

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-538

CHEMISTRY REVIEW(S)

MEMORANDUM

Date: January 7, 2008

To: NDA 21-538

From: Yvonne Yang, Ph.D.
Chemist Reviewer

Subject: Overall Recommendation for Approval from CMC

NDA 21-538 was submitted originally on May-09-2006. An Approvable action was taken on the application pending microbiology deficiencies (see Approvable letter dated Mar-08-2007 for details).

The firm provided, in Amendment dated Jul-20-2007, a complete response to the Agency's Approvable letter dated Mar-08-2007. The Microbiology Staff has completed their review, and the application is **recommended for Approval from the microbiology product quality standpoint** (see Microbiologist review by Robert Mello signed off in DFS on Jan-02-2008 for details).

All other CMC sections of the application have been reviewed and found satisfactory from the standpoint of chemistry, manufacturing and control (see CMC review #1 signed off in DFS on Dec-22-2006 and CMC review #2 signed off in DFS on Feb-20-2007 for details).

NDA 21-538 is recommended for Approval from the standpoint of chemistry, manufacturing and control

Cc: NDA 21-538
DMEP/Division file/K Johnson
ONDQA/Y Yang/S Tran/A Al-Hakim

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/s/

Yvonne Yang
1/7/2008 02:04:50 PM
CHEMIST

Ali Al-Hakim
1/7/2008 02:08:34 PM
CHEMIST

MEMORANDUM

Date: March 5, 2007

To: NDA 21-538

From: Yvonne Yang, Ph.D.
Chemist Reviewer

Subject: Overall Recommendation for Approvable from CMC

The microbiology section of the application was sent to the Microbiology Staff for consultation (May-25-2006 in DFS). The Microbiology Staff has completed their review, and the application is **recommended Approvable from the microbiology product quality standpoint pending receipt of additional information** (see Microbiologist review by Robert Mello signed off in DFS on Mar-03-2007 for details).

All other CMC sections of the application have been reviewed and found satisfactory from the standpoint of chemistry, manufacturing and control (see CMC review #1 signed off in DFS on Dec-22-2006 and CMC review #2 signed off in DFS on Feb-20-2007 for details).

NDA 21-538 is recommended Approvable from the standpoint of chemistry, manufacturing and control pending a satisfactory response to all the microbiology deficiencies.

Cc: NDA 21-538
DMEP/Division file/K Johnson
ONDQA/Y Yang/S Tran/B Fraser

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/s/

Yvonne Yang
3/6/2007 12:12:10 PM
CHEMIST
Approvable pending Microbiology

Blair Fraser
3/6/2007 01:27:48 PM
CHEMIST

ACCRETROPIN™
[somatropin (rDNA origin)]
Injection
NDA 21- 538

Summary Basis for Recommended Action
From Chemistry, Manufacturing, and Controls

Applicant: Cangene Corporation
 155 Innovation Drive
 Winnipeg, Manitoba
 R3T 5Y3 Canada

Indication: intended for use in growth hormone-deficient pediatric patients and in pediatric patients with Turner Syndrome.

Presentation: ACCRETROPIN™ is supplied as a multi-dose sterile 1.15 mL solution of phosphate-buffered saline containing 5 mg/mL somatropin (rDNA origin) and 0.34% w/v phenol as an antimicrobial preservative in a vial

b(4)

EER Status: Acceptable 14-Feb-2007

Consults: Pharm/Tox - Acceptable 8-Feb-2007
 Microbiology – **Unacceptable** 3-Mar-2007
 Biopharm - Acceptable 9-Feb-2007
 Methods Validation – Revalidation by Agency was not requested.
 EA – Categorical exclusion granted under 21 CFR §25.31(c)
 DMETS Labeling - Acceptable 2-Feb-2007

Original Submission: 09-May-2005

Amendments: 12-Jun-2006
 22-Jan-2007
 26-Jan-2007

Post-Approval Agreements:

The applicant agrees to place on stability at least one lot of Accretropin™ drug product, annually, and submit the results in the Annual Report.

Drug Substance

Native human growth hormone (somatropin) is a single-chain, 191-amino-acid protein. It is non-glycosylated and contains two intramolecular disulfide bonds between positions Cys₅₃-Cys₁₆₅ and Cys₁₈₂-Cys₁₈₉. Somatropin (rDNA origin) has a molecular formula of C₉₉₀H₁₅₂₈N₂₆₂O₃₀₀S₇, an isoelectric point of 5.1, and a molecular weight of 22,125 Da.

b(4)

Drug substance was characterized by Amino Acid Analysis, Peptide Mapping
 Liquid Chromatography – Mass Spectrometry (LC/MS),
 circular dichroism (CD), fluorescence, Nuclear Magnetic Resonance Spectroscopy (1D
 and 2D-NOESY, TOCSY), Sodium Dodecyl Sulfate - Polyacrylamide Gel
 Electrophoresis (SDS-PAGE), Western Blot, Isoelectric Focussing (IEF), Size Exclusion
 Chromatography (SEC), Reverse Phase High Pressure Liquid Chromatography
 (RPHPLC), and Anion Exchange Chromatography (AEX).

The biological activity of somatropin (rDNA origin) is determined using an *in vitro* cell proliferation assay using the Nb2-11 rat lymphoma cell line. The biological activity (potency) of somatropin (rDNA origin) is determined using the WHO International Standard (NIBSC Code 98/574) as the reference and is expressed in International Units/mg (IU/mg).

The proposed release specifications include bioburden, identity (SDS-PAGE, peptide mapping), protein concentration (UV), purity (RP-HPLC, SEC, AEX), potency, residual (HPLC), E.coli protein (ELISA), (IR), Pluronic F68 (colorimetric assay), and residual (quantitative PCR). The proposed regulatory methods have been validated. The in-house reference standard for somatropin (rDNA origin) has been developed and characterized.

b(4)

Noteworthy are three categories of product-related impurities for somatropin that will be monitored throughout the shelf life of the drug substance: the aggregated forms, charge-related (deamidated) impurities, and total impurities. The level of E. coli proteins is controlled at release. The level of residual is controlled at release.

b(4)

Stability studies on the bulk drug substance support the proposed shelf life of 18 months when stored in stainless steel containers at or below -20°C.

Conclusion: Drug substance is satisfactory

Drug product

ACCRETROPIN™ is supplied as a multi-dose sterile solution of 1.15 mL in a vial

b(4)

Each vial of Accretropin™ contains 5 mg/mL somatropin (rDNA origin), sodium phosphate USP, sodium phosphate USP, 3.4 mg/mL phenol USP (0.34%), 2 mg/mL Pluronic F68 (Poloxamer 188) USP (0.2%), and 7.5 mg/ml (0.75%) sodium chloride USP.

b(4)

Specifications for the drug product include bioburden, sterility (bulk and final container), potency, purity (RP-HPLC, SEC, AEX), identity (SDS-PAGE, Western blot), pH, color, protein concentration (SEC), phenol (HPLC), (colorimetric assay), Pluronic F68 (colorimetric assay), and appearance. At the end of the shelf life, the product may contain product-related impurities.

b(4)

Acceptable is the proposed expiry for Accretropin™ [somatropin (rDNA origin)] Injection of 18 months at 2-8 °C (36-46 °F); the product must not be stored frozen. Once opened, Accretropin™ may be stored up to 14 days when refrigerated [2-8 °C (36-46 °F)].

Conclusion: Drug product is satisfactory.

Additional Items:

All associated Drug Master Files are acceptable or the pertinent information has been provided in the application.

The analytical methods used in testing are well known and widely used by the biopharmaceutical industry; revalidation by Agency laboratories will not be requested

Overall Conclusion: From a CMC perspective, the application is recommended **Approvable**, pending receipt of additional Microbiology information.

Blair A. Fraser, Ph.D.
Director
DPA I/ONDQA

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/s/

Blair Fraser
3/6/2007 01:56:01 PM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21538/000

Sponsor: CANGENE

Org Code : 510

NO CITY, , XX

Priority : 5S

Brand Name : ACCRETROPIN

Stamp Date : 10-MAY-2006

Estab. Name:

PDUFA Date : 10-MAR-2007

Generic Name: SOMATROPIN RECOMBINANT HUMAN

Action Goal :

GROWTH HORM

District Goal: 09-JAN-2007

Dosage Form: (INJECTION)

Strength : 5 MG/ML

FDA Contacts: K. JOHNSON

Project Manager

301-796-1234

Y. YANG

Review Chemist

301-796-1777

Overall Recommendation: ACCEPTABLE on 14-FEB-2007 by S. ADAMS (HFD-322) 301-827-9051

Establishment : CFN : FEI : 3003999720

CANGENE CORP

155 INNOVATION DRIVE

WINNIPEG, MANITOBA, CA r3t 5y3

DMF No:

AADA:

- Responsibilities:
- FINISHED DOSAGE LABELER
 - FINISHED DOSAGE MANUFACTURER
 - FINISHED DOSAGE PACKAGER
 - FINISHED DOSAGE RELEASE TESTER
 - FINISHED DOSAGE STABILITY TESTER

Profile : SVS

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 14-FEB-07
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI : 3001782611
CANGENE CORP
26 HENLOW BAY
WINNIPEG, MANITOBA, CA

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile : CBI OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 24-JAN-07

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : _____ FEI : _____

b(4)

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

DMF No:

AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 25-MAY-06

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : FEI :

b(4)

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-JUN-06

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

NDA 21-538

**AccretropinTM
Somatropin (rDNA origin)
Injection**

Cangene Corporation

**Yvonne Yang, Ph.D.
Division of Metabolic and Endocrine Products
HFD-510**



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Chemistry Review Data Sheet

1. NDA #: 21-538
2. REVIEW #: #2
3. REVIEW DATE: February-16-2007
4. REVIEWER: Yvonne Yang, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

CMC Review #1

Document Date

Dec-20-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument DateContent

Original	May-09-2006	• Original submission
Amendment	Jun-12-2006	• Labeling (Labels)
Amendment	Jan-22-2007	• Labeling (Package Insert)
Amendment	Jan-26-2007	• CMC response to IR letter dated Jan-10-2007

7. NAME & ADDRESS OF APPLICANT:

Name: Cangene Corporation
Address: 155 Innovation Drive
Winnipeg, Manitoba
R3T 5Y3 Canada
Representative: Chesapeake Biological Laboratories, Inc.
Camden Industrial Park
1111 South Paca Street
Baltimore, MD 21230-2591
Telephone: Tel: (410)843-5005
Fax: (410)843-4414

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Accretropin™
b) Non-Proprietary Name (USAN): Somatropin (rDNA origin)
c) Code Name/# (ONDQA only):



CHEMISTRY REVIEW



Chemistry Assessment Section

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

This NDA is submitted as a 505(b)(1) application.

10. PHARMACOL. CATEGORY: Growth Hormone
11. DOSAGE FORM: Injection
12. STRENGTH/POTENCY: 5 mg/mL
13. ROUTE OF ADMINISTRATION: Subcutaneous
14. Rx/OTC DISPENSED: X Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

 X SPOTS product – Form Completed
 Not a SPOTS product

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

Somatropin (rDNA origin); recombinant human growth hormone
 $C_{990}H_{1528}N_{262}O_{300}S_7$ (MW = 22, 125 Dalton) (see review for structural formula)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
b(4)	III	b(4)	b(4)	3	Adequate	Jan-29-1996	Reviewed by H. B. Patel
	III			3	Adequate	Sept-22-2003	Similar products from the same supplier previously reviewed by D. Lewis
	III			4	Adequate	See Section S.6 of this review for details	Reviewed By Y. Yang

¹ 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



CHEMISTRY REVIEW



Chemistry Assessment Section

7 – Other (explain under "Comments")

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

B. Other Documents: N/A

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Pharm/Tox	Acceptable pending final labeling	Review signed off in DFS Feb-08-2007	Herman Rhee
Biopharm	Acceptable pending final labeling	Review signed off in DFS Feb-09-2007	Wei Qiu
DMETS	<ul style="list-style-type: none"> DMETS has no objections to the use of the proprietary name, Accretropin DMETS recommends implementation of some label and labeling revisions DDMAC finds the proprietary name Accretropin acceptable from a promotional perspective 	Review signed off in DFS Feb-02-2007	Kristina Arnwine
Tradename	Pending OSE consult (Office of Surveillance and Epidemiology)		
Methods Validation	Acceptable		Yvonne Yang
EA	Categorical exclusion granted		Yvonne Yang
EES	Acceptable overall recommendation from OC	Feb-14-2007	
Microbiology	Pending Micro consult		



The Chemistry Review for NDA 21-538

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommendation from the standpoint of chemistry, manufacturing and control is pending: (1) an acceptable recommendation from Microbiology Staff, and (2) final labeling including Tradename.

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

None

II. Summary of Chemistry Assessments

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

Drug Product:

The drug product Accretropin™ [somatropin (rDNA origin)] Injection is manufactured as a sterile formulation containing somatropin (rDNA origin): recombinant human growth hormone manufactured using recombinant DNA technology. The drug product is supplied as a multi-dose sterile solution in a _____ vial _____.

Each vial of Accretropin™ contains 5 mg/mL somatropin (rDNA origin). _____, sodium phosphate _____, sodium phosphate _____,

_____ 3.4 mg/mL (0.34%) phenol, and 7.5 mg/ml (0.75%) sodium chloride. Each vial of the drug product is filled with 1.15 mL to ensure the delivery of 1.0 mL of the product. Accretropin™ Injection is to be administered by subcutaneous injection; the dose and administration schedule should be individualized for each patient. Three categories of product-related impurities for somatropin will be monitored throughout the shelf life of the drug product: the aggregated forms, charge-related (deamidated) impurities, and total impurities. At the end of the shelf life, the product may contain _____ product-related impurities.

b(4)

b(4)

The proposed expiry for Accretropin™ [somatropin (rDNA origin)] Injection is 18 months at 2-8 °C (36-46 °F). The product must be stored under refrigeration at 2-8 °C (36-46 °F), protected from light, and prevented from freezing and shaking. Once opened, Accretropin™ Injection may be stored up to 14 days when refrigerated [2-8 °C (36-46 °F)]. The proposed expiry for the drug product is supported by the available stability data.



Drug Substance:

The drug substance **somatropin (rDNA origin)** is synthesized in genetically engineered *E. coli* in which the gene encoding for recombinant human growth hormone (rhGH) was introduced through recombinant DNA technology. The amino acid sequence of the recombinant human growth hormone is identical to that of the endogenous human growth hormone. **Somatropin** is the official name used by United States Adopted Name (USAN) for human growth hormone manufactured using recombinant DNA technology. Somatropin is a single chain non-glycosylated polypeptide containing 191 amino acids with a molecular mass of 22,125 Daltons. Somatropin contains two intramolecular disulfide bonds. Somatropin has an isoelectric point of 5.1. The biological activity of somatropin, in this application, is determined using an *in vitro* cell-based cell proliferation assay using the Nb2-11 rat lymphoma cell line. The biological activity (potency) of somatropin is determined using the WHO International Standard (NIBSC Code 98/574) as the reference standard, and expressed in International Units/mg (IU/mg). Three categories of product-related impurities for somatropin will be monitored throughout the shelf life of the drug substance: the aggregated forms, charge-related (deamidated) impurities, and total impurities.

The level of **E. coli proteins** (a process-related impurity in the drug substance) is controlled _____ at release. The level of **Residual** : _____
_____ (a product-related impurity in the drug substance) is controlled : _____
_____ at release. The levels of these impurities in the drug substance should be adequately controlled in order to minimize the potential risk for immunogenicity in the patients.

b(4)

The proposed expiration dating for the bulk drug substance is 18 months when stored at or below -20°C. The proposed expiry for the bulk drug substance is adequately supported by the available stability data.

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

Accretropin™ Injection is intended for use in growth hormone-deficient pediatric patients, and pediatric patients with Turner Syndrome. Accretropin™ Injection is to be administered by subcutaneous injection; the dose and administration schedule should be individualized for each patient.



CHEMISTRY REVIEW



Chemistry Assessment Section

C. Basis for Approvability or Not-Approval Recommendation

CMC information provided to support the application includes the following:

- A satisfactory response to all of the CMC questions in the IR letter dated Jan-10-2007 has been provided by the applicant (Amendment dated Jan-26-2007)
- Adequate CMC information for the drug substance somatropin (rDNA origin)
- Adequate CMC information for the drug product Accretropin™ Injection
- Acceptable regulatory specifications for the drug substance somatropin (rDNA origin)
- Acceptable regulatory specification for the drug product Accretropin™ Injection
- Real time stability data to support the proposed expiration dating period for the bulk drug substance (18 months when stored at or below -20°C)
- Real time stability data to support the proposed expiration dating period for Accretropin™ Injection (18 months when stored at 2-8 °C)
- In-use stability data to support the proposed dosing regimen for Accretropin™ Injection: 14 days in the refrigerator, at 2-8 °C

Recommendation from the standpoint of chemistry, manufacturing and controls (CMC) for NDA 21-538 is **pending the following**:

1. an acceptable recommendation from Microbiology Staff, and
2. final labeling including Tradename.

III. Administrative:

- | | |
|-------------------------|--------|
| A. Reviewer's Signature | in DFS |
| B. Endorsement Block: | in DFS |
| C. CC Block: | in DFS |

20 Page(s) Withheld

X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Yvonne Yang
2/20/2007 11:41:37 AM
CHEMIST

Blair Fraser
2/20/2007 11:55:27 AM
CHEMIST



NDA 21-538

**Accretropin™
Somatropin (rDNA origin)
Injection**

Cangene Corporation

Yvonne Yang, Ph.D.

**Division of Metabolic and Endocrine Products
HFD-510**



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A. Labeling & Package Insert	95
B. Environmental Assessment Or Claim Of Categorical Exclusion	95
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Chemistry Review Data Sheet

- 1. NDA #: 21-538
- 2. REVIEW #: #1
- 3. REVIEW DATE: December-20-2006
- 4. REVIEWER: Yvonne Yang, Ph.D.
- 5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

N/A

- 6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

May-09-2006

- 7. NAME & ADDRESS OF APPLICANT:

Name: Cangene Corporation

Address: 155 Innovation Drive
Winnipeg, Manitoba
R3T 5Y3 Canada

Representative: Chesapeake Biological Laboratories, Inc.
Camden Industrial Park
1111 South Paca Street
Baltimore, MD 21230-2591

Telephone: Tel: (410)843-5005
Fax: (410)843-4414

- 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Accretropin™
- b) Non-Proprietary Name (USAN): Somatropin (rDNA origin)
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 5
 - Submission Priority: S



CHEMISTRY REVIEW



Chemistry Assessment Section

9. LEGAL BASIS FOR SUBMISSION:

This NDA is submitted as a 505(b)(1) application.

10. PHARMACOL. CATEGORY: Growth Hormone
11. DOSAGE FORM: Injection
12. STRENGTH/POTENCY: 5 mg/mL
13. ROUTE OF ADMINISTRATION: Subcutaneous
14. Rx/OTC DISPENSED: X Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

 X SPOTS product – Form Completed
 Not a SPOTS product

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

Somatropin (rDNA origin); recombinant human growth hormone
 $C_{990}H_{1528}N_{262}O_{300}S_7$ (MW = 22, 125 Dalton) (see review for structural formula)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

b(4)

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	III			3	Adequate	Jan-29-1996	Reviewed by H. B. Patel
	III			3	Adequate	Sept-22-2003	Similar products from the same supplier previously reviewed by D. Lewis
	III			4	Adequate	See Section S.6 of this review for details	Reviewed By Y. Yang

¹ 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")

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



CHEMISTRY REVIEW



Chemistry Assessment Section

B. Other Documents: N/A

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending OC		
Pharm/Tox	Pending		
Biopharm	Pending OCP		
Methods Validation	Acceptable		Yvonne Yang
DMETS	Pending DMETS		
EA	Categorical exclusion granted		Yvonne Yang
Microbiology	Pending Micro		



The Chemistry Review for NDA 21-538

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommendation from the standpoint of chemistry, manufacturing and control is pending: (1) a satisfactory response to the information request to be forwarded to the applicant, (2) an overall acceptable cGMP recommendation from the Office of Compliance, (3) an acceptable recommendation from Microbiology Staff, and (4) final labeling including Tradename.

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

None

II. Summary of Chemistry Assessments

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

Drug Product:

The drug product **Accretropin™ somatropin (rDNA origin) Injection** is manufactured as a sterile formulation containing somatropin (rDNA origin): recombinant human growth hormone manufactured using recombinant DNA technology. The drug product is supplied as a multi-dose sterile solution in :
vial

Each vial of Accretropin™ contains 5 mg/mL somatropin (rDNA origin), sodium phosphate sodium phosphate, 3.4 mg/mL (0.34%) phenol, and 7.5 mg/ml (0.75%) sodium chloride. Each vial of the drug product is filled with 1.15 mL to ensure the delivery of 1.0 mL of the product. Accretropin™ is to be administered by subcutaneous injection; the dose and administration schedule should be individualized for each patient. Three categories of product-related impurities for somatropin will be monitored throughout the shelf life of the drug product: the aggregated forms, charge-related (deamidated) impurities, and total impurities. At the end of the shelf life, the product may contain product-related impurities.

b(4)

The proposed expiry for **Accretropin™ Somatropin (rDNA origin) Injection** is 18 months at 2-8 °C (36-46 °F), the product must not be stored frozen. Once opened, Accretropin™ may be stored up to 14 days when refrigerated [2-8 °C (36-46 °F)]. However, the currently available stability data only support an



CHEMISTRY REVIEW



Chemistry Assessment Section

expiry of 9 months when stored at 2-8 °C (36-46 °F) unless stability data are provided.

Drug Substance:

The drug substance **somatropin (rDNA origin)** is synthesized in genetically engineered *E. coli* in which the gene encoding for recombinant human growth hormone (rhGH) was introduced through recombinant DNA technology. The amino acid sequence of the recombinant human growth hormone is identical to that of the endogenous human growth hormone. **Somatropin** is the official name used by United States Adopted Name (USAN) for human growth hormone manufactured using recombinant DNA technology. Somatropin is a single chain non-glycosylated polypeptide containing 191 amino acids with a molecular mass of 22,125 Daltons. Somatropin contains two intramolecular disulfide bonds. Somatropin has an isoelectric point of 5.1. The biological activity of somatropin, in this application, is determined using an *in vitro* cell-based cell proliferation assay using the Nb2-11 rat lymphoma cell line. The biological activity (potency) of somatropin is determined using the WHO International Standard (NIBSC Code 98/574) as the reference standard, and expressed in International Units/mg (IU/mg). Three categories of product-related impurities for somatropin will be monitored throughout the shelf life of the drug substance: the aggregated forms, charge-related (deamidated) impurities, and total impurities.

The level of **E. coli proteins** (a process-related impurity in the drug substance) is controlled at the level of _____ at release. The level of **Residual _____** (a product-related impurity in the drug substance) is controlled _____ at release. The levels of these impurities in the drug substance should be adequately controlled in order to minimize the potential risk for immunogenicity in the patients.

b(4)

The proposed expiration dating for the bulk drug substance is 18 months when stored at or below -20°C. The proposed expiry for the bulk drug substance is adequately supported by the available stability data.

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

Accretropin™ is intended for use in growth hormone-deficient pediatric patients, and pediatric patients with Turner Syndrome. Accretropin™ is to be administered by subcutaneous injection; the dose and administration schedule should be individualized for each patient.



CHEMISTRY REVIEW



Chemistry Assessment Section

C. Basis for Approvability or Not-Approval Recommendation

Recommendation from the standpoint of chemistry, manufacturing and controls (CMC) for NDA 21-538 is pending the following:

1. a satisfactory response to the deficiencies/information request to be forwarded to the applicant,
2. an overall acceptable cGMP recommendation from the Office of Compliance,
3. an acceptable recommendation from Microbiology Staff, and
4. final labeling including Tradename.

III. Administrative:

- | | |
|--------------------------------|--------|
| A. Reviewer's Signature | in DFS |
| B. Endorsement Block: | in DFS |
| C. CC Block: | in DFS |

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X Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

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/s/

Yvonne Yang
1/10/2007 08:33:55 AM
CHEMIST

Blair Fraser
1/11/2007 07:44:54 AM
CHEMIST

**Initial Quality Assessment
ONDQA/ Division of Pre-Marketing Assessment I**

NDA: 21-538
OND Division: Division of Metabolic and Endocrine Products (DMEP)
Applicant: Cangene Corporation
Status Date: 10-MAY-2006 (Letter date 09-MAY-2006)
PDUFA Date: 10-MAY-2007
Proposed Proprietary Name: Accretropin™
Established Name: Somatropin (rDNA origin) [*recombinant human Growth Hormone (rhGH)*]
Dosage form and strength: Sterile Liquid for Injection 5 mg/mL
Route of Administration: Subcutaneous Injection
Indications: ——— treatment of pediatric patients with growth failure due to GH deficiency
 · Treatment of short stature in pediatric patients with Turner syndrome

b(4)

Fileability recommendation: Acceptable for filing

Review team recommendation: Single primary reviewer (Chemist Yvonne Yang)

Time Goals	
<i>Discipline/ Division Consulted</i>	<i>Date</i>
NDA 21-985 Clock Date (Stamp Date)	10-MAY-2006
Initial Quality Assessment in DFS	12-JUN-2006
Filing decision "Day 45" Meeting Date	09-JUL-2006
Filing review issues sent to applicant "Day 74"	05-AUG-2006
Mid-cycle meeting "Month 5"	10-OCT-2006
Final Chemistry Review "Month 8"	10-JAN-2007
DMEP Goal Date	10-MAR-2007
PDUFA	10-MAR-2007

Consults/ CMC Related Reviews

<i>Discipline/ Division Consulted</i>	<i>Comment</i>
OCPB	--
CDRH	N.A.
EA	Categorical exclusion granted under 21 CFR§25.31
EES	EER submitted on 24-MAY-2006 ^(a)
OMP/ DDMAC	Adequacy of the proposed carton and container labels request on 13-MAR-2006 ^(b)
ODS/ DMETS	Adequacy of proposed drug product tradename Accretropin™ ^(b)
Methods Validation	Revalidation by Agency laboratories may be requested after test methods are finalized.
Microbiology ^(c)	· Adequacy of the preservative excipients in the formulation and of the proposed container closure to assure sterility of the drug product throughout its proposed shelf life and usage. · Adequacy of the sterilization process validation for the manufacture of Accretropin™ · Adequacy of the Adventitious Agent Safety Evaluation
Pharm/Tox	--

DDMAC = Division Drug Marketing, Advertising, and Communications; CDRH = Center for Devices and Radiological Health;
 DMETS = Division of Medical Errors and Technical Support; EER = Establishment Evaluation Request;
 EES = Establishment Evaluation System; N.A. = Not Applicable; OCPB = Office of Clinical Pharmacology and Biopharmaceutics;
 OMP = Office of Medical Policy; ODS = Office of Drug Safety.

^(a) See attachment

^(b) Originator: Kati Johnson Chief, PM Staff, DMEP

^(c) Originated by Kati Johnson Chief, PM Staff, DMEP on May 25, 2006

Summary:

NDA 21-538, Accretropin™ (somatropin [rDNA origin]) Injection, was submitted by Cangene Corporation on 09-MAY-2006, and filed as a 505(b)(1) application intended for the treatment of long term treatment of pediatric patients with growth failure due to GH deficiency, and the treatment of short stature in pediatric patients with Turner syndrome

Drug Substance (DS):

The active compound, human growth hormone (somatropin), is a 191 amino acid non-glycosylated single chain protein with two intra disulfide bridges.

Structure (protein primary structure¹):

1
FPTIPLSRLF QNAMLRAHRL HQLAFDTYEE FEEAYIPKEQ KYSFLQAPQA SLCFSES IPT PSNREQAQQK
71
SNLQLLRISL LLIQSWLEPV GFLRSVFANS LVYGASDS DV YDLLKDLEEG IQTLMGRLED GSPRTGQAFK
141 191
QTYAKFDANS HNDDALLKNY GLLYCFRKDM DKVETFLRIV QCRSVEGSCG F [C53-C165 & C182-C189]

human Growth Hormone (hGH) or Somatropin C₉₉₀H₁₅₂₈N₂₆₂O₃₀₀S₇ MW = 22,125.19 CAS 12629-01-5

The drug substance, human growth hormone (hGH or somatropin), is obtained by recombinant DNA (rDNA) technology in a bacterial expression system (*E. coli*)

hGH is produced during fermentation in *E. coli* yielding a non-glycosylated protein containing 192 amino acids. The N-terminal amino acid, methionine, is later removed (aminopeptidase treatment) to yield a protein that after folding, disulfide formation and purification, is indistinguishable from pituitary derived human growth hormone, consisting of 191 amino acids in a single polypeptide chain.

b(4)

b(4)

Similarity assessment of hGH drug substance from Accretropin™ (referred as Product A) with the commercial comparator, Humatrope® (Lilly's hGH, rDNA origin, synthesized from *E. coli* fermentation, referred as Product B), included a comprehensive panel of analytical (peptide map, SDS-Page and Western Blot, LC/MS, Mass Mapping and Isoelectric focusing), biological (cell-based bioactivity testing) and structural (CD, NMR, and fluorescence spectroscopy) characterization procedures.

b(4)

- The similarity assessment of Products A and B also included product related impurities, product related substances and stability profiles. No significant differences were noted.
- DS specifications include bioburden _____ identity by SDS PAGE, protein content by UV _____, purity by reverse phase chromatography (RP-HPLC), purity by size exclusion chromatography (SEC), purity by anion exchange chromatography (AEX), potency (cell-proliferation bioactivity assay), peptide mapping _____ host cell protein (*E. coli* protein _____), residual _____ content, and pluronic F68 content. Analytical test methods claimed to be validated. Acceptance criteria consistent with USP monograph for somatropin. **b(4)**
- Primary/working (in-house) rhGH standards are qualified by performing testing in parallel the international reference standard (World Health Organization Somatropin Second International Standard 2000 NIBSC Code 98/574) and/or previously qualified in-house rhGH standards.
- Cangene's bulk drug substance, is prepared as a liquid format _____ Ongoing stability studies conducted at the recommended storage condition (< -20 °C) and at accelerated conditions (2 – 8 °C), up to 12 months data available at the time of the submission, indicate that the container closure has minimal impact on the levels of impurities as monitored by SEC and RP-HPLC. Stability studies on the bulk drug substance clinical material, _____ passed all specification criteria for a period of 24 months. Stability studies on the clinical material did not evaluate storage at 2 to 8 °C. **b(4)**

Drug Product (DP)

- The commercially available drug product, Accretropin™ is presented as a multidose liquid solution for subcutaneous injection containing 1 mL of a 5 mg/mL solution of rhGH (15 IU/mL).
 - Each 1 mL of solution for injection contains 5 mg of recombinant human growth hormone (active), 2 mg pluronic F68, a non-ionic surfactant, also known as Poloxamer 188, _____ sodium phosphate, _____ sodium phosphate, _____ 3.4 mg phenol, antimicrobial agent, and 7.5 mg sodium chloride (isotonic agent). The final pH of the drug product is 6.0 ± 0.3 _____ All components meet compendial requirements. **b(4)**
- _____ **b(4)**

- DP specifications include appearance (color), pH, identification (SDS and Western Blot), potency (bioassay), protein content (SEC), purity by RP-HPLC, purity by anion exchange chromatography,

aggregate forms (high molecular weight proteins by SEC), sterility, bioburden, _____, and content of phenol, _____, and pluronic F58.

b(4)

- Specification's acceptance criteria differ from that of current USP monograph for Somatropin for injection. The applicant claims that the USP monograph acceptance criteria are based on stability of a freeze-dried somatropin product (material for reconstitution) and Cangene's product is a liquid for injection.
- Based on the demonstrated stability of Accretropin™ drug product stored _____ at 2 to 8 °C, for 18 months, a shelf life of 18 months at 2 to 8 °C is proposed. Once opened, Accretropin™ may be stored up to 14 days when refrigerated [2° to 8°C (36° to 46°F)].

b(4)

Critical Issues: (This is not an exhaustive list of critical issues.)

- Corroboration of applicant claims that drug substance material obtained by the original "clinical" process is comparable to the material obtained by the proposed commercial process.
- Adequacy of the process validation _____. The adequacy of the validation process _____ requested to Microbiology
- Acceptability of the DP purity acceptance criteria based on safety demonstrated in clinical lots.
- Need of particle content test (parenteral product)
- Adequacy of analytical stability indicating testing procedures (DS and DP).
- Adequacy of _____ DP.
- Adequacy of proposed shelf life under proposed usage.

b(4)

Comments and Recommendation:

The NDA is considered Fileable from a CMC perspective.
The other critical issues previously listed, will be evaluated as part of the review.

Xavier Ysern, PhD Review Chemist ONDQA/ DPA I/ Branch II 12-JUN-2006

Init. Blair Fraser, PhD Branch Chief ONDQA/ DPA I/ Branch II

Attached:

Page

b(4)

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 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Xavier Ysern
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Blair Fraser
6/12/2006 05:18:40 PM
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