

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-839**

**Chemistry Review(s)**

**NDA 21-839**

**Increlex (mecasermin [rDNA origin] injection) 10 mg/mL**

**CHEMISTRY DIVISION DIRECTOR REVIEW**

- Applicant:** Tercica, Inc.  
2000 Sierra Point Parkway, Suite 400  
Bricaine, CA 94005
- Indication:** Long-term treatment of growth failure in children with primary Insulin-like Growth Factor – 1 (IGF-1) deficiency
- Presentation:** Sterile parenteral solution containing mecasermin 10 mg/mL for subcutaneous injection, filled and packaged in 5 mL vial
- EER Status:** Acceptable 02-AUG-2005
- Consults:** DMETS – Tradename: INCRELEX – Acceptable 02-FEB-2005  
EA –Categorical exclusion granted under 21 CFR 25.31(b)  
Microbiology – Acceptable – 05-AUG-2005  
Methods Validation – Revalidation by Agency not requested

**Post-Approval Agreements:**

- 1) To perform a [ ] stability study on three commercial lots of rhIGF-1 formulated bulk drug substance packaged and stored in [ ] at 2-8 °C, in order to establish an expiration for storage of drug substance. The final stability protocol will be submitted by September 30, 2005, and the study will be completed by June 30, 2007. Cumulative data will be analyzed and provided for establishing shelf-life dating for the formulated bulk drug substance packaged into bags by September 30, 2007.
- 2) To perform studies that identify and characterize the additional [ ] in rhIGF-1 drug product samples (lots 804336 and 804454) observed after [ ] stored at the 25 °C/60 % RH condition, not seen at 2-8 °C. A final protocol will be submitted by September 30, 2005, and studies will be completed by March 31, 2006. The final study report will be provided by May 31, 2006.
- 3) To complete a study initiated in June, 2005 to confirm the preservative effectiveness of benzyl alcohol with rhIGF-1 drug product at the low end of the specified concentration range. The final study report will be provided by September 30, 2005.

The original NDA was received on 24-FEB-2005.

**Drug Substance**

The drug substance is manufactured by:

[ ]

The active pharmaceutical ingredient of Tercica's Increlex™ product is recombinant human Insulin-like Growth Factor-1 (rhIGF-1). rhIGF-1 is a monomeric non-glycosylated polypeptide consisting of 70 amino acid residues with three intramolecular disulfide bridges, and a molecular weight of 7649.6 Daltons. The amino acid sequence of the product is identical to that of endogenous human IGF-1. The United States Adopted Name (USAN) is mecasermin. The drug substance is synthesized in *E. coli* bacteria that have been modified by the addition of the gene for hIGF-1, [ ]

Manufacture of rhIGF-1 is [ ]

[ ] The drug substance manufacturing process is currently performed at [ ] The [ ]

The primary structure (amino acid sequence and disulfide bridge assignments) of rhIGF-1 was confirmed using [ ]

Results obtained using [ ]

[ ] with the proposed structure. The primary structure and the secondary structure content determined by these techniques are consistent with literature reports [ ]

[ ] was developed to measure bioactivity of rhIGF-1. Structural characterization of the drug substance was satisfactory. Specifications were found acceptable. ]

Stability data for the formulated bulk drug substance packaged into [ ] are limited. Insufficient stability data are available at this time to grant a shelf life. However, the applicant agrees to perform a study on three commercial lots of rhIGF-1 formulated bulk drug substance packaged and stored [ ] at 2-8 °C, in order to establish an expiration date for storage of drug substance. The final stability protocol, the study, and the cumulative data will be provided to support a shelf life. ]

**Conclusion:**

Drug substance is satisfactory.

**Drug Product**

The drug product is manufactured by:

Baxter Pharmaceutical Solutions LLC  
927 South Curry Pike  
Bloomington, Indiana 47402

Increlex™ (mecasermin [rDNA origin] injection) is a sterile, aqueous, clear and colorless solution intended for subcutaneous injection. Each multi-dose vial contains 10 mg/mL mecasermin, 9 mg/mL benzyl alcohol, 5.84 mg/mL sodium chloride, 2 mg/mL polysorbate 20, and 0.05 M acetate at a pH of approximately 5.4. The product is supplied as a 10 mg/mL sterile solution in 5 mL multiple dose glass vials (40 mg/vial). For the manufacture of the drug product, no excipients of human or animal origin are used.

Increlex™ injection is manufactured from rhIGF-1 formulated bulk drug substance by conventional processes.

Specifications for Increlex™ drug product include testing of

of the excipients. The applicant has been requested to test.

Drug product stability, primary, data is also scarce, at the time of filing: a total of months of stability data are available for one lot; months for two lots, both at the proposed long-term refrigerated storage condition 2-8 °C and under the accelerated stability condition of 25 °C/60 % RH. All test results are within acceptable criteria. Based on the available primary data and the supportive stability data, the granted expiration dating is 12 months at the storage condition 2-8 °C, protected from light. As satisfactory additional data becomes available, extension of the expiration period under the stability protocol may be granted by the Agency.

**Conclusion:**

Drug product is satisfactory.

**Additional Items:**

- Validation package, describing the test methods and validation procedures, including information supporting the reference standard, is adequately provided. Since the analytical methods used in the testing procedures (release, stability and in-process) are well known and widely used by the biopharmaceutical industry, revalidation by Agency laboratories will not be requested

- Labeling is acceptable.
- Overall Compliance recommendation is acceptable as of 02-AUG-2005.
- All associated DMFs are acceptable

**Overall Conclusion**

From a CMC perspective, the application is recommended for approval.

Blair A. Fraser, Ph.D.  
Deputy Director, DNDC II/ONDC

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this page is the manifestation of the electronic signature.**  
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/s/

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Blair Fraser  
8/24/2005 01:50:11 PM  
CHEMIST

**NDA 21-839**

**Increlex™**  
**[mecasermin (rDNA origin) injection]**  
**Recombinant Human Insulin-Like Growth Factor-1 (rhIGF-1)**

**Tercica Medica**

**CMC Review # 2**

**Xavier Ysern, PhD**  
**HFD-510**

# CHEMISTRY REVIEW

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# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### Chemistry Review Data Sheet

1. NDA 21-839
2. REVIEW #: 2
3. REVIEW DATE: 05-AUG-2005
4. REVIEWER: Xavier Ysern, PhD
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND	08-AUG-1992
IND 39,679 (Tercica Medica; rhIGF-1)	07-JAN-2004
IND (Tercica Medica; rhIGF-1)	11-AUG-2000
IND [ ]	31-MAY-2005 WD
IND [ ]	12-MAY-2005
IND [ ]	LOA 09-AUG-2004 to IND 39,679
IND [ ]	LOA 09-AUG-2004 to IND 39,679

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	24-FEB-2005
Amendment	29-JUN-2005 SU
	13-JUL-2005 BC
	28-JUL-2005 BC

7. NAME & ADDRESS OF APPLICANT:

Name: Tercica Inc. (New address effective 30 June 2005)  
 Address: 2000 Sierra Point Parkway, Suite 400  
 Bricaine, CA 94005  
 Representative: Ira Wallis, PhD Vice President Regulatory Affairs  
 Telephone: (650) 624-4920

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Increlex™
- b) Non-Proprietary Name: Mecasermin (rDNA origin) injection
- c) Code Name: --
- d) Chem. Type/Submission Priority:
  - Chem. Type: 1 (New Molecular Entity)
  - Submission Priority: Priority

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Protein Hormone. Long-term treatment of growth failure in children with primary IGF-1 deficiency.

11. DOSAGE FORM: Liquid/Solution for Injection 4 mL Vial



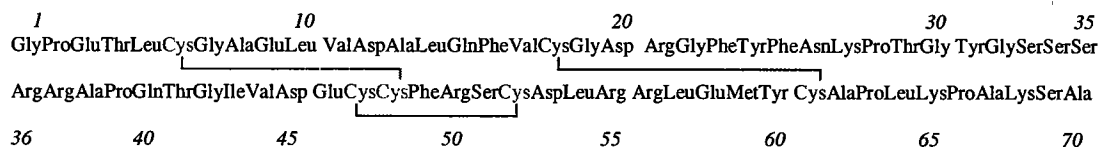
# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

12. STRENGTH/POTENCY: 10 mg/mL
13. ROUTE OF ADMINISTRATION: Subcutaneous injection
14. Rx/OTC DISPENSED: Rx
15. SPOTS: SPOTS product – Form Completed
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Recombinant human insulin-like growth factor (rhIGF-1)



C<sub>331</sub>H<sub>512</sub>N<sub>94</sub>O<sub>101</sub>S<sub>7</sub> MW = 7,649 Da. CAS 68562-41-4

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code <sup>1</sup>	Status <sup>2</sup>	Date Review Completed	Comments
1	III	[Redacted]	[Redacted]	4	Adequate		LOA: 20-SEP-2004
	4			Adequate			
	4			Adequate		LOA: 30-JUL-2004	
	V			Baxter Pharmaceutical Solutions, LLC (BPS)	Facility in Bloomington, IN		

(-) Supportive information. The applicant does not seek approval of the [ ] presentation.

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF; 3 – Reviewed previously and no revision since last review; 4 – Sufficient information in application

5 – Authority to reference not granted; 6 – DMF not available; 7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
--	--	--

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	--	--	--
EES	Acceptable	02-AUG-2005	(EER Summary Response attached)
Pharm/Tox	--	--	--
Biopharm	--	--	--
ODS/DMETS	No objection to the use of the proprietary name "Increlex"	02-FEB-2005	Kimberly Culley, RPh
Methods Validation	Pending	--	--
LNC	--	--	--
EA	Acceptable (Categorical Exclusion granted)	06-FEB-2004	Xavier Ysern, PhD
Microbiology	Pending	--	--



**I. Recommendations**

**A. Recommendation and Conclusion on Approvability**

This NDA can be approved.

**B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**

The firm has made the following Phase 4 Commitments. However, these are deemed acceptable as agreements rather than Post-marketing Commitments.

1) To perform a [ ] stability study on three commercial lots of rhIGF-1 formulated bulk drug substance packaged and stored in — at 2-8 °C, in order to establish an expiration for storage of drug substance. The final stability protocol will be submitted by September 30, 2005, and the study will be completed by June 30, 2007. Cumulative data will be analyzed and provided for establishing shelf-life dating for the formulated bulk drug substance packaged into — by September 30, 2007.

2) To perform studies that identify and characterize the [ ] in rhIGF-1 drug product samples (lots 804336 and 804454) observed after — months stored at the 25 °C/60 % RH condition, not seen at 2-8 °C. A final protocol will be submitted by September 30, 2005, and studies will be completed by March 31, 2006. The final study report will be provided by May 31, 2006.

3) To complete a study initiated in June, 2005 to confirm [ ] with rhIGF-1 drug product [ ] The final study report will be provided by September 30, 2005.

**II. Summary of Chemistry Assessments**

**A. Description of the Drug Product(s) and Drug Substance(s)**

**Drug Substance**

The active pharmaceutical ingredient of Tercica's Increlex™ product is recombinant human Insulin-like Growth Factor-1 (rhIGF-1). rhIGF-1 is a monomeric non-glycosylated polypeptide consisting of 70 amino acid residues with three intramolecular disulfide bridges, and a molecular weight of 7649.6 Daltons. The amino acid sequence of the product is identical to that of endogenous human IGF-1. The United States Adopted Name (USAN) is mecasermin. The drug substance is synthesized in *E. coli* bacteria that have been modified by the addition of the gene for hIGF-1. [ ]

Human insulin like growth factor-1 (IGF-1, also referred as IGF-I) is a hormone structurally, but not functionally-related to human insulin. IGF-1 is produced following binding of growth hormone (GH) to the GH receptor on IGF-1 producing cells in the liver, bone and other tissues and is released into the circulation. IGF-1 induces metabolic and tissue growth responses, particularly those involved in cartilage and bone growth. In addition to the endocrine activities of IGF-1 on cartilage and bone, it also has autocrine and paracrine activities.

The manufacturing process for Tercica's rhIGF-1 formulated bulk drug substance was based upon process development and clinical production experience gained from 1989 to 1997 at Genentech, as well as recent manufacturing experience and development at [ ] Tercica's drug substance contract manufacturer. There were [ ] drug-substance manufacturing process development stages at Genentech. These included [ ]

[ ] All [ ] [ ]



# CHEMISTRY REVIEW



## Executive Summary Section

processes were used to manufacture drug substance material for use in clinical and non-clinical studies supporting this application. The Genentech drug substance process produced [ ] while the Tercica drug substance process produces a fully formulated bulk [ ] drug product process.

The production organism for the manufacturing of rhIGF-1 is the recombinant *E. coli* [ ] system. No changes [ ] used by Tercica for the manufacture of rhIGF-1 [ ] were made during technology transfer of rhIGF-1 manufacturing from Genentech to Tercica. The transcriptional and translational initiation sequences required for expression of the rhIGF-1 gene in *E. coli* are provided by [ ]

Manufacture of rhIGF-1 at [ ] is conducted in [ ]

The drug substance manufacturing process is currently performed [ ]

[ ] The composition of the formulated bulk drug substance is the same as that for Increlex™ drug product.

The primary structure (amino acid sequence and disulfide bridge assignments) of rhIGF-1 was confirmed using [ ] Results obtained using [ ]

Evaluation of the product [ ]

A product related impurity is also evident [ ] These variants have been isolated and identified both in the Genentech produced clinical materials and in the Tercica produced material. [ ]



# CHEMISTRY REVIEW



## Executive Summary Section

Stability data for the formulated bulk drug substance packaged [redacted] are limited. Due to problems encountered with [redacted] all formulated bulk drug substance lots packaged into [redacted] have been discontinued. No data is yet available for the only lot packaged in the proposed [redacted] (lot # 155-1104-022). Consequently, shelf-life estimates for the formulated bulk drug substance packaged into the proposed [redacted] cannot be estimated. According to the applicant, the [redacted] appear to [redacted] as compared with the [redacted] production. Fortunately, formulated bulk drug substance can be entered into the manufacture of the drug product with minimal storage/holding times. There is insufficient stability data at this time to grant a shelf life.

As the formulation of the formulated bulk drug substance does not differ from that of the Increlex™ drug product their specifications are very similar. In addition to the formulated bulk drug substance specifications, Increlex™ drug product specifications incorporate testing [redacted] to accommodate the vial presentation of the drug product. [redacted]

Increlex™ drug product specifications. The applicant has been requested to have at least [redacted] tests capable to discriminate rhIGF-1 based on its primary structure. The rest of the specifications are common to the drug product. [redacted]

## Drug Product

Orphan drug designation was obtained for mecasermin by Genentech, Inc., the former sponsor, on 12 December 1995 [redacted] for mecasermin (rhIGF-1). Tercica received a letter dated 16 September 2004 from the Office of Orphan Product Development acknowledging transfer of the orphan drug designation to Tercica, from Genentech, Inc., (appended to User fee Cover Sheet, FDA Form 3397).

Increlex™ (mecasermin [rDNA origin] injection) is a sterile, aqueous, clear and colorless solution intended for subcutaneous injection. Each multi-dose vial contains 10 mg/mL mecasermin, 9 mg/mL benzyl alcohol, 5.84 mg/mL sodium chloride, 2 mg/mL polysorbate 20, and 0.05M acetate at a pH of approximately 5.4. The product is supplied as a 10 mg/mL sterile solution in 5 mL [redacted] multiple dose glass vials (40 mg/vial). For the manufacture of the drug product, no excipients of human or animal origin are used. Therefore, no contamination risk can be expected with regard to transmissible spongiform encephalopathy (TSE) or other adventitious agents from excipients.

Development studies carried out by Genentech and by Tercica after transfer from Genentech have demonstrated that [redacted] The main observations were:

(1) [redacted]

(2) [redacted]

During development, two formulations, the single use formulation and the multi-use formulation, have been used in clinical and non-clinical studies supporting this application. Each formulation is intended for use as a sterile parenteral (subcutaneous injection) product. The original [redacted] formulation was developed as a single-use (single dose) presentation, and was adequate for evaluation in the multiple clinical indications being considered at early developmental stages. The drug substance used in this formulation was obtained from the [redacted] process. The modified formulation, multi-use presentation, allowed for implementation of a multi-dose presentation for the drug product, as well as evaluation of higher concentrations in various clinical studies. The change in formulation included an [redacted] as well as incorporation of benzyl alcohol as a

## CHEMISTRY REVIEW

### Executive Summary Section

preservative. The change in [ ] was based on developmental findings. The use of preservative is a requirement for multi-dose presentations.

Increlex™ injection is manufactured from rhIGF-1 formulated bulk drug substance by conventional [ ] processes. The bulk is received at the drug product manufacturing facility as a stable, fully formulated solution (formulated bulk drug substance) that is maintained at 2 to 8 °C and stored in [ ] No formulation or compounding is performed at the drug product manufacturing site, [ ] of the bulk containers is required. The manufacturing procedure is based on conventional techniques [ ] as well as packaging. The drug product is filled by [ ]

Critical manufacturing steps are adequately controlled by [ ]

No new impurities are introduced during the manufacture of the drug product.

Specifications for Increlex™ drug product include testing [ ]

Drug product stability primary data is also scarce, at the time of filing, a total of ~ months of stability data are available for one lot, and ~ months for two lots, both at the proposed long-term refrigerated storage condition 2-8 °C, and from accelerated stability testing at 25 °C/60 % RH. Vials are stored inverted as well as upright, at each temperature condition, in order to evaluate the effects of the container closure on stability. The stability data show no discernable change in any of the product attributes over this time at the real-time 2-8 °C storage condition. At accelerated conditions, 25 °C/60 % RH, some changes are detected in the impurity profile as analyzed by [ ] The primary changes seen in the [ ] were a [ ] corresponding [ ]

results also showed some minor changes. There appear to be no consistent differences between vials stored upright and inverted, at either condition. Although limited, ~ months maximum data, all test results are within acceptable criteria. Photostability studies (naked vial) showed a large increase [ ] Light exposure appears to induce a different degradation [ ] Vials boxed in [ ] showed no changes compared with the dark controls, showing the adequacy of the secondary packaging to protect the product from light.

The solution for the injectable is filled into 5 mL ~ vials made of [ ] glass complying with pertinent USP requirements for ~ glass containers. The vials are closed with [ ] stopper, and a [ ] flip-off seal. The stopper is the only closure component having a direct contact with the drug product.

In addition to the long term and accelerated stability studies previously mentioned, the container-integrity test showed the adequacy of the container-closure packaging to assure the quality of the product. Although the applicant requested a shelf life period of [ ] based on the limited stability data provided by the applicant a 12 month expiry dating is granted for the drug product stored at the recommended storage condition of 2-8 °C protected from light.

### B. Description of How the Drug Product is Intended to be Used

Increlex™ (mecasermin [rDNA origin] injection) is indicated for the long-term treatment of growth failure in children with primary IGF-1 deficiency (Primary IGFD). It has also been used successfully to treat growth failure in children with GH gene deletion who have developed neutralizing antibodies to Growth hormone (GH). Increlex™ treatment is most appropriate for children whose height standard deviation score is less than or equal to -3.0 and basal IGF-1 standard deviation score is less than or equal to -3.0, in the presence of normal or elevated growth hormone (GH).

**Executive Summary Section**

Increlex™ is supplied as a 10 mg/mL sterile solution in 5 mL multiple dose glass vials (40 mg/vial). There are no drug product diluents or dosing devices associated with the administration of Increlex™, as it is delivered directly via subcutaneous injection. The product is provided as a ready-to-use liquid formulation, without the need for dilution or mixing prior to injection.

The dosage of Increlex™ should be individualized for each patient. The recommended starting dose of Increlex™ is 0.080 mg/kg twice daily by subcutaneous injection. If well-tolerated for at least one week, the dose may be increased to 0.120 mg/kg given twice daily. If hypoglycemia occurs, the dose should be reduced. Doses of greater than 0.120 mg/kg given twice daily have not been evaluated in children with Primary IGFD. Increlex™ is described to be administered shortly before or after a meal or snack. If the patient is unable to eat for any reason, Increlex™ treatment is described to be withheld. Although there is no actual clinical experience with overdosage of Increlex™, based on known pharmacological effects, acute overdosage could lead to hypoglycemia. Long-term overdosage may result in signs and symptoms of acromegaly, consistent with overproduction of IGF-1. Treatment of overdose of Increlex™ is described to be directed at alleviating any hypoglycemic effects.

Unopened Increlex™ vials should be stored in a refrigerator, 2 °C - 8 °C (36 °F - 46 °F), protected from intense light. It should not be stored in the freezer and it should not be allowed to freeze. Opened vials (in use), are stable within 30 when stored at 2 °C - 8 °C (36 °F - 46 °F). After a month, unused Increlex™ from opened vials should be discarded. Vial contents should be clear without particulate matter. If the solution is cloudy or contains particulate matter, the contents must not be injected. Increlex™ should not be used after its expiration date.

**C. Basis for Approvability or Not-Approval Recommendation**

This application can be approved from a CMC viewpoint. This recommendation is based upon the following:

- (1) Several minor issues have been identified. However, these issues, listed in the June 20, 2005 communication, have now been adequately addressed;
- (2) Three agreements have been made by the firm to perform additional CMC studies; and
- (3) All facilities involved in the manufacture, testing and packaging of drug substance and drug product are in compliance with cGMP.

**III. Administrative****A. Reviewer's Signature**

See electronic signature page.

**B. Endorsement Block**

Chemist Name/Date:	Xavier Ysern, PhD/05-AUG-2005
Chemistry Team Leader Name/Date	Stephen Moore, PhD

**C. CC Block**

Eric Duffy, PhD	HFD-820
Blair Fraser, PhD	HFD-820
Enid Galliers	HFD-510 Project Manager Name

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

       § 552(b)(5) Deliberative Process

       § 552(b)(5) Draft Labeling





# CHEMISTRY REVIEW



ATTACHED:

(sOP□&k4S□&17.27c66F 02-AUG-2005

FDA CDER EES

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## ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application :	NDA 21839/000	Sponsor:	TERCICA
Org Code :	510		651 GATEWAY BLVD STE 950
Priority :	1P		SOUTH SAN FRANCISCO, CA 94080
Stamp Date :	28-FEB-2005	Brand Name :	INCRELEX (MECASERMIN [RDNA
PDUFA Date :	31-AUG-2005		ORIGIN] INJ)
Action Goal :		Estab. Name:	

District Goal: 02-JUL-2005	Generic Name: MECASERMIN [RDNA ORIGIN]
	Dosage Form: (INJECTION)
	Strength : 10 MG/ML

FDA Contacts:	E. GALLIERS	Project Manager (HFD-510)	301-827-6429
	X. YSERN	Review Chemist (HFD-510)	301-827-6420
	S. MOORE	Team Leader (HFD-510)	301-827-6401

Overall Recommendation: ACCEPTABLE on 02-AUG-2005 by J. D AMBROGIO(HFD-322) 301-827-9049

Establishment : CFN : FEI : [ ]

DMF No: AADA:

Responsibilities: [ ]

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 30-MAR-05

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : 1833527 FEI : 1000115571

BAXTER PHARMACEUTICALS SOLUTIONS, LLC

927 S CURRY PIKE

BLOOMINGTON, IN 47403

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE PACKAGER

Profile : SVS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-AUG-05

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : [ FEI :



# CHEMISTRY REVIEW



02-AUG-2005

## FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

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DMF No:

AADA:

Responsibilities:

[ ]

Profile : CBI  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 02-AUG-05  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

OAI Status: NONE

Establishment :

CFN [ ] FEI: [ ]

DMF No:

[ ]

AADA:

Responsibilities:

[ ]

Profile : CTL  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 30-MAR-05  
Decision : ACCEPTABLE  
Reason : BASED ON PROFILE

OAI Status: NONE

Establishment :

CFN : [ ] FEI : [ ]

DMF No:

[ ]

AADA:

Responsibilities:

[ ]

Profile : CTL  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 30-MAR-05  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

OAI Status: NONE

Establishment :

CFN : [ ] FEI [ ]

DMF No:

[ ]

AADA:

Responsibilities:

[ ]

Profile : CTL  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 30-MAR-05  
Decision : ACCEPTABLE  
Reason : BASED ON PROFILE

OAI Status: NONE



# CHEMISTRY REVIEW



02-AUG-2005

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

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Establishment :	CFN : L J	FEI : L J
DMF No:		AADA:
Responsibilities:		
Profile :	CTL	OAI Status: NONE
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	30-MAR-05	
Decision :	ACCEPTABLE	
Reason :	BASED ON PROFILE	

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Xavier Ysern  
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CHEMIST

Stephen Moore  
8/5/05 06:22:52 PM  
CHEMIST



**NDA 21-839**

**Increlex<sup>TM</sup>**  
**[mecasermin (rDNA origin) injection]**

**Tercica Medica**

**Xavier Ysern, PhD**  
**HFD-510**



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Chemistry Assessment

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# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### Chemistry Review Data Sheet

1. NDA 21-839
2. REVIEW #: 1
3. REVIEW DATE: 03-JUN-2005
4. REVIEWER: Xavier Ysem, PhD
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>		<u>Document Date</u>
IND [	J	08-AUG-1992
IND 39,679 (Tercica Medica; rhIGF-1)		07-JAN-2004
IND ~ (Tercica Medica; rhIGF-1)		11-AUG-2000
IND [	J	31-MAY-2005 WD
IND [	J	12-MAY-2005
IND [	J	LOA 09-AUG-2004 to IND 39,679
IND [	J	LOA 09-AUG-2004 to IND 39,679

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	24-FEB-2005

7. NAME & ADDRESS OF APPLICANT:

Name: Tercica Inc.  
 Address: 651 Gateway Boulevard, Suite 950  
 South San Francisco, CA 94080  
 Representative: Ira Wallis, PhD Vice President Regulatory Affairs  
 Telephone: (650) 624-4920

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Increlex™
- b) Non-Proprietary Name: Mecasermin (rDNA origin) injection
- c) Code Name: --
- d) Chem. Type/Submission Priority:
  - Chem. Type: 1 (New Molecular Entity)
  - Submission Priority: Priority

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Protein Hormone. Long-term treatment of growth failure in children with primary IGF-1 deficiency.

11. DOSAGE FORM: Liquid/Solution for Injection 4 mL Vial

12. STRENGTH/POTENCY: 10 mg/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous injection



# CHEMISTRY REVIEW



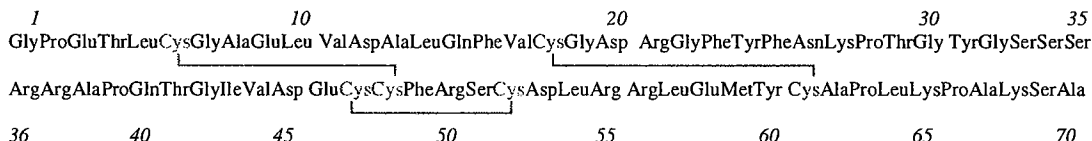
## Chemistry Review Data Sheet

14. Rx/OTC DISPENSED: Rx

15. SPOTS: SPOTS product – Form Completed

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Recombinant human insulin growth factor (rhIGF-1)



C<sub>331</sub>H<sub>512</sub>N<sub>94</sub>O<sub>101</sub>S<sub>7</sub> MW = 7,649 Da. CAS 68562-41-4

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code <sup>1</sup>	Status <sup>2</sup>	Date Review Completed	Comments
/	III	[	]	4	Adequate		LOA: 20-SEP-2004
	III			4	Adequate		LOA: 30-JUL-2004
	V			Baxter Pharmaceutical Solutions, LLC (BPS)	Facility in Bloomington, IN		

( ) supportive information. The applicant does not seek approval of the [ ] presentation.

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
--	--	--

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	--	--	--
EES	Pending		
Pharm/Tox	--	--	--
Biopharm	--	--	--
ODS/DMETS	No objection to the use of the proprietary name "Increlex"	02-FEB-2005	Kimberly Culley, RPh
Methods Validation	Pending	--	--
LNC	--	--	--
EA	Acceptable (Categorical Exclusion granted)	06-FEB-2004	Xavier Ysern, PhD
Microbiology	Pending	--	--





Executive Summary Section

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is APPROVABLE pending (1) submission of additional CMC information described in List of Deficiencies; and (2) Satisfactory cGMP inspection of facilities used to manufacture the drug substance and the drug product.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not Applicable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

The active pharmaceutical ingredient of Tercica's Increlex™ product is recombinant human Insulin-like Growth Factor-1 (rhIGF-1). rhIGF-1 is a monomeric non-glycosylated polypeptide consisting of 70 amino acid residues with three intramolecular disulfide bridges, and a molecular weight of 7649.6 Daltons. The amino acid sequence of the product is identical to that of endogenous human IGF-1. The United States Adopted Name (USAN) is mecasermin. The drug substance is synthesized in E. coli bacteria that have been modified by the addition of the gene for hIGF-1, [ ]

Human insulin like growth factor-1 (IGF-1, also referred as IGF-I) is a hormone structurally, but not functionally-related to human insulin. IGF-1 is produced following binding of growth hormone (GH) to the GH receptor on IGF-1 producing cells in the liver, bone and other tissues and is released into the circulation. IGF-1 induces metabolic and tissue growth responses, particularly those involved in cartilage and bone growth. In addition to the endocrine activities of IGF-1 on cartilage and bone, it also has autocrine and paracrine activities.

The manufacturing process for Tercica's rhIGF-1 formulated bulk drug substance was based upon process development and clinical production experience gained from 1989 to 1997 at Genentech, as well as recent manufacturing experience and development at [ ] Tercica's drug substance contract manufacturer. There were [ ] drug-substance manufacturing process development stages at Genentech. These included [ ]

[ ] All [ ] processes were used to manufacture drug substance material for use in clinical and non-clinical studies supporting this application. The Genentech drug substance process produced [ ] while the Tercica drug substance process produces [ ] requiring no further compounding or dilution during the drug product process.

The production organism for the manufacturing of rhIGF-1 is the recombinant E. coli [ ] used by Tercica for the manufacture of rhIGF-1 at [ ] were made during technology transfer of rhIGF-1 manufacturing from Genentech to Tercica. The transcriptional and translational initiation sequences required for expression of the rhIGF-1 gene in E. coli are provided by [ ]

]



# CHEMISTRY REVIEW



Executive Summary Section  
Manufacture of rhIGF-1 at \_\_\_\_\_ is conducted in \_\_\_\_\_

The drug substance manufacturing process is currently performed \_\_\_\_\_

The rhIGF-1 is initially produced \_\_\_\_\_

The composition of the formulated bulk drug substance is the same as that for Increlex™ drug product.

The primary structure (amino acid sequence and disulfide bridge assignments) of rhIGF-1 was confirmed using \_\_\_\_\_

Stability studies for the formulated bulk drug substance packaged \_\_\_\_\_ are scarce. Due to problems encountered with the initial \_\_\_\_\_ all formulated bulk drug substance lots packaged into \_\_\_\_\_ have been discontinued, and no data was provided for the only one lot packaged in the proposed \_\_\_\_\_ (lot # 155-1104-022) because it was manufactured at the time of the submission of this NDA. Consequently, shelf-life estimates for the formulated bulk drug substance packaged into the proposed \_\_\_\_\_ cannot be estimated. According to the applicant, the \_\_\_\_\_, as compared with the \_\_\_\_\_. Fortunately, formulated bulk drug substance can be entered into the manufacture of the drug product with minimal storage/holding times. There is insufficient stability data at this time to grant a shelf life.

As the formulation of the formulated bulk drug substance does not differ from that of the Increlex™ drug product their specifications are very similar. In addition to the formulated bulk drug substance specifications, Increlex™ drug product specifications incorporate \_\_\_\_\_ presentation of the drug product, \_\_\_\_\_, which are tests expected for



Executive Summary Section

pharmaceutical parenteral products; testing carried out in the formulated bulk drug substance is not part of Increlex™ drug product specifications. The applicant has been requested to have tests capable to discriminate rhIGF-1 based on its primary structure. The rest of the specifications are common to the drug product.

Drug Product

Orphan drug designation was obtained for mecasermin by Genentech, Inc., the former sponsor, on 12 December 1995 for mecasermin (rhIGF-1). Tercica received a letter dated 16 September 2004 from the Office of Orphan Product Development acknowledging transfer of the orphan drug designation to Tercica, from Genentech, Inc., (appended to User fee Cover Sheet, FDA Form 3397).

Increlex™ (mecasermin [rDNA origin] injection) is a sterile, aqueous, clear and colorless solution intended for subcutaneous injection. Each multi-dose vial contains 10 mg/mL mecasermin, 9 mg/mL benzyl alcohol, 5.84 mg/mL sodium chloride, 2 mg/mL polysorbate 20, and 0.05M acetate at a pH of approximately 5.4. The product is supplied as a 10 mg/mL sterile solution in 5 mL multiple dose glass vials (40 mg/vial). For the manufacture of the drug product, no excipients of human or animal origin are used. Therefore, no contamination risk can be expected with regard to transmissible spongiform encephalopathy (TSE) or other adventitious agents from excipients.

Development studies carried out by Genentech and by Tercica after transfer from Genentech have demonstrated that The main observations were:

- (1)
(2)

During development, two formulations, the single use formulation and the multi-use formulation, have been used in clinical and non-clinical studies supporting this application. Each formulation is intended for use as a sterile parenteral (subcutaneous injection) product. The original formulation was developed as a single-use (single dose) presentation, and was adequate for evaluation in the multiple clinical indications being considered at early developmental stages. The drug substance used in this formulation was obtained from The modified formulation, multi-use presentation, allowed for implementation of a multi-dose presentation for the drug product, as well as evaluation of higher concentrations in various clinical studies. The change in formulation included as well as incorporation of benzyl alcohol as a preservative. The change in was based on developmental findings. The use of preservative is a requirement for multi-dose presentations.

Increlex™ injection is manufactured from rhIGF-1 formulated bulk drug substance by conventional processes. The bulk is received at the drug product manufacturing facility as a stable, fully formulated solution (formulated bulk drug substance) that is maintained at 2 to 8 °C and stored in No formulation or compounding is performed at the drug product manufacturing site, The manufacturing procedure is based on conventional techniques The drug product is filled by Critical manufacturing steps are adequately controlled by in-process controls (IPCs).



## Executive Summary Section

⌋ No new impurities are introduced during the manufacture of the drug product.

Specifications for Increlex™ drug product include testing ⌋

⌋ The applicant has been requested ⌋  
⌋ test.

Drug product stability primary data is also scarce, at the time of filing, a total of months of stability data are available for one lot, and months for two lots, both at the proposed long-term refrigerated storage condition 2-8 °C, and from accelerated stability testing at 25 °C/60 % RH. Vials are stored inverted as well as upright, at each temperature condition, in order to evaluate the effects of the container closure on stability. The stability data show no discernable change in any of the product attributes over this time at the real-time 2-8 °C storage condition. At accelerated conditions, 25 °C/60 % RH, some changes are detected in the impurity profile as analyzed by ⌋  
The primary changes seen in ⌋ were ⌋

results also showed some minor changes. There appear to be no consistent differences between vials stored upright and inverted, at either condition. Although limited, months maximum data, all test results are within acceptable criteria. Photostability studies (naked vial) showed ⌋  
⌋ Light exposure appears to induce a different degradation ⌋  
⌋ Vials boxed ⌋ showed no changes compared with the dark controls, showing the adequacy of the secondary packaging to protect the product from light.

The solution for the injectable is filled into 5 mL/13 mm vials made of ⌋ glass complying with pertinent USP requirements for glass containers. The vials are closed with ⌋ stopper, and a flip-off seal. The stopper is the only closure component having a direct contact with the drug product. The contact portion of the stopper complies with the requirements ⌋

⌋. In addition to the long term and accelerated stability studies previously mentioned, the container-integrity test showed the adequacy of the container-closure packaging to assure the quality of the product. Although the applicant requested a shelf life period of ⌋, based on the limited stability data provided by the applicant a 12 month expiry dating is granted for the drug product stored at the recommended storage condition of 2-8 °C protected from light.

### B. Description of How the Drug Product is Intended to be Used

Increlex™ (mecasermin [rDNA origin] injection) is indicated for the long-term treatment of growth failure in children with primary IGF-1 deficiency (Primary IGF1D). It has also been used successfully to treat growth failure in children with GH gene deletion who have developed neutralizing antibodies to Growth hormone (GH). Increlex™ treatment is most appropriate for children whose height standard deviation score is less than or equal to -3.0 and basal IGF-1 standard deviation score is less than or equal to -3.0, in the presence of normal or elevated growth hormone (GH).

Increlex™ is supplied as a 10 mg/mL sterile solution in 5 mL multiple dose glass vials (40 mg/vial). There are no drug product diluents or dosing devices associated with the administration of Increlex™, as it is delivered directly via subcutaneous injection. The product is provided as a ready-to-use liquid formulation, without the need for dilution or mixing prior to injection.

The dosage of Increlex™ should be individualized for each patient. The recommended starting dose of Increlex™ is 0.080 mg/kg twice daily by subcutaneous injection. If well-tolerated for at least one week, the dose may be increased to 0.120 mg/kg given twice daily. If hypoglycemia occurs, the dose should be reduced. Doses of greater than 0.120 mg/kg given twice daily have not been evaluated in children with Primary IGF1D. Increlex™ is described to be administered shortly before or after a meal or snack. If the patient is unable to eat for any reason, Increlex™ treatment is described to be withheld. Although there is no actual clinical experience with overdosage of Increlex™, based on known pharmacological effects, acute overdosage could lead to hypoglycemia. Long-term

**Executive Summary Section**

overdosage may result in signs and symptoms of acromegaly, consistent with overproduction of IGF-1. Treatment of overdose of Increlex™ is described to be directed at alleviating any hypoglycemic effects.

Unopened Increlex™ vials should be stored in a refrigerator, 2 °C - 8 °C (36 °F - 46 °F), protected from intense light. It should not be stored in the freezer and it should not be allowed to freeze. Opened vials (in use), are stable within 30 when stored at 2 °C - 8 °C (36 °F - 46 °F). After a month, unused Increlex™ from opened vials should be discarded. Vial contents should be clear without particulate matter. If the solution is cloudy or contains particulate matter, the contents must not be injected. Increlex™ should not be used after its expiration date.

**C. Basis for Approvability or Not-Approval Recommendation**

This application is approvable from a CMC viewpoint. This recommendation is based upon several issues identified in this review. Several minor issues have also been identified. The applicant is requested to incorporate testing as part of the formulated bulk drug substance specifications. This test, adequately described in the application, were used in the characterization studies of the drug substance. The preservative effectiveness for the preservative benzyl alcohol should be confirmed at the lowest acceptable concentration limit of [ ]. Also modifications to the [ ] testing and to the purity acceptance criteria for both formulated bulk drug substances and drug product are requested. A final recommendation by the Office of Compliance for the manufacturing facilities is pending.

**III. Administrative****A. Reviewer's Signature**

See electronic signature page.

**B. Endorsement Block**

Chemist Name/Date:	Xavier Ysem, PhD/03-JUN-2005
Chemistry Team Leader Name/Date	Stephen Moore, PhD
Project Manager Name/Date	Enid Galliers

**C. CC Block**

Eric Duffy, PhD	HFD-820
Blair Fraser, PhD	HFD-820

165 Page(s) Withheld

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§ 552(b)(5) Draft Labeling

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