM contains the entire NDA amendment in eCTD format. Tercica has scanned the enclosed CD-ROM using Symantec Anti-virus, version 8.1.0.825 (virus definition file 7/6/2005 rev.8), and declares the media to be virus-free.

If you have any questions or comments on this submission, please contact me by phone at (650) 624-4993 or email: shawn.mclaughlin@tercica.com. For technical assistance, please contact Esther Herrick, Associate Director, Regulatory Documentation, at (650) 624-4926 or e-mail: esther.herrick@tercica.com.

Sincerely,

{See appended electronic signature page}

Shawn D. McLaughlin, M.B.A.
Associate Director
Regulatory Affairs



eSign Approval Form

As per 21CFR, Part 11 regulations, your electronic signature is a legally binding equivalent of your handwritten signature, and it indicates you have read, understood, and approved the attached document.

UserName: Shawn McLaughlin (smclaughlin)

Title:

Date: Wednesday, 13 July 2005, 10:35 AM Pacific Standard Time

Meaning: Document Approval

7/13/05

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE <i>(Title 21, Code of Federal Regulations, Parts 314 & 601)</i>	Form Approved: OMB No. 0910-0338 Expiration Date: August 31, 2005 See OMB Statement on page 2.
	FOR FDA USE ONLY
	APPLICATION NUMBER 021839

APPLICANT INFORMATION	
NAME OF APPLICANT Tercica, Inc.	DATE OF SUBMISSION 13 July 2005
TELEPHONE NO. (Include Area Code) (650) 624-4900	FACSIMILE (FAX) Number (Include Area Code) (650) 624-4989
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 2000 Sierra Point Parkway, Suite 400 Brisbane, CA 94005	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE NA

PRODUCT DESCRIPTION		
NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) mecasermin	PROPRIETARY NAME (trade name) IF ANY INCRELEX™	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) Recombinant human insulin-like growth factor-1	CODE NAME (If any) rhIGF-1	
DOSAGE FORM: Liquid	STRENGTHS: 10 mg/mL	ROUTE OF ADMINISTRATION: Subcutaneous injection
(PROPOSED) INDICATION(S) FOR USE: Long-term treatment of growth failure in children with primary IGF-1 deficiency		

APPLICATION DESCRIPTION		
APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)		
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)		
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____		
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO APENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER		
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____		
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)		
REASON FOR SUBMISSION Information amendment: Chemistry		
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)		
NUMBER OF VOLUMES SUBMITTED <u>NA</u> THIS APPLICATION IS <input type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input checked="" type="checkbox"/> ELECTRONIC		

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
IND ~ IND 39,679; IND ~ IND ~ ; IND ~ IND ~ DMF ~ DMF ~ DMF ~

This application contains the following items: (Check all that apply)

<input checked="" type="checkbox"/>	1. Index index.dot.xml
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input checked="" type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2) Revised Section 3.2.P.8.2
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input checked="" type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) Responses to Chemistry Discipline Review, Orphan Designation correspondence

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT {See appended electronic signature}	TYPED NAME AND TITLE Shawn D. McLaughlin, Associate Director, Regulatory Affairs	DATE: 13 July 2005
ADDRESS (Street, City, State, and ZIP Code) 2000 Sierra Point Parkway, Suite 400, Brisbane, CA 94005		Telephone Number (650) 624-4993

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CDER, HFD-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER (HFD-94) 12229 Wilkins Avenue Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
--	---	--



eSign Approval Form

As per 21CFR, Part 11 regulations, your electronic signature is a legally binding equivalent of your handwritten signature, and it indicates you have read, understood, and approved the attached document.

UserName: Shawn McLaughlin (smclaughlin)

Title:

Date: Wednesday, 13 July 2005, 10:34 AM Pacific Standard Time

Meaning: Document Approval



6/20/05

DISCIPLINE REVIEW LETTER

NDA 21-839

Tercica, Inc.
Attention: Ira Wallis, Ph.D.
Vice President, Regulatory Affairs
651 Gateway Blvd., Suite 950
South San Francisco, CA 94080

Dear Dr. Wallis:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for INCRELEX (mecasermin [rDNA origin] injection); 10 mg/mL.

Our review of the chemistry, manufacturing, and controls section of your submission is complete, and we have identified the following deficiencies:

I. Drug Substance

A. Characterization

(1) Table 3.2.S.3.1-10 shows

Please provide the rationale for these assignments.

B. Control of Drug Substance

(2) As the test employing under reduced conditions does not discriminate between rhIGF-1,

The proposed under reduced conditions does not discriminate based on the expected primary structure for rhIGF-1 Either unreduced are potentially able to discriminate based on the expected primary structure for IGF-1. Provide test that discriminates which do not conform to the expected IGF-1 primary structure.

(3) The antibodies used in the commercial kit [redacted] used for the [redacted] determination [redacted] in the pharmaceutical industry. Clarify if E. coli [redacted] is one of the strains used in [redacted] antibodies used in the kit. If this is not the case, provide a rationale for the validity of the proposed ELISA test.

(4) [redacted]

C. Stability

(5) The information on the stability of the formulated bulk drug substance into [redacted] is very limited. Due to the problem encountered with the [redacted] all formulated bulk drug substance lots packaged into [redacted] have been discontinued. The only one lot packaged in the proposed [redacted] was manufactured at the time of the submission of this NDA and no stability data were provided. Clearly, shelf-life estimates for the formulated bulk drug substance cannot be estimated. A shelf-life dating for the formulated bulk drug substance packaged into the proposed [redacted] is not grantable, because of the limited data available. Therefore, drug substance batches should be immediately used for the manufacture of the drug product.

II. Drug Product

A. Control of Drug Product

(6) Based on the limited stability data you provided, the acceptance criteria of the purity testing [redacted] should be modified. The area [redacted] must be tightened to [redacted] % instead of the originally proposed [redacted]. [redacted] should be [redacted] instead of [redacted] and [redacted] should be changed from [redacted] to [redacted].

(7) The antimicrobial effectiveness of the benzyl alcohol was demonstrated at the target concentration of [redacted]. Because the specified limit for benzyl alcohol in the final formulation is [redacted] you should confirm the preservative effectiveness at the lowest acceptable concentration limit of [redacted].

B. Stability

(8) Several [redacted] [redacted], not seen at 2-8°C, appeared after [redacted] in samples stored at the 25°C/60% RH condition (lots 804336 and 804454). It would be of interest to identify these [redacted] to clarify if these [redacted] represent new degradation products not detected by [redacted] method.

(9) Based on the available primary data (a total of [redacted] with lot 804210, [redacted] with lots 804336 and [redacted] with 804454, at 2-8°C and at 25°C/60% RH storage

conditions) and the supportive stability data, the granted expiration dating is 12 months at the storage condition 2-8°C and protected from light. As satisfactory additional data become available, extension of the expiration period may be granted by the Agency.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call me at (301) 827-6429.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Enid Galliers
6/20/05 11:57:52 AM

The attached MEMORANDUM OF TELECON has the incorrect date below the heading of the first page and a different incorrect meeting date in the header of subsequent pages. The telecon took place on June 10, 2005.

*Appears This Way
On Original*

MEMORANDUM OF TELECON

DATE: 10 July 2005

APPLICATION NUMBER: NDA 21-839
INCRELEX (mecasermin [rDNA origin] injection)

BETWEEN:

Thorsten Von Stein, MD, PhD	Sr. Vice President-Clinical & Regulatory, Chief Medical Officer
George Bright, MD	Vice President and Medical Director, Endocrinology
Ira Wallis, PhD	Vice President – Regulatory Affairs
Joyce Kuntze, RN	Director – Medical Science Liaisons
Jim Frane, PhD	Acting Director – Biostatistics
Shawn McLaughlin, MBA	Associate Director – Regulatory Affairs
Christine Kubik	Manager – Regulatory Affairs
Russ Clark	Chief Technical Officer
Jane Bailey	Division of Technical Communications

Phone: Conference Call-in Number
Representing: Tercica, Inc.

AND

FDA: Dragos Roman, MD, Medical Officer, DMEDP
Todd Sahlroot, PhD, Statistical Team Leader, DB II, OPaSS
Enid Galliers, CPMS, DMEDP

SUBJECT: Request for clarification of clinical and statistical information in NDA 21-839

BACKGROUND: On June 6, 2005, FDA sent (by secure email) a list of issues that the medical and statistical reviewers for this NDA wanted to discuss with Tercica (attached).

DISCUSSION:

The issues identified in the attachment were clarified, and the firm agreed to respond to them promptly. The firm offered to submit any responses that could be assembled quickly by secure email and they would target completing all responses and including them in the eCTD submission of the 120-day safety update, which was scheduled to be delivered on June 30, 2005. The FDA reviewers agreed to those time frames.

{See appended signature page.}

Enid Galliers
CPMS, DMEDP

ATTACHMENT:

FDA Information request sent by secure email on June 6, 2005

CLINICAL ISSUES TO BE DISCUSSED

General questions

1. Was mecasecmin dose-titration in patients enrolled late in Study 1419 done as outpatient or inpatient? If it was done as outpatient, was it as safe as the inpatient treatment initiation?
2. In SAS files “Study year” columns are described as “time from initiation of IGF-1 treatment.” The assumption is that any values ≤ 0 in this column represent baseline or pre-baseline values. Confirm this explanation or provide an alternative explanation if necessary. Why do some patients have multiple negative values in this column?

Efficacy questions

1. Height velocity < 50 th percentile for age and sex was an inclusion criterion. Yet the range of height velocity (HV) at baseline was up to 7.6 cm and/or 1.8 SD score. Was this baseline height velocity a protocol violation of the HV entry criterion? If so, were other such violations (provide patient ID and GH values for such patients) and how did they affect the primary efficacy analysis, if any.
2. The baseline range of maximum GH concentration was 0.5 to 209.0 ng/mL. Since patients were all supposed to be GH sufficient, was the value of 0.5 ng/mL a protocol violation? If so, were other such violations (provide patient ID and HV values for such patients) and how did they affect the primary efficacy analysis, if any.
3. Explain how the “expected” height was calculated based on the published growth curves for Laron Syndrome patients for the 6 patients with near-adult heights.

Safety

1. It was stated in the NDA that patients underwent funduscopic examinations at baseline and periodically during treatment as part of the routine physical examination and that “there were no reports of retinopathy or loss of vision during the study for any subject.” Where is such an analysis detailed in the NDA? If not presented, provide it.
2. Provide (or indicate where in the NDA submission are located) the mean \pm SD values at baseline, on treatment and at end of treatment for the following variables: hemoglobin, platelet counts, LDH, ALT, AST, calcium, phosphorus, T4, TSH, triglycerides. If not in the NDA, present this data in a table format indicating baseline, Year 1, Year 2, Year 3, etc. descriptive statistics (including the number of patients providing information for each yearly time point). For eosinophilia, present the number and percentage of patients with values above normal at each timepoint (baseline, Year 1, Year 2, Year 3, etc.) Indicate where in the NDA there is a summary of urinalysis results; if not, provide one.

3. Were the 23 patients who provide most of the safety laboratory data to study 1419, the Study F0671g patients which were “rolled” into 1419?

4. Explain and comment why such a large proportion of patients had abnormal baseline laboratory values (as an example, as many as 61% of AST values and 76 % of LDH values were abnormal prior to mecaseemin treatment).

5. In the investigator study F0363s, which enrolled patients with non GH-deficient short stature and Laron Syndrome, two patients had liver enzyme elevations (one of them had LFT elevation on re-challenge). Provide the specific LFTs on these two patients and comment on this finding.

Similarly, comment on the high cholesterol and triglyceride levels and the low phosphate serum concentrations (2-3.9 mg/dL) noted in a few patients in study 1419.

6. Identify in the submission the vital signs information for study 1419 (is it in essence the data of Study F0671g?) and the report of ECG results in any of the studies conducted (where any ECG analyses conducted, including QTc evaluations?).

7. Provide an explanation as why several patients had intermittent and end-of-trial echocardiographic abnormalities (described as “right and/or left ventricular hypertrophy/enlargement,” “pulmonary hypertension and tricuspid insufficiency,” “supranormal left ventricular performance.”) Also, comment on why adverse events of cardiomegaly Not Otherwise Specified (NOS) (2 patients), ventricular hypertrophy (3 patients), cardiac murmurs NOS (5 patients), tachycardia NOS (2 patients), dyspnea (1 patient) were considered by the investigators treatment-related. Provide an explanation as why all these findings should not alter unfavorably the risk/benefit balance of the product.

8. Provide graphic depictions of individual renal length values at baseline, on trial and at end of trial with mean and SD curves for all the patients evaluated. Similarly, provide graphic depiction of spleen length information at baseline, on trial and at end of trial (with 10th and 90th percentile references) as presented in a subgroup of patients (published data by Backeljaw et al in *J Clin Endocrinol Metab* **86**: 1504–1510, 2001). Present the GFR information in a similar way.

9. What were the specific adverse events labeled as “mucosal membrane hyperplasia” (4 patients) and “hypertrophy NOS” (3 patients)?

STATISTICAL ISSUES TO BE DISCUSSED:

1. How was the pre-dose height velocity calculated? That is, if multiple measurements were available pre-dose, which measurements were selected for the calculation of height velocity? Was any pre-dose height data collected prospectively?

2. Is there a variable in the electronic database to indicate which height measurements used in the efficacy analyses were made at the 2 primary centers, and which were made by the local endocrinologists?

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Enid Galliers
8/10/05 02:15:01 PM
CSO

Galliers, Enid M

6/6/05

From: Galliers, Enid M
Date: Monday, June 06, 2005 5:16 PM
To: 'Shawn McLaughlin'
Cc: Roman, Dragos; Sahlroot, Jon T
Subject: RE: NDA 21-839

Dear Shawn:

Thank you for the dial-in information and for the pediatric study plan exemption.

You are welcome to send the peds study plan exemption request by secure email; however, an official submission to the NDA is needed. That request may be included in the 120-day safety update submission -- along with any labeling revisions you propose and the mock-ups of the container and carton labels.

Issues for the June 10 telecon:

Clinical issues to be discussed

General questions

1. Was mecasermin dose-titration in patients enrolled late in Study 1419 done as outpatient or inpatient? If it was done as outpatient, was it as safe as the inpatient treatment initiation?
2. In SAS files "Study year" columns are described as "time from initiation of IGF-1 treatment." The assumption is that any values ≤ 0 in this column represent baseline or pre-baseline values. Confirm this explanation or provide an alternative explanation if necessary. Why do some patients have multiple negative values in this column?

Efficacy questions

1. Height velocity < 50 th percentile for age and sex was an inclusion criterion. Yet the range of height velocity (HV) at baseline was up to 7.9 cm and/or 1.8 SD score. Was this baseline height velocity a protocol violation of the HV entry criterion? If so, were other such violations (provide patient ID and HV values for such patients) and how did they affect the primary efficacy analysis, if any.
2. The baseline range of maximum GH concentration was 0.5 to 209.0 ng/mL. Since patients were all supposed to be GH sufficient, was the value of 0.5 ng/mL a protocol violation? If so, were other such violations (provide patient ID and HV values for such patients) and how did they affect the primary efficacy analysis, if any.
3. Explain how was the "expected" height calculated based on the published growth curves for Laron Syndrome patients for the 6 patients with near-adult heights.

Safety

1. It was stated in the NDA that patients underwent fundoscopic examinations at baseline and periodically during treatment as part of the routine physical examination and that "there were no reports of retinopathy or loss of vision during the study for any subject." Where is such an analysis detailed in the NDA? If not resented provide it.
2. Provide (or indicate where in the NDA submission are located) the mean \pm SD values at baseline, on treatment and at end of treatment for the following variables: hemoglobin, platelet counts, LDH, ALT, AST, calcium, phosphorus, T4, TSH, triglycerides. If not in the NDA, present this data in a table format indicating baseline, Year 1, Year 2, Year 3, etc. descriptive statistics (including the number of patients providing information for each yearly time point). For eosinophilia, present the number and percentage of patients with values above

6/6/2005

Memo

To: David Orloff, MD
Director, Division of Metabolic and Endocrine Drug Products; HFD-510

From: Felicia Duffy, RN
Safety Evaluator, Division of Medication Errors and Technical Support
Office of Drug Safety; HFD-420

Through: Alina Mahmud, RPh, MS, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support
Office of Drug Safety; HFD-420

Date: June 1, 2005

Re: ODS Consult 04-0186-1; Increlex (Mecasermin [rDNA origin] Injection) 40 mg/4 mL; NDA 21-839

This memorandum is in response to a May 5, 2005 request from your Division for a re-review of the proprietary name, Increlex. The proposed proprietary name, Increlex, was found acceptable by DMETS in a review dated August 20, 2004 (ODS Consult #04-0186). Container labels, carton, and insert labeling were submitted for review and comment with this consult.

Since the last review, DMETS has not identified any additional proprietary or established names that have the potential for confusion with Increlex. Therefore, we have no objections to the use of this proprietary name. However, DMETS has identified the following areas of improvement in the labels and labeling which may minimize potential user error. We also recommend consulting the Division of Surveillance, Research, and Communication Support (DSRCS) to review the patient package insert as this is a patient use injection product.

A. GENERAL COMMENT

Draft copies of the labels and labeling were provided in black and white, and do not represent the true color of the labels and labeling. It is not possible to fully assess the safety of the labels and labeling because the information provided does not reflect the presentation that will actually be used in the marketplace (i.e. color, placement of name, design, etc.). Please forward copies of the revised labels and labeling when available.

B. CONTAINER LABEL (40 mg/4 mL multi-use vial)

1. Please ensure that the established name is at least ½ the size of the proprietary name in accordance with CFR 201.10(g)(2).

2. In order to avoid confusion, we recommend expressing the strength in terms of total drug content as follows:

40 mg/4 mL
(10 mg/mL)

3. If space permits, include the net quantity statement on the container label.

4. The statement, “For subcutaneous use only” should be prominently presented on the primary display panel to ensure the appropriate route of administration. Please revise.

5. The storage instructions direct the user to ‘ \square ’. Since ‘ \square ’ is subjective, we recommend providing examples of what is considered \square , or revising the statement to read “Protect from light” to ensure the appropriate storage of the product. In addition, in the package insert, and on the carton label, the storage statement also includes protecting the vial from \square ; however, this statement is not mentioned on the container label. In the event the vial becomes separated from the carton, if the package insert is misplaced, and to maintain consistency, please include the \square statement in the storage section.

C. CARTON LABELING (40 mg/4 mL multi-use vial)

1. See comments B1 through B5.

2. Please add the important statement “Use within 30 days of initial vial entry”, as it does not appear on the carton.

D. PACKAGE INSERT

1. Trailing zeros are present throughout the package insert. To avoid confusion, delete the trailing zeros throughout the package insert labeling since it may be misinterpreted, and potentially create a 10-fold error. In accordance with the 2004 USP General Notices chapter, “Use of Leading and Terminal Zeros” subsection (page 10), “In order to minimize the possibility of errors in the dispensing and administration of the drugs, the quantity of active ingredient when expressed in whole numbers shall be shown WITHOUT a decimal point that is followed by a terminal zero.” We also note that the Joint Commission for Accreditation of Hospitals (JCAHO), 2005 Hospitals National Patient Safety Goals includes the goal: Improve the effectiveness of communication among caregivers. A requirement to meet this goal is that each hospital must “Standardize a list of abbreviations, acronyms and symbols that are not to be used throughout the organization.” The use of trailing zeros is specifically listed as a dangerous abbreviation, acronym, or symbol. Other healthcare organizations, such as ISMP have also published similar lists containing symbols that can lead to medication errors.

2. The second paragraph in the “Dosage and Administration” section states that “Increlex should be administered shortly before or after a meal or snack.” We recommend including a specific time frame of when Increlex should be administered with regard to meals. The phrase “shortly before of after a meal or snack” is vague and may be interpreted anywhere from 5 minutes to 30 minutes. Please provide more specific information since this product may cause hypoglycemia if it is not taken in a timely manner with regard to meals. Additionally please elaborate \square

3. See comment B5.
4. The “How Supplied” section describes Increlex as a “10 mg/mL sterile solution in 5 mL multiple dose glass vials (40 mg/vial).” Delete the vial size (5 mL) as it is irrelevant.

E. PATIENT PACKAGE INSERT

1. How Should I use Increlex?

See comment D2.

2. What are the Possible Side Effects of Increlex?

Line 16 of this section states: “You should not take Increlex if you are sick or unable to eat.” Since this is important information related to taking Increlex, relocate this statement to “How Should I use Increlex?”

F. INSTRUCTIONS FOR USE

1. In order to make it easier for the user to follow the instructions on the proper use of Increlex, label the illustrations (e.g., Figure 1, Figure 2, etc.). The illustrations should follow along with the step-by-step instructions.

2. Preparing the Dose

Step 6 states, ¹ Simplifying the instructions can increase the proper preparation of Increlex. For example, “Pull back on the plunger to draw air into the syringe equal to the Increlex dose”.

3. Injecting the Dose

Step 3 is very vague in the instructions on how to appropriately inject Increlex: ¹ We recommend more specificity in the injection instructions, as patients may not have had adequate education to inject Increlex. For example, there is no mention of aspirating prior to injection. This is important since intravenous administration of Increlex is contraindicated. Please revise.

In summary, we have no objections to the use of the proprietary name, Increlex. Additionally, DDMAC finds the proprietary name Increlex acceptable from a promotional perspective. We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the signature date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward. If you have any questions or need clarification, please contact Diane Smith at 301-827-1998.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Felicia Duffy
6/24/05 10:03:29 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
6/24/05 10:49:11 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
6/24/05 10:58:54 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/24/05 12:11:49 PM
DRUG SAFETY OFFICE REVIEWER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 39,679

5/9/05

Tercica, Inc.
Attention: Ira Wallis, Ph.D.
Vice President, Regulatory Affairs
651 Gateway Boulevard, Suite 950
South San Francisco, CA 94080

Dear Dr. Wallis:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for mecasermin (rDNA origin) injection [rhIGF-1].

We also refer to the January 24, 2005, meeting between representatives of your firm and FDA to discuss ☐

☐ We further refer to the minutes of that meeting issued on February 23, 2005.

At that time, we were unable to provide an answer to your question # 11 ☐

☐ Recently, the Office of Orphan Products Development provided its response to your question. Your question is restated below and the Agency response follows in **bold** type.

Question 11:

☐

FDA response:

The Office of Orphan Products Development has determined that rhIGF-1 is the active moiety of interest in this case. ☐

If you have any questions, contact Enid Galliers, Chief, Project Management Staff, at (301) 827-6429.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

David Orloff
5/9/05 05:16:29 PM



FILING REVIEW LETTER

NDA 21-839

Tercica, Inc.
Attention: Ira Wallis, Ph.D.
Vice President, Regulatory Affairs
651 Gateway Blvd., Suite 950
South San Francisco, CA 94080

Dear Dr. Wallis:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for INCRELEX (mecasermin [rDNA origin] injection), 10 mg/mL.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on April 29, 2005, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

However, we request that you submit the following information or tell us where they are located in the application:

BIOPHARMACEUTICS

1. Please submit electronic files for the NONMEM analysis of the population pharmacokinetic study. The file format should be plain text format (i.e., .txt).

Please respond only to the above request for additional information.

5/4/05 FN

NDA 21-839

Page 2

If you have any questions, call Enid Galliers, Chief, Project Management Staff, at (301) 827-6429.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.

Director

Division of Metabolic and Endocrine Drug Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

4.13.05
74-day Ltr.

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 39,679

Tercica, Inc.
Attention: Ira Wallis, Ph.D.
Vice President, Regulatory Affairs
651 Gateway Blvd.
Suite 950
South San Francisco, CA 94080

Dear Dr. Wallis:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Mecasermin Injection, 10 mg/mL.

We also refer to your amendment dated June 8, 2005, containing a request for the Agency to comment on the acceptability of the name "INCRELEX" you proposed as the trademark for a mecasermin injection NDA. We further refer to your submissions dated July 7, 2004, and January 11, 2005, which contained additional information requested by the Agency for its evaluation.

We have completed our review of your submissions and have the following comments.

At this time we have no objection to the use of the proprietary name, INCRELEX. However, you should be aware that the name will be re-reviewed within 3 months of an approval action to rule out any objections based upon approvals of other proprietary or established names that take place in the meantime.

If you have any questions, call Enid Galliers, Chief, Project Management Staff, at 301-827-6429.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

David Orloff
4/13/05 05:39:43 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

3/18/05 AC

NDA 21-839

3/18/05

Tercica, Inc.
Attn: Ira Wallis, Ph.D.
Vice President, Regulatory Affairs
651 Gateway Boulevard, Suite 950
South San Francisco, CA 94080

Dear Dr. Wallis:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Increlex™ [mecasermin (rDNA origin) injection]
Review Priority Classification:	Priority (P)
Date of Application:	February 24, 2005
Date of Receipt:	February 28, 2005
Our Reference Number:	NDA 21-839

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 29, 2005, in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be August 31, 2005.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. However, you have received an orphan designation for this drug and the indication proposed in the application, therefore, this application is exempt from the pediatric study requirements.

NDA 21-839

Page 2

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6429.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Enid Galliers
3/18/05 10:15:29 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

**PRESCRIPTION DRUG
USER FEE COVER
SHEET**

Form Approved: OMB No. 0910-0297
Expiration Date: December 31, 2006.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

<p>1. APPLICANT'S NAME AND ADDRESS Tercica, Inc. 651 Gateway Boulevard, Suite 950 South San Francisco, CA 94080</p>	<p>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER N021839</p>
<p>2. TELEPHONE NUMBER (Include Area Code) (650) 624-4920</p>	<p>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA).</p>
<p>3. PRODUCT NAME INCRELEX (mecasermin [rDNA origin] injection), mecasermin (rhIGF-1)</p>	<p>6. USER FEE I.D. NUMBER Not Applicable</p>

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input checked="" type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FORTHIS APPLICATION? YES NO
(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

<p>JRE OF AUTHORIZED COMPANY REPRESENTATIVE</p>	<p>TITLE Vice President, Regulatory Affairs</p>	<p>DATE 2/22/2005</p>
---	---	---------------------------



eSign Approval Form

As per 21CFR, Part 11 regulations, your electronic signature is a legally binding equivalent of your handwritten signature, and it indicates you have read, understood, and approved the attached document.

UserName: Ira Wallis (iwallis)

Title:

Date: Tuesday, 22 February 2005, 02:40 PM Pacific Standard Time

Meaning: Document Approval

2/16/05

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: June 28, 2004	DESIRED COMPLETION DATE: September 22, 2004	ODS CONSULT #: 04-0186
DATE OF DOCUMENT: June 8, 2004		

TO: David Orloff, MD
Director, Division of Metabolic and Endocrine Drug Products (HFD-510)
HFD-510

THROUGH: Monika Johnson
Project Manager
HFD-510

PRODUCT NAME: Increlex (Mecasermin Injection) (rDNA origin) 40 mg/4 mL (10 mg/mL)	IND SPONSOR: Tercica, Inc.
IND#: 39,679	

SAFETY EVALUATOR: Kimberly Culley, RPh

RECOMMENDATIONS:

- DMETS has no objections to the use of the proprietary name, Increlex from a safety perspective. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated upon submission of the NDA and approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
- Please provide labels and labeling upon receipt to DMETS for review and comment.
- DDMAC finds the proprietary name Increlex acceptable from a promotional perspective.

Carol Holquist, RPh
Director, Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242
Fax: (301) 443-9664

**Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: August 20, 2004

IND# 39,679

NAME OF DRUG: Increlex (Mecasermin Injection) (rDNA origin)
40 mg/4 mL (10 mg/mL)

IND HOLDER: Tercica, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510) for an assessment of the proprietary name, Increlex, in regard to potential name confusion with other proprietary or established drug names. Container labels and insert labeling were not provided for review and comment at this time.

PRODUCT INFORMATION

Increlex contains mecaseimerin from rDNA origin, which is a human insulin-like growth factor-1 (hIGF-1). IGF-1 is a hormone that is structurally related to insulin and induces metabolic and tissue growth response (particularly that of cartilage and bone growth). This effect is in addition to autocrine and paracrine activities. Increlex is a sterile, aqueous, clear and colorless solution for subcutaneous injection. The indication for use is long-term treatment of growth failure in children with primary IGF-1 deficiency. Increlex will be supplied in a multi-dose vial containing 10 mg/mL with a total vial content of 40 mg of mecaseimerin. The recommended starting dose is 0.08 mg/kg, twice daily; administered subcutaneously with or shortly after a meal. The patient should be titrated to a maximum of 0.12 mg/kg based on tolerability.

**Appears This Way
On Original**

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Increlex to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Increlex. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Error Prevention Staff with representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical skill, professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name of Increlex acceptable from a promotional perspective.
2. The Expert Panel identified ten proprietary names that were thought to have the potential for confusion with Increlex. Additionally, two names were identified by independent review. These products, with their available dosage forms and usual dosage, are listed in table 1 (see page 4).

Appears This Way
On Original

¹ MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://tess2.uspto.gov/bin/gate.exe?f=searchstr&state=m2pu5u.1.1>

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel and Independent Review			
Product Name	Established name, Dosage Form(s), Strength(s), Available dispensing size (if applicable)	Usual adult dose*	Other**
Increlex™	Mecasermin Injection, 10 mg/mL (40 mg vial)	0.08 mg/kg (up to 0.12 mg/kg) twice daily by subcutaneous injection.	
Antiflex	Orphenadrine Solution for Injection, 30 mg/mL (10 mL vial)	60 mg every 12 hours as needed	LA/SA
Azelex®	Azelaic Acid, 20% cream	Massage a thin film into the affected areas twice daily, in the morning and evening.	SA
Celebrex®	Celecoxib Capsules, 100 mg, 200 mg and 400 mg	<u>Osteoarthritis</u> : 200 mg/day; as a single dose or as 100 mg twice/day. <u>Rheumatoid arthritis</u> : 100 to 200 mg twice/day. <u>Acute pain and primary dysmenorrhea</u> : 400 mg initially, followed by an additional 200 mg dose if needed on the first day with subsequent days at 200 mg twice daily as needed. <u>Familial adenomatous polyposis</u> : 400 mg twice daily.	SA
Cerebyx®	Fosphenytoin Sodium Injection, 2 mL vial containing 150 mg Fosphenytoin Sodium equivalent to 100 mg of Phenytoin Sodium. 10 mL vial containing 750 mg Fosphenytoin Sodium equivalent to 500 mg of Phenytoin Sodium	<u>Status Epilepticus</u> : loading dose of 15 to 20 mg phenytoin sodium equivalent units (PE)/kg administered at 100 to 150 mg PE/min. <u>Nonemergent Loading and Maintenance Dosing</u> : loading dose of Cerebyx is 10-20 mg PE/kg given IV or IM. The initial daily maintenance dose of Cerebyx is 4-6 mg PE/kg/day. <u>Pediatric</u> : The safety of Cerebyx in pediatric patients has not been established. However dosing currently applied in clinical use in this population is 10-20 mg PE/kg for status epilepticus and seizure disorder loading dose with maintenance of 4 -6 mg PE/kg.	SA
Enablex	Darifenacin Hydrobromide Extended-release Tablets 7.5 mg and 15 mg	7.5 mg to 15 mg taken once daily.	SA/LA
Granulex®	0.12 mg Trypsin USP, 87 mg Balsam Peru, 788 mg Castor oil USP, an emulsifier and propellants (water dispersible) are contained in each gram.	Hold upright and approximately 12 inches from the area to be treated. Press valve and coat wound rapidly. Wound may be left unbandaged or a wet dressing may be applied. Apply twice daily or as often as necessary. To remove, wash gently with water.	LA

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel and Independent Review

Product Name	Established name, Dosage Form(s), Strength(s), Available dispensing size (if applicable)	Usual adult dose*	Other**
Increlex™	Mecasermin Injection, 10 mg/mL (40 mg vial)	0.08 mg/kg (up to 0.12 mg/kg) twice daily by subcutaneous injection	
Imitrex®	Sumatriptan Tablets: 25mg, 50mg , 100mg Injection: 6 mg/0.5 mL Nasal Spray: 5 mg and 20 mg	<u>Oral</u> : single doses of 25, 50, or 100 mg that may be repeated in 2 hours, not to exceed a total daily dose of 200 mg. <u>Injection</u> : maximum single adult dose is 6 mg injected SC. <u>Intranasal</u> : single doses of 5, 10, or 20 mg administered in 1 nostril are effective for the acute treatment of migraine in adults. A 10 mg dose may be achieved by administering a single 5 mg dose in each nostril. If headache returns, the dose may be repeated once after 2 hours, not to exceed a total daily dose of 40 mg.	LA/SA
Infanrix®	Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine, Adsorbed (DTAP) Injection: 25 Lf units Diphtheria Toxoid, 10 Lf units Tetanus Toxoid, 25 mcg Inactivated Pertussis Toxin, 25 mcg FHA, 8 mcg Pertactin per 0.5 mL	The primary series consists of three-0.5 mL IM doses. The customary age for the first dose is 2 months of age, but it may be given as early as 6 weeks of age and up to the seventh birthday. Preterm infants should be vaccinated according to their chronological age from birth.	SA
Insulin	Various	Varied	LA
Invirase®	Saquinavir Capsules, 200 mg	Three 200 mg capsules 3 times daily taken within 2 hours after a full meal in combination with a nucleoside analog	SA
Secremax™	Secretin Powder for Injection, 16 mcg	<u>Pancreatic Secretion Stimulation</u> : 0.2 mcg/kg IV over 1 minute <u>Gastrin Secretion Stimulation</u> : 0.4 mcg/kg IV over 1 minute <u>Pancreatic Secretion to aid in ERCP (endoscopic retrograde cholangiopancreatography)</u> : 0.2 mcg/kg IV over 1 minute	LA
Vincrex (discontinued)	Vincristine Injection, 5 mg vial	<u>Adults</u> : 1.4 mg/m ² <u>Children</u> : 2 mg/m ² . For children weighing ≤10 kg or having a body surface area < 1 m ² , give 0.05 mg/kg once a week.	LA/SA

*Frequently used, not all-inclusive.

**L/A (look-alike), S/A (sound-alike)

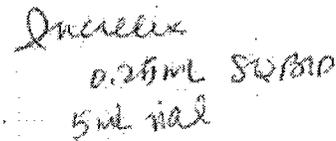
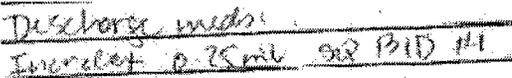
B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Increlex were captured by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Increlex with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Increlex (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail and sent to a random sample of the participating health professionals for their interpretation and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p><u>Outpatient RX:</u></p> 	<p>Increlex 0.25 mL SubQ twice a day Dispense one 5 milliliter vial</p>
<p><u>Inpatient RX:</u></p> 	

2. Results:

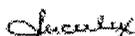
None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Increlex, the primary concerns related to look-alike and sound-alike confusion with Antiflex, Azelex, Celebrex, Cerebyx, Enablex***, Granulex, Imitrex, Infanrix, Insulin, Invirase, Secremax and Vincrex. Upon further review of the names gathered from EPD and independent analysis, Invirase was not reviewed further due to a lack of convincing sound-alike similarity with Increlex. In addition, the products do not share significant overlapping characteristics such as strength, indication of use, frequency of administration and route of administration.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Increlex.

1. Imitrex may look and sound similar to Increlex. Imitrex contains sumatriptan for the treatment of migraine and cluster headache. Imitrex is available in tablets (25 mg, 50 mg and 100 mg), injection (6 mg/0.5 mL) and nasal spray (5 mg and 20 mg). The auditory similarities are the result of the shared sounds in the leading syllables of "In" and "Im", central "e" (as in event with ĭ or ē sound) and finalizing "ex." These characteristics are also applicable to the visual similarities; the leading "n" and "m" may appear identical in script, which is also true of the central "i" and "e". For visual similarities, the upstrokes "t" and "l" may also lead to a similar resemblance (see below).



The products differ in dosing frequency (once, with the potential to repeat compared with twice daily), indication of use (migraines compared with growth failure in children), storage (room temperature compared to refrigeration) and strength (6 mg/0.05 mL compared with 10 mg/mL). However, they overlap in route of administration and dosage form (subcutaneous injection). Moreover, there is the potential for a dose of Increlex to overlap with Imitrex in a child who weighs 50 kilograms receiving 6 mg. The dispensing amount could also overlap if a practitioner ordered "#1", which could relate an auto-injector or a single vial. Although the frequency of dosing would not typically overlap, it would not be uncommon to see "Use as directed" and "dispense one" written on a prescription for either drug product. Due to the potential for overlapping characteristics, DMETS is concerned with the possibility for confusion. However, the sponsor has indicated that Increlex will have a limited distribution. This distribution will primarily involve ordering through one third-party logistics company for direct shipment to the patient via a provider (specialty and home health care pharmacies) who will complete the product order and insurance submission. Direct distribution helps to provide another method of distinction between the two drug products. The probability for a patient written a prescription for Increlex to be confused with Imitrex is

higher compared with the converse due to name recognition and higher dispensing numbers of Imitrex. As the distribution will be specific and the patient/provider will be expecting an injectable product requiring syringes/needles to be delivered to their home, the possibility for an error in administration lessens. In addition, since this Increlex will be used in a specific patient population, the patients/providers will likely be educated on the use of the product; henceforth aware of what to expect. This special ordering process, in adjunct with specificity of use, should help to minimize confusion between these two products.

2. Enablex may sound similar to Increlex when spoken and look similar when scripted. Enablex is the proposed proprietary name for darifenacin hydrobromide extended-release tablets indicated for the treatment of overactive bladder. The proprietary name of Enablex was reviewed by DMETS on 08 September 2004 (DMETS consult number 02-0006-2) and found acceptable. This drug product will be available as 7.5 mg and 15 mg extended-release tablets. The proposed dose is 7.5 mg daily, which may be increased to 15 mg daily. Enablex will be marketed in bottles of 30, 90, and 500 tablets. The phonetic similarities are due to the shared ending of "lex", equivalent auditory interpretation of "En" and "In" and identical syllable count. The remaining central syllable of "ab" and "cre" should serve as a distinct characteristic, but this could depend on where the emphasis or stress is placed in the name when spoken. If the speaker focuses on the "blex" of Enablex; this could result in the central "a" to be pronounced as "ə" not "ā". This is akin to the emphasis placed on the "lex" or Increlex, which could result in the central "e" pronounced as "ə" not "ē". The visual similarities stem from the shared ending of "lex", which is compounded by the possibility for the leading "en" and "in" to appear alike when scripted (see below). In addition, the "a" and "cr" of Increlex may resemble each other when scripted. However, the presence of two upstrokes in Enablex may contribute to name distinction.

There is also a possibility for dosing in close proximity to the 7.5 mg strength of Enablex and Increlex. For example, a 63 kilogram patient receives 0.12 mg/kg of Increlex, the resultant dose would be 7.56 mg. This dose is within the dosing range of both products, and could result in confusion. However, this is not a direct overlap in dose, only dosing in close proximity and the drugs products differ in the following characteristics: route of administration (oral compared with injectable), dosage form (tablets compared with injectable solution in vials), frequency of dosing (daily compared with twice daily), and indication of use (overactive bladder compared with growth failure in children). Although the products differ in dosage form, each may have prescriptions written with the instructions "use as directed" and the dispensing amount as a days supply (e.g. one month supply, etc).

However, the sponsor has indicated that Increlex will have a limited distribution. This distribution will primarily involve ordering through one third-party logistics company for direct shipment to the patient via a provider (specialty and home health care pharmacies) who will complete the product order and insurance submission. Direct distribution helps to provide another method of distinction between the two drug products. As the distribution will be specific and the patient/provider will be expecting an injectable product requiring syringes/needles to be delivered to their home instead of tablets, the possibility for an error in administration lessens. In addition, since this Increlex will be used in a specific patient population, the patients/providers will likely be educated on the use of the product; henceforth aware of what to expect. This special ordering process, in adjunct with specificity of use, should help to minimize confusion between these two products.

3. Antiflex may sound similar to Increlex when spoken and look similar when scripted. Antiflex contains orphenadrine for the treatment of muscle spasms or Parkinson's disease. The drug product is available in an injectable solution containing 30 mg/mL. Dosing is 60 mg intramuscularly twice daily as needed. The verbal similarities route in the three syllable composition, likeness of "an" and "in", tendency to speak the middle syllable of both names as "ā", and shared "lex" ending. The "t" of Antiflex and the "cr" of Increlex should help to distinguish the products verbally. The visual similarities result from a possibility for the leading "A" and "I" to appear similar when scripted, shared "n" as the second letter in the name and the shared concluding "lex" (see below). The "f" of Antiflex and the "cr" of Increlex should help to distinguish the products visually.

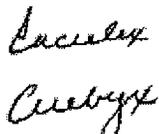
Antiflex Increlex

The drug products share a dosing frequency (twice daily) and dosage form (injection), but differ in method of administration (intramuscularly or intravenous Antiflex compared to subcutaneous Increlex). The products can be differentiated by their strengths (30 mg/mL compared with 10 mg/mL), dose (60 mg compared with 0.08 mg/kg up to 0.12 mg/kg), duration of therapy (switch as soon as possible to oral tablets compared with maintenance therapy), and indication (muscle spasm/Parkinson disease compared to long-term treatment of growth failure in children with primary IGF-1 deficiency). As the products differ in both dose and indication augmented by the lack of convincing look-alike and sound-alike similarities, DMETS believes the possibility for confusion to be minimal.

4. Azelex may sound like Increlex when spoken. Azelex contains azelaic acid in a cream for the treatment of acne vulgaris. The dosing regimen is twice daily to affected areas after washing and patting dry. The primary auditory similarities in name involve the shared ending of "lex" with the possibility of the central "ze" and "cre" sharing the same tone (ə, as in Zebeta® and Lycra). However, the names should be distinguished by the leading "Az" and "In", which are distinct in speech. This is especially true of the "A" of Azelex, if verbalized as a hard "ā" as in the words ache or atypical. Furthermore, the products do not share overlapping characteristics, such as route of administration (topical compared with injectable), strength (20% compared with 10 mg/mL), dosage form (cream compared with injectable), dose (thin film compared with 0.08 mg/kg up to 0.12 mg/kg) and indication (acne compared to long-term treatment of growth failure in children with primary IGF-1 deficiency). The products share the dosing frequency of twice daily, but the overwhelming differences should outweigh this similarity. Therefore, DMETS believes the chance of name confusion is minimal.

5. Celebrex may sound like Increlex when spoken. Celebrex contains celecoxib that is indicated for the treatment of osteoarthritis, rheumatoid arthritis, acute pain, primary dysmenorrhea, and familial adenomatous polyposis. Celebrex is available as 100 mg, 200 mg and 400 mg capsules. Dosing ranges from 100-400 mg twice daily or can be administered as 200 mg in a single dose for the treatment of osteoarthritis. The verbal similarities route in the shared syllable count, second “e” in Celebrex sounding as “a” and the concluding “ex.” However, the leading “Cel” and “In” should help to differentiate the two drug names. In addition, the products only share the dosing frequency of twice daily. They differ in route of administration (oral compared with subcutaneous injection), dosage form (capsule compared with injectable), strength (100 mg, 200 mg and 400 mg compared with 40 mg/4 mL), patient population (children under 18 have not been investigated with Celebrex compared with pediatric use), and dispensing amount (number of capsules compared with number of vials). Due to the differing product characteristics, DMETS believes the chance of error to be minimal.

6. Cerebyx may sound similar to Increlex when spoken and look similar when scripted. Cerebyx contains fosphenytoin sodium as an injection for short-term parenteral administration for status epilepticus indicated when other means of phenytoin administration are unavailable, inappropriate or deemed less advantageous. Indications include the prevention and treatment of seizures occurring during neurosurgery and control of generalized convulsive status epilepticus. Cerebyx can be substituted for oral phenytoin (less than 5 days). The verbal similarities stem from the shared three syllable composition and ending sound of “ex” (“yx” and “ex”). However, the leading “cere” as in the word “cerebral” and “incre” as in the word “incredible” should provide a differentiating characteristic in speech. The visual similarities route in the possibility for a leading “C” to resemble an “I”, shared central “re”, shared upstroke with similar placement of “b” and “l” and shared concluding “x” (see below).



 Increlex

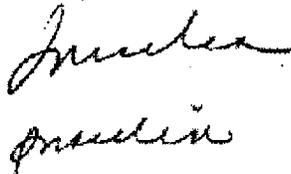
 Cerebyx

Visually they differ with the downstroke of the “y” in Cerebyx and the “nc” of Increlex. The products share the same dosage form (injectable), but differ in route of administration as Cerebyx is administered intravenous or intramuscular compared to subcutaneous administration of Increlex. Both products are also refrigerated. However, they differ in dose (4-20 mg PE/kg compared with 0.08 mg/kg up to 0.12 mg/kg), strength (150 mg and 750 mg compared with 40 mg/ 4 mL or 10 mg/mL), dosing frequency (constant infusion compared with twice daily administration), and indication (seizure activity compared with growth failure in children with primary IGF-1 deficiency). DMETS does not believe the probability of error to be great due to the differing indications, dosing regimens and lack of substantial verbal/visual similarities.

7. Infanrix may sound similar to Increlex when spoken. Infanrix is an active simultaneous immunization for diphtheria, tetanus, and pertussis in infants to children (6 weeks to 7 years). The first dose is administered at 2 months of age, but it may be given as early as 6 weeks of age and up to the seventh birthday. The CDC recommends the three doses of 0.5 mL to be administered at 2 months, 4 months, and 6 months of age. The primary phonetic similarities

result from the shared beginning of “In” and ending of “x” compounded by the shared syllable count. The middle phonemes of “fan” and “cre” and letters of “r” and “l” (before the shared “ix”) ending should help differentiate the names. Both products are stored under refrigeration and share a similar patient population (pediatrics) and route of administration (subcutaneous). In addition, there could be an overlap in Infanrix and Increlex delivery amount (0.5 mL) that would be would applicable for a child weighing 42 to 63 kilograms. However, this would conflict with the age appropriate use of Infanrix and would serve as a differentiating characteristic. Additionally, immunizations are usually written as only a one dose order (e.g. Infanrix 0.5 mL x 1 dose) and commonly this specific vaccination is written as “DPT” (e.g. DPT 0.5 mL x 1), both of which could help practitioners properly identify the correct drug product. Furthermore, the products do not share a similar dosing frequency (one dose compared with twice daily administration), route of administration (intramuscular compared with subcutaneous), dispensing vial size (single dose 0.5 mL vials compared with 4 mL multi-dose vial) and indication of use (immunization for diphtheria, tetanus, and pertussis compared with growth failure in children). Due to the distinct nature of immunizations and the lack of convincing auditory similarities, DMETS believes the potential for confusion to be low.

8. Insulin may look similar to Increlex when scripted. Insulin is indicated for Type 1 and Type 2 diabetes mellitus, hyperkalemia, and severe ketoacidosis/diabetic coma. The primary visual similarity results from the shared leading “In” and the congruently positioned “li” and “le” that gives the product names the same visual flow. In addition, a concluding “n” may resemble an “x”; therefore the centrally placed “cre” and “su” provide the only distinct visual cue for identification. Unfortunately, these do not hold power for busy practitioners who often obscure the central letters in lazy scripting (see below).



The image shows two lines of handwritten text in cursive. The top line is 'Insulin' and the bottom line is 'Increlex'. The letters 'In' at the start of both words are written in a very similar, slanted, cursive style. The 'li' in 'Insulin' and 'le' in 'Increlex' also appear to have a similar visual flow and shape, making them look alike when written quickly.

Overlapping characteristics include dose, storage, dosing frequency and route of administration. However, insulin is often written with a modifier (70/30, N or NPH, R, etc), brand name (Humulin, Novolin, etc), dosing regimen (sliding scale) or dose in number of units. Due to the necessity of a modifier and/or brand name, DMETS believes the possibility for confusion to be minimal.

9. Granulex® may look similar to Increlex when scripted. Granulex contains trypsin, balsam peru, castor oil in an emulsifier with propellants for the treatment of varicose ulcers, dehiscent wounds, decubital ulcers, sunburn and debridement of eschar. It may also used for general wound healing. Granulex is packaged as a 4 oz aerosol can. The visual similarities stem from the possibility for a capitalized, scripted “G” to look similar to an “I”, the “ne” of Granulex to look similar to “re” of Increlex and the shared “lex” ending (see below).

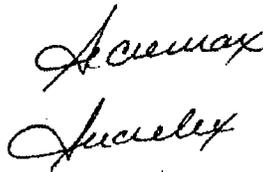


The image shows two lines of handwritten text in cursive. The top line is 'Granulex' and the bottom line is 'Increlex'. The capital 'G' in 'Granulex' is written in a way that makes it look like a capital 'I'. The 'ne' in 'Granulex' and 're' in 'Increlex' are also written in a similar, slanted, cursive style, making them look alike when written quickly.

The products overlap in frequency of dosing (twice daily). They differ in route of administration (topical compared with subcutaneous injection), strength (none to be specified compared with 10 mg/mL), dose (none to be specified compared with 0.08mg or

0.12 mg/kg), duration of therapy (until wound heals compared with maintenance), and indication (would healing compared with growth failure). Due to the numerous differences in product characteristics, DMETS believes the possibility of error to be minimal.

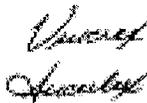
10. SecreMax may look similar to Increlex when scripted. SecreMax is a sterile powder acetate salt of secretin, a peptide hormone. SecreMax is indicated for use in secretin stimulation testing for stimulation of pancreatic secretions, including bicarbonate, to aid in the diagnosis of pancreatic exocrine dysfunction; stimulation of gastrin secretion to aid in the diagnosis of gastrinoma and; stimulation of pancreatic secretions to facilitate the identification of the ampulla of Vater and accessory papilla during endoscopic retrograde cholangiopancreatography (ERCP). The usual dose of SecreMax for each indication is 0.2 mcg/kg, 0.4 mcg/kg, and 0.2 mcg/kg respectively. SecreMax is supplied as a lyophilized sterile powder in vials containing 16 mcg secretin. The visual similarities result from the likeness of the starting capitalized and scripted "I" and "S", the shared central "cre" and "x" ending (see below).



The image shows two lines of handwritten cursive script. The top line reads 'Secremax' and the bottom line reads 'Increlex'. The letters 'I' and 'S' at the beginning of each word are notably similar in shape, as are the 'cre' and 'x' endings.

However, the "m" and "l" should provide a differentiating characteristic for Secremax and should serve as a distinct scripting difference; thus providing a significant visual cue. In addition, the drug products differ in indication (stimulation of secretin, gastrin and pancreatic secretions for diagnostic use compared with growth failure in children), dosing regimen (ex. referencing 150 pound patient: 5-8 mg twice daily compared with 13 mg to 27 mg for one dose), route of administration (intravenous compared with subcutaneous), and context of use (diagnostic tool compared with treatment regimen). The products overlap in dosage form (injection), but DMETS does not believe there is a strong potential for confusion due to the differing characteristics and lack of strong visual similarity.

11. Vincrex may look like and sound like Increlex. Vincrex contains vincristine for the treatment of acute leukemia and in combination therapy for Hodgkin's disease, non-Hodgkin's malignant lymphomas (lymphocytic, mixed-cell, histiocytic, undifferentiated, nodular and diffuse types), rhabdomyosarcoma, neuroblastoma and Wilms' tumor. Vincrex is no longer marketed in the US, but this proprietary name is well known. Therefore, practitioners may write for Vincrex and a generic substitution would occur upon order completion. The auditory and visual similarities are due to the shared phonemes of "in", "cr" and "ex." In regard to auditory similarities, the shared "ex" holds weight in speech, but the difference in the leading letter should create a distinction; especially since "v" holds power in speech. They also differ in syllable count (two compared with three) and appearance in name length (due to the upstroke of the "l", Increlex appears longer). In regard to visual similarities, the leading "V" may be mistaken for a capitalized, scripted "I", which is compounded by the aforementioned, shared letter combinations (see below).



The image shows two lines of handwritten cursive script. The top line reads 'Vincrex' and the bottom line reads 'Increlex'. The leading 'V' in Vincrex is written with a sharp upstroke, making it look like a capital 'I' or 'V' that could be confused with the 'I' in Increlex.

The products may also overlap in dose/dosing. Children under 10 kilogram with under 1 m² surface area are dosed at 0.05 mg/kg, which is similar to the 0.08 mg/kg dosing of Increlex. In addition, the dose may overlap with various ranges of weight and height; a patient weighing 150 pounds and having a height of 66 inches will receive 2.49 mg of vincristine. This potentially overlaps with the higher dosing of Increlex. However, Vincrex is an oncology medication and most hospitals have protocols for order completion of chemotherapy to assure accuracy. This should help to decrease errors and confusion between Increlex and Vincrex. An important difference is the frequency of dosing, which is weekly for Vincrex and twice daily for Increlex. This difference should be significant in the detection of a misinterpreted order. Vincristine is also marketed as a 5 mg (5 mL) vial compared with the proposed 40 mg (4 mL) vial of Increlex. In addition, the drug products differ in indication (leukemia and lymphomas compared with growth deficiency in children), route of administration (intravenous compared with subcutaneous), and context of use (diagnostic tool compared with an oncology treatment regimen). DMETS believes the potential for error to be low due to the differences in product characteristics and lack of strong visual similarity.

E. INDEPENDENT NAME ANALYSIS [_____]

Upon review of the information submitted by the [_____] the following additional names were identified as potential sound or look-alike products.

[_____] identified three names including Imitrex, Indocin, and Mycelex that were considered by DMETS to look and/or sound similar to Increlex. With respect to the promotional aspects of the name, the majority of respondents noted "no conflict" with respect to implied claims. However, one respondent indicated the name suggested increased height. DMETS does not have concerns with this interpretation of the name since increased height relates to the indication for the proposed drug product. The [_____] computer analysis found the following thirteen names that were considered for look-alike or sound-alike characteristics: Anaplex, Antiflex, Celebrex, Coreplex, Crantex, Etroflex, Granulex, Haniplex, Incremin, Inosiplex, Lincorex, Mediplex and Menoplex.

After evaluation of the aforementioned names, product characteristics, and knowledge of the distribution process, DMETS does concur that the names do not pose a significant problem with the proposed name, Increlex.

Appears This Way
On Original

III. RECOMMENDATIONS:

- A. DMETS has no objections to the use of the proprietary name, Increlex from a safety perspective. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated upon submission of the NDA and approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
- B. Please provide labels and labeling upon receipt for review and comment.
- C. DDMAC finds the proprietary name Increlex acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

Kim Culley, RPh
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A: DMETS Prescription Study Results (Increlex)

Inpatient	Outpatient	Voice
Incrolet	Increlex	Incolex
Increlex	Incillex	Incrulex
Increlex	Increlex	Inthelect (inthelet)
Increlex	Increlex	Incolac
Increlex	Increlex	Encrelex
Increlex	Increlux	Incrolex
Incredex	Increlix	Endolac
Increlet	Inallex	Incrolex
Increlex	Increeix	Invalex
Increclex	Incillex	Incrulex
Inerclet	Increlix	Encrolex
Increlex	Increlux	Increlex
Increlex	Increlix	Incrolex
Increlet	Increex	Incralex
Increlet	Increlex	
Increlst	Increlex	
Increlex		
Increlex		

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Kimberly Culley
2/16/05 12:40:51 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
2/16/05 03:15:05 PM
DRUG SAFETY OFFICE REVIEWER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 39,679

6/24/04

Tercica, Inc.
Attention: Ira Wallis, PhD
Vice President, Regulatory Affairs
651 Gateway Blvd. Suite 950
South San Francisco, CA 940800

Dear Dr. Wallis:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Recombinant Human Insulin-Like Growth Factor-I (rhIGF-I) 10 mg/ml for the treatment of short stature ☐

J

We also refer to the PreNDA meeting between representatives of your firm and the FDA on May 27, 2004. The purpose of the meeting was to discuss the format, content and timing of a New Drug Application.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-9087.

Sincerely,

{See appended electronic signature page}

Monika Johnson, PharmD
Regulatory Project Manager
Division of Metabolic and Endocrine
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure
May 27, 2004 Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: May 27, 2004
TIME: 1:30-2:30 PM
LOCATION: 14B39 Parklawn Building (teleconference)
APPLICATION: IND 39,679
DRUG NAME: Recombinant Human Insulin-Like Growth Factor-I (rhIGF-I)
TYPE OF MEETING: Pre-NDA
MEETING CHAIR: David G. Orloff, MD
MEETING RECORDER: Monika Johnson, PharmD

FDA ATTENDEES: (Title and Office/Division)

Division of Metabolic and Endocrine Drug Products

David G. Orloff, MD/Division Director
Dragos Roman, MD/Medical Reviewer
Xavier Ysern, PhD/Chemistry Reviewer
Todd Sahlroot, PhD/Statistics Teamleader
Monika Johnson, PharmD/Regulatory Project Manager

Office of Orphan Drug Products

Jeff Fritsch, RPh/Office of Orphan Drug Products
Diana Deshields, RPh/Office of Orphan Drug Products

EXTERNAL CONSTITUENT ATTENDEES:

Tercica Medica Inc.

George Bright, MD/Vice President, Clinical Affairs
Rose G. Clark, PhD/Chief Technical Officer
Andy Grethlein, PhD/Vice President, Manufacturing
Ester Herrick/Associate Director/Regulatory Documentation
Mike Parker/Vice President, Quality
John Scarlett, MD/President, CEO
Ira Wallis, PhD/Vice President, Regulatory Affairs

BACKGROUND:

Tercica submitted a Pre-NDA meeting request on March 29, 2004. We received a background package on April 30, 2004.

DISCUSSION POINTS:

Following introductions, the Sponsor began by requesting Agency comments to their proposed questions. The italicized text represents discussion during the teleconference.

Clinical:

- 1) As stated in the FDA communication of 05 March 2003, the primary efficacy endpoint will be change in height velocity from baseline. An integrated database is being constructed which contains the individual efficacy data for all subjects enrolled in studies F0206s, F0375g, F0632g, F0671g and F0930s [1419]). Using this database the primary efficacy analysis will consist of paired t-tests of baseline annualized height velocity to annualized height velocity for all subjects completing a given year of treatment. The analysis is repeated for years one through eight. The secondary end point will be change in height standard deviation scores (HT-SDS) from baseline and will be similarly analyzed. Results from individual Genentech sponsored studies (F0375g, F0632g and F0671g) and Investigator Sponsored study (F0206s), will be summarized and offered as supporting evidence. Does the DMEDP agree with the proposed efficacy analysis?

FDA comment: The proposed efficacy analysis is acceptable.

The Division requested that the height velocity and IGF-I serum concentration data be presented in the NDA also as standard deviation scores in addition to cm/year and ng/ml, respectively.

- 2) A statistical analysis plan to support the claimed indication will be presented as Appendix A to the briefing document. The plan will specify the analyses, data tables and listings to be presented in the NDA to support the indication. Tercica considers that the list is both adequate and complete. Does the DMEDP agree?

FDA comment: You should provide a graph of mean height velocity and HT-SDS by dropout cohorts (cohorts of patients with similar times on study). The raw data in the electronic database should include all observations, not just those that were used to compute annualized height velocities.

The Division requested that the yearly efficacy data for height velocity and height SDS be presented in two ways: 1) for patients with complete efficacy data from baseline through Year 8 of treatment and 2) for all patients with data at each yearly time point irrespective of availability of data for prior or subsequent timepoints. The sponsor clarified that currently there are only 5 patients with measured final height data in the dataset (final height being defined as the height associated with a bone age ≥ 14 years for girls and ≥ 16 years for boys).

- 3) The subjects pertinent to the claimed indication are children with growth failure and primary IGFD. A safety profile will be constructed from exposure of 65 children exposed to doses of 80–240 µg/kg·day for a total of 231 patient treatment-years, and will form the basis of the integrated safety summary for the NDA. Genentech also sponsored other studies using rhIGF-1, including trials in HIV-AIDS wasting, type 1 diabetes and type 2 diabetes. Because we believe the adverse events experienced in studies of these disorders is substantially influenced by the coexisting morbidities of these diseases, the use of numerous concomitant medications by the populations studied, and in some cases by intravenous administration, and because these studies were conducted with late-adolescent, adult or elderly subjects, we do not propose to include the individual patient data from these studies in the integrated safety database for IGFD in the application. We do, however, propose to provide safety summaries from the individual non-statural studies sponsored by Genentech in the NDA. Also, because retinopathy was explicitly stated as a safety signal in the Type C meeting communication of March 2003 from the DMEDP to Tercica, Tercica plans to present and discuss the ophthalmologic findings related to the rhIGF-1 treatment of diabetic subjects in the NDA. Does the DMEDP agree with this strategy?

FDA comment: The proposed plan is acceptable.

The Division requested that, for non-statural studies, an additional safety summary be presented for the subgroup of patients <18 years of age. In addition, and importantly, the sponsor was requested to state clearly the extent and the depth of safety testing in each of the statural studies.

- 4) Tercica will file a request for rhIGF-1 use in Primary IGFD to be granted Fast Track Designation. Does the DMEDP agree that Tercica can submit the NDA as a rolling submission if this Designation is approved?

FDA comment: It is the judgment of the Division that rhIGF-I treatment for short stature in patients with primary IGFD does not qualify for fast track designation.

- 5) Independent of Fast Track status, Tercica's rhIGF-1 for primary IGFD meets the criterion for priority review, as set forth in CDER's Manual of Policies and Procedures; "Priority Review Policy", in that, "...if approved, would be a significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease". rhIGF-1 will meet an unmet medical need and therefore should receive a priority review. Does DMEDP agree with this assessment?

FDA comment: The Division is in favor of granting priority review to the rhIGF-I NDA. The final decision will be made at the time of filing of the application.

- 6) Tercica plans to submit the NDA in an eCTD format, and will comply with the recommendations set forth in available guidelines and from the Office of Information Management. Tercica has already established contact with the Office of Information Management to submit a sample pilot eCTD. Does the DMEDP support filing the NDA in the eCTD format?

FDA comment: The Division supports the submission of the NDA in eCTD format.

- 7) rhIGF-1 was manufactured by Genentech using a very similar manufacturing process to that currently employed by Tercica. The dating for the Genentech-produced material was recently extended from 7 to 8 years after re-testing confirmed the material continued to demonstrate adequate stability (Serial No 0039, 23DEC03). For the purposes of the NDA submission, Tercica is proposing that at the time of filing, comparability will be established between the Tercica-produced and Genentech-produced material, and stability data will be provided on three Tercica-produced GMP lots having 6 real-time data, respectively. Accelerated ageing data up to 6 will also be submitted. Does DMEDP agree this proposed stability data will be sufficient for the Division to accept the NDA for filing?

FDA comment: The proposed stability data is acceptable for filing. Expiration dating will be based on the evaluation of the available data from material manufactured by Tercica.

- 8) As stated in the *FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products* (April 1996), "Determinations of product comparability may be based on chemical, physical and biological assays". Based on this statement, Tercica submitted a CMC Information Amendment, (Serial No. 0036, submitted 07 November 2003), proposing to demonstrate comparability strictly via physical, biochemical and functional testing between drug substance produced using the Genentech process made by Tercica following the transfer of that process to Tercica. The Company received a verbal communication indicating that the DMEDP reviewer did not have any comments on the proposed comparability testing plan. Tercica assumes that the plan as submitted in Serial No.0036 is acceptable. Does the Division agree with this assumption?

FDA comment: Your proposal for demonstrating comparability between the drug substance manufactured by Genentech and Tercica, as described under 'Analytical Comparability' on pages 78 and 79 of your briefing document, is acceptable.

- 9) As summarized in the nonclinical data section, a large number of nonclinical studies on rhIGF-1 have been performed, including a two-year rat carcinogenicity study. Tercica believes that the nonclinical information to be provided in the NDA is sufficient for filing. Does the DMEDP agree?

FDA comment: Yes, the available nonclinical information is adequate to support NDA filing.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

The sponsor was informed that a formal orphan designation transfer would need to be completed from the original sponsor, Genentech to the current sponsor, Tercica, Inc. Consult 21CFR316.27 for details.

Minutes prepared by

**Monika Johnson, PharmD
Regulatory Project Manager**

Concurrence: //s/ June 24, 2004

**David G. Orloff, MD
Director, DMEDP**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Monika Johnson
6/24/04 05:00:00 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-839	Efficacy Supplement Type SE-	Supplement Number n/a	
Drug: INCRELEX (mecasermin [rDNA origin] injection), 10 mg/mL		Applicant: Tercica, Inc.	
RPM: Enid Galliers	8/11/05	HFD-510	Phone # 827-6429
<p>Application Type: (<input checked="" type="checkbox"/>) 505(b)(1) (<input type="checkbox"/>) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p>() Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):	
❖ Application Classifications:			
• Review priority		() Standard (<input checked="" type="checkbox"/>) Priority	
• Chem class (NDAs only)		1	
• Other (e.g., orphan, OTC)		V	
❖ User Fee Goal Dates		8.31.2005	
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2	
❖ User Fee Information			
• User Fee		() Paid UF ID number None	
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)	
• User Fee exception		<input checked="" type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)	
Application Integrity Policy (AIP)			
• Applicant is on the AIP		() Yes (<input checked="" type="checkbox"/>) No	

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? () Yes () No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? () Yes () No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> • Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	8.05.05 No.
<ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	() Yes, Application # _____ (✓) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	8.04.05;

Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	PN
❖ Clinical review(s) (indicate date for each review)	8.05.05
❖ Microbiology (efficacy) review(s) (indicate date for each review)	n/a
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	Included in 8.05.05 MOR
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	Included in 8.05.05 MOR
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	8.08.05
❖ Demographic Worksheet (NME approvals only)	n/a
❖ Statistical review(s) (indicate date for each review)	In draft
❖ Biopharmaceutical review(s) (indicate date for each review)	5.03.05; 7.22.05
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	n/a
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	n/a
• Bioequivalence studies	n/a
Nonclinical Pharmacology Information	
❖ CMC review(s) (indicate date for each review)	6.17.05; 8.05.05
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	6.17.05 CMC # 1
• Review & FONSI (indicate date of review)	n/a
• Review & Environmental Impact Statement (indicate date of each review)	n/a
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	8.05.05
❖ Facilities inspection (provide EER report)	Date completed: 8.02.05 (✓) Acceptable () Withhold recommendation
❖ Methods validation	(✓) Completed () Requested () Not yet requested
Nonclinical Pharmacology Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	4.21.05; 7.21.05
❖ Nonclinical inspection review summary	n/a
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	7.26.05
❖ CAC/ECAC report	7.12.05

6 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling



3/6/03

IND 39,679

Tercica Medica, Inc.
Attention: Kevin Dwyer
Acting Head, Regulatory Affairs
651 Gateway Blvd., Suite 950
South San Francisco, CA 94080

Dear Mr. Dwyer:

Please refer to the meeting between representatives of your firm and FDA on March 5, 2003. The purpose of the meeting was to discuss the development of recombinant human insulin-like growth factor-I (rIGF-I) for treatment of growth hormone [

]

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-827-9087.

Sincerely,

{See appended electronic signature page}

Monika Johnson, PharmD
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

March 5, 2003 meeting minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 5, 2003

TIME: 11:00 am- 12:00 noon EST

LOCATION: Teleconference (Parklawn Building, 15B45)

APPLICATION: IND 39,679 Recombinant human insulin-like growth factor-I

TYPE OF MEETING: Guidance

MEETING CHAIR: David G. Orloff, MD

MEETING RECORDER: Monika Johnson, PharmD

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

David G. Orloff, MD/Director/Division of Metabolic and Endocrine Drug Products (DMEDP), HFD-510
Robert Perlstein, MD/Medical Reviewer/DMEDP, HFD-510
Dragos Roman, MD/Medical Reviewer/DMEDP, HFD-510
Enid Galliers/Chief, Project Management Staff/DMEDP, HFD-510
Monika Johnson, PharmD/Regulatory Project Manager/DMEDP, HFD-510
Xavier Ysern, PhD/Chemistry Reviewer/Office of New Drug Chemistry II, HFD-820
Jon Sahlroot, PhD/Statistics Team Leader/Division of Biometrics II, HFD-715
Hae Young Ahn, PhD/Biopharmaceutics Team Leader/Office of Clinical Pharmacology & Biopharmaceutics, HFD-870
Herman Rhee, PhD/Pharmacology Reviewer/DMEDP, HFD-510

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Ira Wallace/Vice President Regulatory Affairs/Tercica Medica, Inc. (TM)
Kevin Dwyer/Acting Head, Regulatory Affairs/TM
Ross G. Clark, PhD/Chief Technical Officer/TM
[] Consultant/
[] Consultant
John A. Scarlett, MD/ President and Chief Medical Officer/TM

BACKGROUND:

Tercica Medica, Inc. proposed the use of recombinant human insulin-like growth factor-I (rhIGF-I) to treat patients with growth hormone deficiency including patients with Laron syndrome.]

On April 19, 2002, Genentech, Inc. transferred this IND to Tercica who also acquired the intellectual property rights, data, and manufacturing process for rhIGF-1.

Since there has been minimal activity in this IND for a long period of time, Tercica requested a meeting with the Agency to provide an update on current clinical data and confirm any previous agreements made with Genentech, Inc., i.e., adequacy of data to support a marketing application, and to begin a collaborative relationship with the division.

MEETING OBJECTIVE:

To reach an agreement with the division as to the definition of primary insulin-like growth factor-1 deficiency and that the use of rhIGF-1 in this population is replacement therapy.

DISCUSSION POINTS :

Following introductions, questions posed by the sponsor were addressed.

Italicized comments provided to Tercica Medica represent discussion that took place during the meeting.

Question 1:

Does the Division tentatively accept that the wording of the treatment indication for IGF-I replacement therapy could be analogous to that for growth hormone replacement therapy for growth hormone deficiency in children and thereby might take the following form?

FDA response:

If the data submitted in the NDA demonstrate that IGF-I administration to patients with primary IGF-I deficiency is effective in promoting linear growth and is associated with a favorable safety profile, IGF-I therapy can be approved for the treatment of primary IGF-I deficiency. An approval for the "long-term treatment" of growth failure in children with primary IGF-I deficiency will require proof that short-term efficacy gains are sustained. To this end, present all available evidence from the database and published literature that measures the effects of IGF-I treatment on long-term efficacy (i.e., greater than 1-2 years), final or near-final height, rate of bone age maturation, and timing of onset of puberty and puberty progression. If IGF-I therapy is

approved for the treatment of IGF-I deficiency, we will request subsequent collection of final height data on all patients studied.

There was general agreement on the importance of long-term efficacy data in order to obtain a claim of "long-term treatment". The sponsor stated that there is considerable patient exposure accumulated in the clinical trials (e.g., approximately 230 patient-years, 2 patients treated for >10 years, mean duration of exposure of 3.5 years, etc.). At the time of the NDA submission, the sponsor will present detailed data on bone age maturation, timing and progression of puberty, and final height in patients who can be analyzed for these variables.

Question 2:

Does the Division agree that the indicated population for IGF-I replacement therapy would be defined as having stature equal to or less than - 3.0 SDS and IGF-I levels equal to or below - 3.0 SDS in the presence of intact growth hormone secretion?"

FDA response:

The proposed definition of primary IGF-I deficiency based on (1) intact growth hormone (GH) secretion, (2) height equal to or less than -3.0 SDS, and (3) basal IGF-I levels equal to or below -3.0 SDS may include some patients with "idiopathic short stature" (ISS). In order to exclude this heterogeneous group of patients, we suggest using the IGF-I generation test in response to exogenous GH as an additional diagnostic criterion. Alternatively (and more desirably), one can use genetic testing (e.g. mutation analysis) to verify the diagnosis of a GH receptor (GHR) defect (i.e., Laron type short stature), biochemical evidence of a post GHR defect in signal transduction, and the presence of a substantial amount of neutralizing anti-GH antibodies in patients with GH gene deletion as additional diagnostic criteria..

The agency asked for stricter criteria for the diagnosis of primary IGFD in order to differentiate the primary IGFD patients from the relatively few patients with ISS who may meet the proposed auxological and biochemical criteria defined in the question. The sponsor stated that there was no intention to treat patients with idiopathic short stature and will reassess the feasibility of the IGF-I generation test or genetic testing as possible additional diagnostic criteria.

Question 3:

Does the Division agree that the data from the clinical trials performed by Genentech along with supporting data from other important clinical studies, as outlined in the briefing document, are adequate in terms of total patient exposure, duration of therapy, dose regimens explored, and study designs utilized to support the filing of an NDA for the use of IGF-I in children with primary IGF-I deficiency?

FDA response:

The Division acknowledges the difficulty of conducting randomized, controlled trials in patients with primary IGF-I deficiency because of both ethical considerations and the limited number of

patients with the severe form of the condition. At the time of NDA submission, the Division will review the available data, which should include the results of study 1419 (the largest study to be included in the NDA), and will make a determination regarding approval based on a risk benefit analysis of all submitted data.

Comments for specific components of the question:

Dose regimen: The data presented seem to establish a dose regimen for IGF-I therapy in patients with primary IGF-I deficiency.

Duration of therapy and total patient exposure: Both are difficult to assess in the absence of the data from study 1419. If study 1419 is informative, it will augment significantly both the efficacy (duration of therapy and sustainability of effect) and safety databases.

Trial design: We note that no statistics are presented in any of the open label studies that compare height velocity (HV) on treatment with HV at baseline. Therefore, a statistical analysis of annualized HV changes on IGF-I treatment for the treatment-naïve patients enrolled in study 1419 must be provided. HV data from the other open-label studies should be analyzed statistically as well (i.e., on-treatment HV compared with pre-treatment HV). Height SDS changes and HV information from published studies will complement and support the five original studies listed in the package.

The agency stressed the importance of study 1419 in substantially expanding the amount and quality of efficacy and safety data to be presented in the final NDA. Such data, in addition to the data already obtained in the Genentech studies and studies published in the medical literature, can be the basis of a reviewable New Drug Application.

With respect to trial design issues, the agency asked for inferential statistics for annual height velocity changes in study 1419 (which contains 42 IGF-I naïve patients) and in the already completed Genentech studies. For study 1419, such statistics will include at least construction of 95% confidence intervals for changes from baseline in height velocity. For the Genentech studies, a similar approach, or a t-test, or an alternative analysis at the discretion of the sponsor was recommended. The sponsor agreed with these requests and may submit a statistical analysis plan for review prior to the NDA submission.

With respect to safety issues, the sponsor is already evaluating the list of safety signals presented in the "Additional issues" section, below.

Additional issues:

1) Safety:

Provide extensive safety information for the following safety signals:

- hypoglycemia
- hearing loss (conductive vs. sensorineural vs. mixed)

- organomegaly (i.e., spleen, heart, kidney [with emphasis on renal function at the end of therapy])
- benign intracranial hypertension
- acromegalic facial changes
- lipohypertrophy
- obstructive sleep apnea, incidence of T&As, evidence of nasopharyngeal/oropharyngeal lymphoid tissue hypertrophy
- edema/arthritis/myalgia/carpal-tunnel syndrome
- change in body composition (i.e., increase in total body fat)
- tumorigenesis
- retinopathy

2) Pharmacokinetics

In your ongoing clinical trial, draw 3 blood samples at steady state using a sparse sampling technique: one at predose and 2 samples after T_{max}, and conduct a population PK analysis for IGF-I. Fixed time sampling should be avoided. Alternatively, PK information from previously studied diabetic patients (comparable age group such as 2 to 15 years of age) who were treated with IGF-I may be presented for the whole range of the therapeutic regimens tested (60, 80, 120 µg/kg BID).

The sponsor will analyze the already available PK data in adolescents with diabetes and young children with Laron Syndrome and will submit it for discussion/further guidance to the agency.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ATTACHMENTS/HANDOUTS:

None

Minutes Preparer: _____
Monika Johnson, PharmD
Regulatory Review Officer

Chair Concurrence: /s/ March 6, 2003
David G. Orloff, MD
Division Director

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Monika Johnson
3/6/03 02:58:42 PM