CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-426

CHEMISTRY REVIEW(S)

OMNITROPE™
(somatropin [rDNA origin]) for injection
NDA 21- 426

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

Applicant: Sandoz, Inc.
506 Carnegie Center, Suite 400
Princeton, NJ 08540

Indication: (1) long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone and (2) long-term replacement therapy in adults with growth hormone deficiency (GHD) of either childhood- or adult- onset etiology (post exclusivity).

Presentation: OMNITROPE™1.5 mg is supplied with two vials, one containing Somatropin [rDNA origin] as a powder and the other vial containing the diluent (Sterile Water for Injection). – Single use

OMNITROPE™ 5.8 mg is supplied with two vials, one containing Somatropin [rDNA origin] as a powder and the other vial containing diluent (Bacteriostatic Water for Injection containing benzyl alcohol as a preservative). – Multi-use

EER Status: Acceptable 13-AUG-2004

Consults: Microbiology – Approval 2-AUG-2004
Methods Validation – Revalidation by Agency was not requested
EA – Categorical exclusion granted under 21 CFR §25.31(c)

Post-Approval Agreements: None

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. The endogenous hormone exists in two principal forms: full length and a form missing 15 internal amino acids due to an alternate splicing of the mRNA (the latter form is therefore not a metabolite). Growth hormone circulates mostly as a monomer (55%), but significant amounts of dimeric (27%) and tri-, tetra-, and pentameric forms (18% of total) are observed. Approximately 50% of circulating growth hormone is complexed to growth hormone binding protein.

Somatropin (rDNA origin) is composed of the same 191 amino acids with the two disulfide bonds. It is synthesized in *Escherichia coli* K-12, strain MG1655, transformed with expression plasmid pHGH which contains the cDNA sequence for human growth hormone (hGH).

The biological activity of rhGH drug substance batches produced at full scale was determined by the rat weight gain assay. The biological activities of the batches correspond to the biological activity of WHO international reference standard, Somatropin NIBSC 88/624, and Genotropin.

The applicant performed four characterization studies of the rhGH drug substance.Three of these studies used Genotropin as a comparator. One of the studies used the WHO reference standard, Somatropin CRS (European Somatropin reference standard) and Genotropin as comparators. Extensive physicochemical and biological characterization established the applicant's somatropin [rDNA origin] to be somatropin and demonstrated similarity to the somatropin in Genotropin.

Stability studies on the bulk drug substance support the applicant's proposed shelf life of [redacted] the drug substance at a temperature [redacted]

Conclusion: Drug substance is satisfactory

Drug product

Omnitrope (somatropin [rDNA origin] for injection) 5.8 mg is is supplied as a sterile, white, lyophilized powder in a vial containing 5.8 mg of somatropin (approximately 17.4 IU), glycine (27.6 mg), disodium hydrogen phosphate heptahydrate (2.09 mg), and sodium dihydrogen phosphate dihydrate (0.56 mg). The product is provided with a vial containing 1.14 ml diluent (water for injection with 1.5% benzyl alcohol as a preservative). After reconstitution of the lyophilized powder, the solution has a concentration of 5.0 mg/mL (approx. 15 IU/mL). The deliverable volume is 1.0 mL. The applicant requested a 24-month shelf life for the 5.8 mg/vial when stored at 2 - 8°C. The applicant provided stability data for the 5.8 mg/vial supporting a [redacted] shelf life when stored at 2 - 8°C and for the Bacteriostatic Water for Injection supporting a 36 month shelf life when stored at 2 - 8°C. Later, the applicant provided stability data for one batch, at commercial scale, for the 5.8 mg/vial supporting a 24-month shelf life when stored at 2 - 8°C.

Omnitrope (somatropin [rDNA origin] for injection), 5.8 mg, will have a 24-month shelf life when stored at 2 - 8°C in a light-tight container. In-use stability studies support storage, after reconstitution, for 3 weeks at 2° to 8°C (36° to 46°F).

Omnitrope (somatropin [rDNA origin] for injection) 1.5 mg lyophilized powder is supplied as a sterile, white, lyophilized powder in a vial containing 1.5 mg of active substance (approximately 4.5 IU), glycine (27.6 mg), disodium hydrogen phosphate heptahydrate (0.88 mg), and sodium dihydrogen phosphate dihydrate (0.21 mg). The product is provided with a vial containing 1.13 ml of diluent (water for injection). The applicant requested a 24-month shelf life for the 1.5 mg/vial when stored at 2 - 8°C. The applicant provided stability data for the 1.5 mg/vial supporting a 24-month shelf life when stored at 2 - 8°C and for the Sterile Water for Injection supporting a 36 month shelf life when stored at 2 - 8°C.

Omnitrope (somatropin [rDNA origin] for injection), 1.5 mg, will have a 24-month shelf life when stored at 2 - 8°C in a light-tight container. In-use stability studies support storage, after reconstitution, for up to 24 hour at 2° to 8°C (36° to 46°F).

The applicant performed one comparative study with the Omnitrope drug product. The impurity profiles of [redacted] lots of Omnitrope drug product were characterized and compared to the impurity profiles of eight lots of Genotropin. The profiles are not identical. Certain of these impurities were structurally characterized. [redacted] impurities, [redacted], are present in the Omnitrope batches and are not in any Genotropin batches. These new impurities were qualified in a PharmTox study.

Conclusion: Drug product is satisfactory.

Additional Items:

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

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

Blair A. Fraser, Ph.D.
Branch Chief, Branch II
DPA I/ONDQA

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/s/

Blair Fraser
5/26/2006 03:32:32 PM
CHEMIST

8.30.04 5:05P

CHEMISTRY REVIEW

NDA 21-426

Omnitrope (somatropin for injection) 5.8 mg & 1.5 mg Lyophilized Powder

Biochemie U.S., Inc.

Janice Brown, HFD-510
Division of Metabolic and Endocrine Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA: 21-426

2. REVIEW #: 2

3. REVIEW DATE: 10-Aug-2004

4. REVIEWER: Janice Brown, HFD-510

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original (N000)	30-Jul-2003
Amendment (N000BZ)	08-Aug-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (N000DH)	06-Jul-2004
Amendment (N000BC)	06-Jul-2004
Amendment (N000BC)	14-Jul-2004
Amendment (N000BC)	18-Aug-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Biochemie U.S., Inc.

Address: 101 Morgan Lane, 2nd Floor

Chemistry Review Data Sheet

Representative :	Authorized U.S. Agent Beth Brannan Geneva Pharmaceuticals, Inc. 2555 W. Midway Blvd. Broomfield, CO 80038 Phone: 303-438-4237 Fax: 303-438-4600
Telephone:	609-750-4700

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Omnitrope (somatropin for injection) Somatropin (rhGH) for injection
b) Non-Proprietary Name (USAN): Somatropin, recombinant human growth hormone
c) Code Name/# (ONDC only): EP2000, BC rhGH
d) Chem. Type/Submission Priority (ONDC only)
e) Chem. Type: 5 (New Manufacturer)
f) Submission Priority: S (Standard Review)

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2) proposed

10. PHARMACOL. CATEGORY: Human growth hormone

11. DOSAGE FORM: Injection, Powder, For Solution

12. STRENGTH/POTENCY: 1.5 mg/vial and 5.8 mg/vial

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: See review #1

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: See review #1
B. Other Documents: None

18. STATUS: See review #1

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-426

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has satisfactorily addressed all chemistry deficiencies sent on 20-May-2004. From a CMC standpoint, NDA 21-426 can be APPROVED.

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)

See chemistry review #1.

This review addresses the deficiencies communicated to the applicant in FDA letter dated 20-May-2004. The amendments reviewed cover characterization of the somatropin drug substance, additional controls in the purification process, revisions of the drug substance, drug product, and diluent specifications, product comparability data, and stability data.

The applicant has satisfactorily demonstrated by full physico-chemical and biological characterization that the active ingredient of Omnitrope is human growth hormone (somatropin). Additionally, the applicant has demonstrated that the somatropin in Omnitrope is comparable to the somatropin in Genotropin (Pfizer).

Establishment Inspection – The Office of Compliance has issued an overall Acceptable recommendation for this NDA.

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

See chemistry review #1.

C. Basis for Approvability or Not-Approval Recommendation

CMC information is satisfactory.

III. Administrative

Chemistry Review Data Sheet

A. Reviewer's Signature: See electronic signature sheet.

B. Endorsement Block

Janice Brown/Date: Same date as review
Stephen K. Moore/Date
Monika Johnson/Date

C. CC Block

Eric Duffy, Division Director
Blair Frasier, Deputy Division Director

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/s/

Janice Brown
8/30/04 04:49:38 PM
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Stephen Moore
8/30/04 05:05:37 PM
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CHEMISTRY REVIEW

NDA 21-426

Omnitrope (somatropin for injection) 5.8 mg & 1.5 mg Lyophilized Powder

Biochemie U.S., Inc.

Janice Brown, HFD-510
Division of Metabolic and Endocrine Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA: 21-426

2. REVIEW #: 1

3. REVIEW DATE: 12-May-2004

4. REVIEWER: Janice Brown, HFD-510

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original (N000)	30-Jul-2003
Amendment (N000BZ)	08-Aug-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Biochemie U.S., Inc.

Address: 101 Morgan Lane, 2nd Floor

Chemistry Review Data Sheet

Authorized U.S. Agent
Beth Brannan
Geneva Pharmaceuticals, Inc.
Representative: 2555 W. Midway Blvd.
Broomfield, CO 80038
Phone: 303-438-4237
Fax: 303-438-4600

Telephone: 609-750-4700

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Omnitrope (somatropin for injection) Somatropin (rhGH) for injection
b) Non-Proprietary Name (USAN): Somatropin, recombinant human growth hormone
c) Code Name/# (ONDC only): EP2000, BC rhGH
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5 (New Manufacturer)
- Submission Priority: S (Standard Review)

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2) proposed

10. PHARMACOL. CATEGORY: Human growth hormone

11. DOSAGE FORM: Injection, Powder, For Solution

12. STRENGTH/POTENCY: 1.5 mg/vial and 5.8 mg/vial

13. ROUTE OF ADMINISTRATION: Subcutaneous

14. Rx/OTC DISPENSED: _X_Rx ___OTC

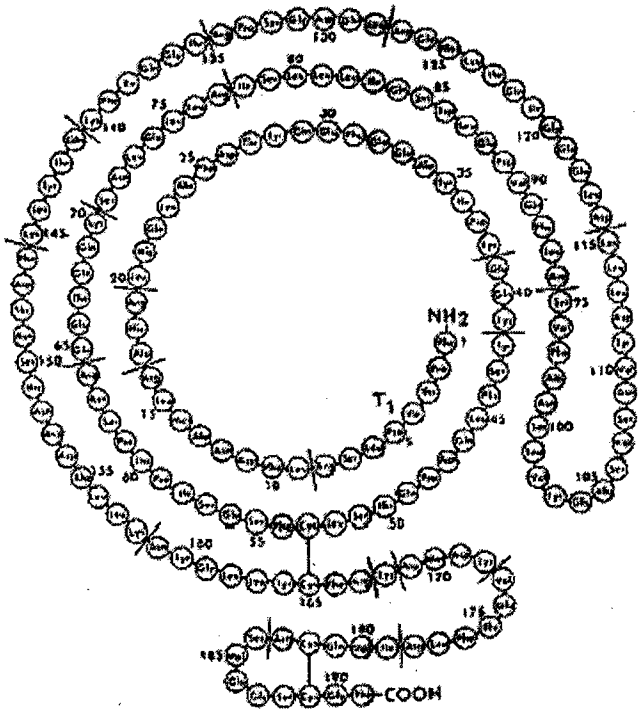
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_X_ SPOTS product – Form Completed

_Not a SPOTS product

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

The amino acid sequence of BC rhGH is illustrated below (solid lines indicate trypsin cleavage sites). BC rhGH is composed of 191 amino acids and contains two disulfide bonds between positions Cys53-Cys165 and Cys182-Cys189.



Chemical Name:

INN: Somatropin

Proprietary: Omnitrope (somatropin for injection)™ (Somatropin (rhGH) for injection)

Established: Somatropin

Company or laboratory code: EP2000, rhGH, or BC rhGH

Molecular Formula: $C_{980}C_{990}H_{1528}N_{262}O_{300}S_7$

Molecular Weight:

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM	CODE[1]	STATUS[2]	DATE	COMMENTS

Chemistry Review Data Sheet

			REFERENCED			REVIEW COMPLETED	
				4	Adequate	13-May-2004	None
				4	Adequate	13-May-2004	None
				4	Adequate	13-May-2004	None
				4	Adequate	13-May-2004	None

[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)

B. Other Documents: None

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES			
Pharm/Tox			
Biopharm			
LNC			
Methods Validation			
DMETS	Approvable		Linda Y. Kim-Jung
DDMAC	Approved		
EA			
Microbiology	Pending		Bryan Riley

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-426

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC standpoint, the recommendation for NDA 21-426 is APPROVABLE (see list of deficiencies).

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 - Omnitrope (somatropin for injection) lyophilized powder will be marketed two strengths, 5.8mg/vial and 1.5mg/vial.

Omnitrope (somatropin for injection) 5.8 mg lyophilized powder is supplied as a sterile, white, lyophilized powder in vials, containing 5.8 mg of active substance. It is provided with a vial containing a diluent comprised of water for injection (WFI) with 1.5% benzyl alcohol as a preservative, and is intended for multiple use by subcutaneous administration. The investigational formulation was used in clinical studies and a bioequivalence study with Genotropin. There was a minor quantitative formulation change in the 5.8 mg in the to-be-marketed drug product from the investigational formulation. No comparative stability results were provided to assess whether the new formulation has the same or similar stability profile as the investigational formulation. Omnitrope (somatropin for injection) 5.8 mg is dispensed in a vial containing 5.8 mg of somatropin (approximately 17.4 IU), glycine (27.6 mg), disodium hydrogen phosphate heptahydrate (2.09 mg), and sodium dihydrogen phosphate dihydrate (0.56 mg). The product is provided with a vial containing 1.14 ml diluent (water for injection with 1.5% benzyl alcohol as a preservative). After reconstitution of the lyophilized powder, the solution has a concentration of 5.0 mg/mL (approx. 15 IU/mL). The deliverable volume is 1.0 mL. The applicant requested a [redacted] shelf life for both strengths; however, the [redacted]. Based on these results, [redacted] the 5.8 mg strength is supported.

OMNITROPE (somatropin for injection) 1.5 mg lyophilized powder is supplied as a sterile, white, lyophilized powder in vials, containing 1.5 mg of active substance. It is provided with a vial containing WFI, and is intended for single use by subcutaneous administration. The 1.5 mg

strength and diluent were not used in any clinical study but was used in a bioequivalence study with Genotropin. Omnitrope (somatropin for injection) 1.5 mg is dispensed in a vial containing 1.5 mg of active substance (approximately 4.5 IU), glycine (27.6 mg), disodium hydrogen phosphate heptahydrate (0.88 mg), and sodium dihydrogen phosphate dihydrate (0.21 mg). The product is provided with a vial containing 1.13 ml of diluent (water for injection). After reconstitution of the lyophilized powder, the solution has a concentration of 1.33 mg/ml (approx. 4 IU/mL). The deliverable volume is 1.0 mL.The 1.5mg Omnitrope (somatropin for injection) lyophilized powder should be stored refrigerated at 2 ° to 8 °C (36 ° to 46 °F) protected from light. The product is light sensitive. Omnitrope (somatropin for injection) 1.5 mg lyophilized powder contains a diluent with no preservative. After reconstitution, the vial may be stored under refrigeration for up to 24 hours. The in-use stability analysis should be performed using two additional 1.5mg lots.

The applicant submitted a single lot (#S00100) and supportive data from another lot which was manufactured by the previous manufacturing process (#592003) to support the 24-month shelf life. Both lots stored at 2-8°C met the current shelf life specification. Long term and accelerated stability results should be submitted for two additional 1.5mg batches produced by the current process to support the 24-month shelf life.

During development, the investigational formulations included a 5.8 mg lyophilized powder and diluent (Bacteriostatic water for injection), 1.5 mg lyophilized powder and diluent (Sterile water for injection and a 5 mg/mL (15 IU/1.5 mL) liquid .

ESTABLISHMENT INSPECTION – The Office of Compliance has recommended a WITHOLD for EBEWE, the diluent manufacturer.

DRUG SUBSTANCE – Biochemie's GmbH's recombinant human growth hormone is produced in *Escherichia coli* K-12 strain MG1655 transformed with expression plasmid pHGH which contains the cDNA sequence for hGH. Human growth hormone (somatropin) is a nonglycosylated protein composed of 191 amino acids. The protein contains 4 cysteines, which forms 2 intramolecular disulfide bonds.

The applicant performed four characterization studies of the BC rhGH drug substance and one comparative study with the Omnitrope drug product. The drug substance characterization studies are described in items 1-4 below. The drug product study is described in item 5 below.

The applicant also compared BC rhGH to Pfizer's EU Genotropin. To support the use of EU Genotropin, the applicant performed a comparative characterization study of U.S. Genotropin and an EU Genotropin (item 6). This study was performed with the EU Genotropin because the applicant could not obtain sufficient quantities of the U.S. Genotropin to complete the clinical and comparative characterization studies.

A brief description and a summary findings of these studies are described below:

1. Characterization of a pilot lot (batch B2083005) of drug substance produced at Covance. The

analysis did not include a reference standard or the comparator Genotropin. This study provided minimal interpretable characterization results.

2. Characterization of four full scale batches of BC rhGH produced at Kundl using the WHO reference standard, Somatropin CRS (European Somatropin reference standard) and Genotropin as comparators. The analysis included comparative 2D-NMR. The results of this study physico-chemically and biologically characterize the BC rhGH batches produced at Kundl; however, the characterization is incomplete (see #4 below). The results of this study also demonstrate that BC rhGH produced at full scale is comparable to Genotropin pending the completion of the characterization of BC rhGH (see #4 below).
3. Characterization of four pilot scale batches produced at Covance using Genotropin as the comparator. The results of this study demonstrated that BC rhGH produced at pilot scale is comparable to Genotropin pending the completion of the characterization of BC rhGH (see #4 below).
4. Characterization of four pilot scale batches produced at Covance and four full scale batches produced at Kundl using the WHO reference standard, Somatropin CRS (European Somatropin reference standard) and Genotropin as comparators (Appendix 3). This is considered the critical characterization and comparative study. The results of this study physico-chemically and biologically characterize the full-scale BC rhGH batches produced at Kundl and bridge it to the pilot scale batches. However, the characterization is incomplete. The peptide map with mass spectrometric detection needs to be completed with an additional endopeptidase to generate overlapping peptide fragments. Also, the cDNA sequence analysis also needs to be confirmed on the end-of-production cells. The results of this study also demonstrate that the BC rhGH produced at full scale is comparable to Genotropin pending the completion of the characterization of BC rhGH.
5. Characterization of the impurity profile of four lots of Omnitrope drug product with [redacted] lots of Genotropin as a comparator. The impurity profile of the Omnitrope drug product shares some similarity with Genotropin; however, the profiles are not identical. Certain of these impurities were structurally characterized. [redacted] impurities, [redacted], are present in the Omnitrope batches and are not in any Genotropin batches (see table 6). Additionally, there appears to be a higher level of deamidated variants in the Omnitrope samples.
6. Comparative characterization of Genotropin obtained in the U.S. with Genotropin obtained in the EU (Appendix 3). The results of this study demonstrate that Genotropin obtained in the E.U. is comparable to the Genotropin obtained in the U.S.

The applicant manufactured the first batches of drug substance used in the clinical studies at Covance, North Carolina. This API was used to manufacture the drug product used in the early clinical trials, including the first 9 months of the Phase III study. The clinical study did not bridge the product manufactured at Covance (pilot) to the product produced at Kundl (full scale); however, this bridge was made by comparative characterization studies submitted in CMC section of this application. An important event during the Omnitrope (somatropin for injection) clinical development has been the observation that "Covance" Omnitrope (somatropin for injection) was immunogenic. Exposure of patients to "Covance" Omnitrope (somatropin for injection) resulted in a progressive increase in incidence of antibody-positive patients; at the end of 9 months of treatment 24 (57%) patients were anti-GH antibody positive. The applicant states that the drug substance manufactured by Covance, USA was subsequently found to have a high

content of Host Cell Proteins (HCP). Following this observation, production of Omnitrope (somatropin for injection) drug substance was changed to a different site (Biochemie in Kundl, Austria) and a modified manufacturing process was used which decreased the HCP content of the product. The drug substance manufactured at Biochemie was used in all subsequent Omnitrope (somatropin for injection) drug products. The percentage of patients who were antibody-positive was reduced when administered the drug substance produced at Kundl. To reduce the host cell protein content the manufacturing process at Kundl was modified and a new host cell protein assay was developed. Together these changes resulted in a lower host cell protein level.

The applicant has satisfactorily provided the results to support the proposed [redacted] shelf-life for the bulk drug substance when stored at [redacted]

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

OMNITROPE (somatropin for injection)™ Lyophilized Powder is indicated for (1) long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone and (2) long-term replacement therapy in adults with growth hormone deficiency (GHD) of either childhood- or adult- onset etiology (post exclusivity).

C. Basis for Approvability or Not-Approval Recommendation

There were a number of major deficiencies which include the following:

Drug substance: incomplete amino acid sequence determination, incomplete description of the process scale-up and supportive comparability analysis, lack of DNA sequencing of the hGH coding region for the end of production cells, inadequate in-process monitoring and identification of an impurity, incomplete demonstration of removal of [redacted] by downstream process, acceptance criterion for level of structural variant not provided, in-house working reference standard requalification protocol and corresponding specifications not provided, drug substance specifications lacked specifications for product-related substances, bioidentity, and bioburden, and inadequate justification for exclusion from specification of [redacted] impurities.

Drug product: Inadequate specifications for two product-related substances which are present and increase upon storage of the drug product, quantitative change in excipients between the investigational and to-be-marketed formulation with no stability data provided, stability data from only one lot of the 1.5 mg strength product to support in-use period for the reconstituted solution, inadequate routine quality control testing of the diluent (1.5% Benzyl Alcohol Water for Injection), and inadequate specifications for Sterile Water for Injection.

Establishment Inspection – The Office of Compliance has recommended a WITHOLD for EBEWE, the diluent manufacturer.

III. Administrative

A. Reviewer's Signature: See electronic signature sheet.

B. Endorsement Block

Janice Brown/Date: Same date as draft review
Stephen K. Moore/Date
Monika Johnson/Date

C. CC Block

Eric Duffy, Division Director
Blair Frasier, Deputy Division Director

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Withheld Track Number: Chemistry- 3

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/s/

Janice Brown
8/30/04 04:46:03 PM
CHEMIST

Stephen Moore
8/30/04 05:00:40 PM
CHEMIST