CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-905

CHEMISTRY REVIEW(S)

VALTROPIN™
(somatropin [rDNA origin]) for injection
NDA 21- 905

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

Applicant: LG Life Sciences, Ltd
Sung Choo and/or Hyi-Jeong
20, Yoido-dong
Youngdungpo-gu
Seoul 150-721, Korea

Indication: (1) [redacted] of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone; (2) [redacted] b(4

Presentation: VALTROPIN ™ is supplied as

One vial containing 5 mg (15 IU) of somatropin [rDNA origin] as a sterile, non-pyrogenic, white, lyophilized powder and

One pre-filled syringe containing 1.5 mL of diluent (Sterile Water For Injection with 0.3% w/v metacresol as an antimicrobial preservative)

for Multiple use.

EER Status: **Pending**

Consults: Microbiology – **Pending**
Methods Validation – Revalidation by Agency was not requested
EA – Categorical exclusion granted under 21 CFR §25.31(c)
Labeling - **Pending**

Original Submission: 01-Dec-2005

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 Cys_{53}-Cys_{165} and Cys_{182}-Cys_{189}.

Drug substance [somatropin (rDNA origin)] is composed of the same 191 amino acids with the two disulfide bonds. It is synthesized in *Saccharomyces cerevisiae (Baker's yeast)* by recombinant DNA technology. Briefly,

b(4)

Consequently, the bulk drug substance was produced through

Drug substance was characterized in terms of structural, physicochemical, immunochemical, and biological properties. It was physicochemically characterized by

b(4)

The biological activities of rhGH drug substance batches produced at scale were determined by the rat weight gain assay. The biological activities of the batches correspond to that for the WHO international reference standard, Somatropin NIBSC 88/624 (98/574) and the Ph.Eur. somatropin CRS.

Somatropin (rDNA origin) drug substance has 191 amino acid residues, identical to that of human growth hormone (hGH) of pituitary origin; a chemical formula: $C_{990}H_{1528}N_{262}O_{300}S_7$; a molecular weight of 22,125.19 Daltons; and an isoelectric point of approximately 5.

Stability studies on the bulk drug substance support the applicant's proposed shelf life of 18 months when stored below -15°C and for no more than three weeks at 5°C. The drug substance may undergo a maximum of 6 freeze/thaw cycles

Conclusion: Drug substance is satisfactory

Drug product

Valtropin™ (somatropin [rDNA origin] for injection) 5 mg is supplied as a sterile, white, lyophilized powder in a 5 cc vial containing 5 mg of somatropin (15 IU), mannitol (45 mg), glycine (10 mg), disodium hydrogen phosphate heptahydrate (2.98 mg), and [redacted] (0.22 mg). The product is provided with a pre-filled, 2.25 cc, glass barrel syringe containing 1.5 ml diluent (Water for Injection with 0.3% meta-cresol as an antimicrobial agent). b(4)

After reconstitution of the lyophilized powder, the solution has a concentration of 3.33 mg/mL (approx. 10 IU/mL). The reconstituted Valtropin™ is used as a multidose product for repeat use.

The applicant requested a 36-month shelf life for the 5 mg/vial when stored at 2 - 8°C. The applicant provided stability data for the 5 mg/vial supporting a 36-month shelf life when stored at 2 - 8°C and for the diluent supporting a 30 month shelf life when stored at 2 - 8°C. Reconstituted Valtropin™ drug product is stable for up to 3 weeks, when stored in the refrigerator (2-8°C) and taken out daily for five minutes.

Conclusion: Drug product is satisfactory.

Additional Items:

The applicant plans to [redacted] and report such in the Annual Report. b(4)

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

Overall Conclusion: From a CMC perspective, the application is recommended for **approval** pending the microbiology consult review and a satisfactory cGMP status.

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

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

/s/

Blair Fraser
8/31/2006 03:00:05 PM
CHEMIST

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
CDER, Office of New Drug Quality Assessment
Mail Room 2562
10903 New Hampshire Ave.
Silver Spring, Maryland 20993
(301) 796-1679
(301) 796-9747 (FAX)

MEMORANDUM

DATE: 11-NOV-2006

FROM: John C. Hill, Ph.D., CMC Reviewer, DPA-I

THROUGH: Blair Fraser, Ph.D., Chief, DPA-I

TO: Jena Weber, Regulatory Health Project Manager, DMEP

SUBJECT: Status update: Labeling, Micro consult, and CGMP Status of Facilities Associated with NDA 21-905

- LG submitted revised labeling for the Valtropin drug product on 26-OCT-2006. After review of this revised labeling with the medical officer, the following CMC related labeling changes are required:

  1. At the top of page 22 of the proposed package insert (tab 3) remove the following statement, '[redacted]

  2. At the bottom of page 22 of the proposed package insert (tab 3) change the word [redacted] to "diluent".

- The microbiology consult was completed and deemed acceptable on 14-SEP-2006.

- The Office of Compliance has completed its inspection of manufacturing facilities referenced in support of LG Life Sciences NDA 21-905. A copy of this report, dated 26-OCT-2006, is attached to this memo. The overall recommendation is "Withhold".

Faxed to Co - 11/13/06 (FAX)

b(4)

The CMC Review of this application is complete. From a CMC viewpoint, this application is approvable, pending satisfactory resolution of the unacceptable CGMP status at the [redacted]

b(4)

[redacted] manufacturing facility. This facility manufactures [redacted] b(4)

The wording of the deficiency is:

This application is approvable, pending satisfactory resolution of the unacceptable CGMP status at the [redacted] b(4) manufacturing facility.

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 21905/000	Action Goal:	
Stamp:	01-DEC-2005	District Goal:	02-AUG-2006
Regulatory Due:	01-OCT-2006	Brand Name:	VALTROPIN (SOMATROPIN)
Applicant:	LG LIFE	Estab. Name:	
	NO CITY, , XX	Generic Name:	SOMATRAPIN
	5S		
Priority:	510	Dosage Form:	(FOR INJECTION)
Org Code:		Strength:	5 MG (15 IU)

Application Comment:

FDA Contacts:	J. WEBER	301-796-1306	, Project Manager
	J. HILL	301-796-1679	, Review Chemist
	S. TRAN	301-796-1764	, Team Leader

Overall Recommendation: WITHHOLD on 26-OCT-2006by S. ADAMS (HFD-322)301-827-9051

Establishment: CFN [redacted] FEI [redacted]

[redacted]

b(4)

BERLIN, , GM

DMF No: AADA:

Responsibilities: [redacted]

Profile: [redacted] OAI Status: NONE b(4)

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-DEC-2005				TRANS
SUBMITTED TO DO	16-DEC-2005	GMP			ADAMSS
ASSIGNED INSPECTION T	23-DEC-2005	GMP			ADAMSS
INSPECTION SCHEDULED	10-AUG-2006		18-SEP-2006		ADAMSS
INSPECTION PERFORMED	18-SEP-2006		18-SEP-2006		ADAMSS b(4)
INSPECTION PERFORMED	18-SEP-2006		18-SEP-2006		[redacted]
DO RECOMMENDATION	26-OCT-2006			ACCEPTABLE	ADAMSS
				INSPECTION	
BASED ON REVIEW OF 483 AND FIRM'S RESPONSE. AWAITING EIR.					
OC RECOMMENDATION	26-OCT-2006			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	

Establishment: CFN [redacted] FEI [redacted]

[redacted] b(4)

[redacted]

DMF No:

AADA:

Appears This Way
On Original

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Responsibilities: [redacted]

Profile: [redacted] OAI Status: NONE b(4)

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-DEC-2005				TRANS
SUBMITTED TO DO	19-DEC-2005	10D			FERGUSONS
DO RECOMMENDATION	19-DEC-2005			ACCEPTABLE	ESMITH1
				BASED ON FILE REVIEW	
THIS PROFILE CLASS WAS FOUND ACCEPTABLE DURING 12/04 INSPECTION					
OC RECOMMENDATION	19-DEC-2005			ACCEPTABLE	FERGUSONS
				DISTRICT RECOMMENDATION	

Establishment: CFN [redacted] FEI [redacted] b(4)

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile: [redacted] OAI Status: NONE b(4)

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-DEC-2005				TRANS
OC RECOMMENDATION	19-DEC-2005			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: CFN FEI

[redacted] b(4)

DMF No: AADA:

Responsibilities: [redacted]

Profile: [redacted] OAI Status: POTENTIAL OAI

Estab. Comment: [redacted] b(4)

[redacted] (on 14-DEC-2005 by S. TRAN () 301-796-1764)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-DEC-2005				TRANS
SUBMITTED TO DO	16-DEC-2005	GMP			ADAMSS
ASSIGNED INSPECTION T	10-JAN-2006	GMP			ADAMSS
INSPECTION SCHEDULED	10-AUG-2006		20-SEP-2006		IRIVERA
INSPECTION PERFORMED	20-SEP-2006		20-SEP-2006		[redacted]
DO RECOMMENDATION	26-SEP-2006			WITHHOLD	ADAMSS

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

PEND REG ACTION - WARNING LTR

OC RECOMMENDATION 26-SEP-2006 WITHHOLD ADAMSS

DISTRICT RECOMMENDATION

Establishment: CFN FEI

LG LIFE SCIENCES LTD

104-1 MUNJI-DONG, YUSEONG-GU

DAEJEON, , KS 305-380

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Profile: CBI OAI Status: NONE

Estab. Comment: BIOASSAY (RAT WEIGHT GAIN) TESTER:

RELEASE OF DRUG SUBSTANCE AND STABILITY OF DRUG PRODUCT (on 16-DEC-2005 by S. TRAN () 301-796-1764)

CBI PROFILE IS INCORRECT FOR TESTING. (on 16-DEC-2005 by S. ADAMS (HFD-

322) 301-827-9051)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-DEC-2005				TRANS
REQUEST CANCELLED	16-DEC-2005				ADAMSS
				IRRELEVANT FACILITY/PROFILE	
SUBMITTED TO OC	26-SEP-2006				ADAMSS
SUBMITTED TO DO	26-SEP-2006	GMP			ADAMSS
ASSIGNED INSPECTION T	26-SEP-2006	GMP			ADAMSS
INSPECTION SCHEDULED	26-SEP-2006		11-OCT-2006		ADAMSS
INSPECTION PERFORMED	17-OCT-2006		17-OCT-2006		ADAMSS
DO RECOMMENDATION	25-OCT-2006			ACCEPTABLE	ADAMSS
				INSPECTION	

BASED ON REVIEW OF 483 OBSERVATIONS AND INVESTIGATOR'S RECOMMENDATION. AWAITING FIRM'S RESPONSE AND EIR.

OC RECOMMENDATION	25-OCT-2006			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	

Profile: CTL OAI Status: NONE

Estab. Comment: INVESTIGATOR ONLY NEEDS TO SPEND 1/2 DAY INSPECTING THIS FACILITY.

BIOASSAY (RAT WEIGHT GAIN) TESTER:

RELEASE OF DRUG SUBSTANCE AND STABILITY OF DRUG PRODUCT (on 16-DEC-2005 by S. ADAMS (HFD-322) 301-827-9051)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-DEC-2005				TRANS

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

SUBMITTED TO DO	16-DEC-2005	GMP		ADAMSS
ASSIGNED INSPECTION T	23-DEC-2005	GMP		ADAMSS
INSPECTION SCHEDULED	07-SEP-2006	13-OCT-2006		IRIVERA
INSPECTION PERFORMED	18-OCT-2006	18-OCT-2006		ADAMSS
DO RECOMMENDATION	25-OCT-2006		ACCEPTABLE	ADAMSS
			INSPECTION	
BASED INVESTIGATOR'S RECOMMENDATION. AWAITING EIR.				
OC RECOMMENDATION	25-OCT-2006		ACCEPTABLE	ADAMSS
			DISTRICT RECOMMENDATION	

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

/s/

John C. Hill
11/8/2006 12:50:52 PM
CHEMIST

Blair Fraser
11/8/2006 01:22:32 PM
CHEMIST

NDA 21-905

Valtropin™ (somatropin)

LG Life Sciences, Ltd.

John C. Hill, Ph.D.
ONDQA/DPA I/DMEDP/HFD-510

CHEMISTRY REVIEW #2

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-905

2. REVIEW #2

3. REVIEW DATE: 27-JUN-2006

4. REVIEWER: John C. Hill, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA Filing	01-DEC-2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
BC Amendment (Facility and Characterization Data)	07-FEB-2006 ✓
BC Amendment (Response to DR Letter)	30-MAY-2006 ✓

7. NAME & ADDRESS OF APPLICANT:

Name:	LG Life Sciences, Ltd Youn Sung Choo and/or Hyi-Jeong Ji
Address:	20, Yoido-dong Youngdungpo-gu Seoul 150-721, Korea Tel: 822-3773-0693 Fax: 822-785-0324
Representative:	PAREXEL International (US Agent) Bruce Babbitt and/or Hoss Dowlat and/or Alberto Grignolo 200 West Street Waltham, MA 02451-1163 Tel: 781-434-4057 Fax: 978-848-2221

Telephone: Noted above

8. DRUG PRODUCT NAME/CODE/TYPE:

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

- Chem. Type: 3
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Hormone Replacement

11. DOSAGE FORM: Lyophilized Powder

12. STRENGTH/POTENCY: 5 mg (15 IU) in 1.5 ml

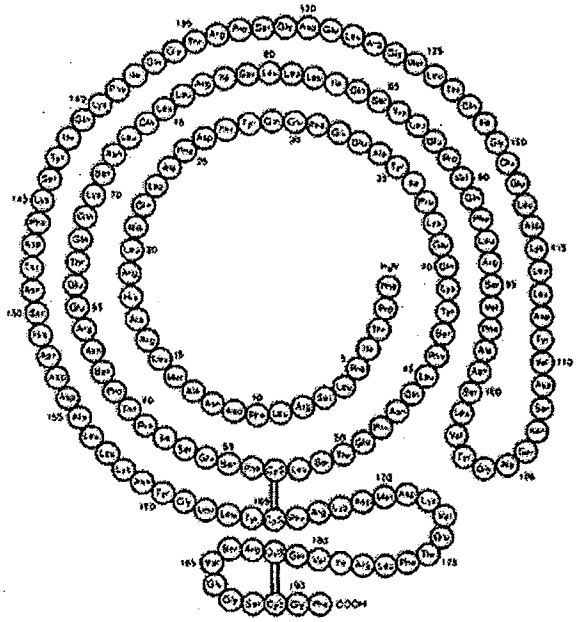
13. ROUTE OF ADMINISTRATION: Subcutaneous Injection

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X___Not a SPOTS product

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



Amino acid sequence of human growth hormone

Chemical Formula: $C_{990}H_{1528}N_{262}O_{300}S_7$
Molecular Weight: 22,125.19 Daltons (22.12519 kDa)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]					Adequate	24-FEB-2003	LOA 27-APR-2005
					Adequate	9-AUG-2005	LOA 15-SEP-2005

b(4)

Chemistry Review Data Sheet

	Adequate	Acceptable DMF for sterile manufacturing facility	LOA 24-APR-2005
	Adequate	15-SEP-2000 24-FEB-2003 3-MAY-2000 19-FEB-2000	LOA 15-SEP-2005

b(4)

b(4

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –
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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	IND 62,376	
IND	IND 69,726	

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	EER was drafted on 14-DEC-2005. Waiting for Compliance's database entry of a new facility ([redacted] before sending the EER to Compliance.		John Hill, Ph.D.
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Not Required		John C. Hill, Ph.D.
DMETS	Labeling consult request will be sent.		
OPDRA			
EA	Acceptable		John C. Hill, Ph.d.
Microbiology	Consult request will be sent for the review of 1) microbiology controls proposed for the drug substance, drug product, and diluent, 2) sterilization and aseptic processing validation for the drug product and diluent, and 3) antimicrobial effectiveness in the reconstituted multi-dose product.		

b(4)

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

Chemistry Review Data Sheet

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

Appears This Way
On Original

The Chemistry Review for NDA 21-905

The Executive Summary

I. Recommendations

Recommendation and Conclusion on Approvability

From a CMC viewpoint this NDA can be approved, pending:

1. CGMP compliance status review,
2. Microbiology evaluation, and
3. Final labeling evaluation.

II. Summary of Chemistry Assessments

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

Drug Product

The Valtropin™ drug product powder is presented in a 5 cc/13 mm vial which is closed with a bromobutyl stopper/closure with a polymer coating. The rubber stopper is covered with an aluminum overseal and a polypropylene flip-off cap.

The solvent co-product is presented in a 2.25 mL glass syringe with Luer lock and rubber tip cap. The syringe barrel is closed with a bromobutyl rubber plunger stopper with an inert FluroTec® contact surface to the aqueous cresol solvent.

Valtropin™ is manufactured from somatropin drug substance that is compounded with excipients as a solution and meets USP sterility testing. The compounded solution is aseptically filled into vials, vacuum lyophilized under a controlled environment and the vials are stoppered under a positive pressure of sterile nitrogen. b(4)

The Valtropin™ drug product formulation is based on the known formulation of the majority of somatropin preparations. The active principle, recombinant human growth hormone (rhGH) is ——— with glycine; ——— mannitol) is included for ———. The formulation is also buffered with ———, which is consistent with all the somatropin products except for Saizen® which is an exception because it is ——— The composition of the Valtropin™ drug product is summarized in the following table:

Table 3.2.P.1-1: Composition

Name of Ingredient	Unit and/or Percentage	Function	Reference to Standard
Active ingredient			
Somatropin	5 mg	Active ingredient	Current USP*
Other ingredients			
Glycine	10 mg		USP/Ph. Eur.
Mannitol	45 mg		USP/Ph. Eur.
Sodium phosphate monobasic	0.22 mg		USP
Sodium phosphate dibasic	2.98 mg		USP
Water for injection	to 2 ml		USP/Ph. Eur.

* Complies with USP plus additional specifications that are Ph. Eur. conforming
1N Sodium hydroxide and 1N hydrochloric acid are used to adjust pH

b(4)

b(4)

The solvent copackaged with the lyophilized drug product, consisting of water for injection (WFI) containing 0.3% metacresol as an antimicrobial agent, is presented in a 1.5 ml glass pre-filled syringe, The composition of the diluent is provided in the following tables:

Table 3.2.P.1-1: Composition of a single pre-filled syringe (1.5 mL) of the solvent (0.3%)[1]

Ingredient	Unit	Function	Reference to Standard
m-Cresol	4.5 mg		Ph. Eur.[2]
Water for Injections	ad 1.5 mL		Ph. Eur./USP

[1] Conforms to USP. Prior to 2005 was tested against in house specifications, which were tighter than Ph. Eur.

b(4)

Table 3.2.P.1-2: Composition of the solvent per mL (0.3%)

Ingredient	Unit	Function	Reference to Standard
m-Cresol	3 mg		Ph. Eur.
Water for Injections	ad 1 mL		Ph. Eur./USP

b(4)

This solvent is similar to that used with other somatropin products, but omits glycerine (Humatrope®), mannitol (Genotropin®) or benzyl alcohol (Nutropin® and Norditropin®).

The reconstitution of a Valtropin™ vial with the full contents of a 1.5 ml solvent syringe results in a final product concentration of 3.33 mg/ml. When Valtropin™ is reconstituted with 1.5 ml of solvent, osmolalities of approximately 317 mOsm/kg are obtained, which is close to the ideal tonicity of 240 to 340 mOsm/kg, falling within the physiologically desired range. The reconstituted Valtropin™ is then used as a multidose product for repeat use.

Drug Substance

Somatropin (rDNA origin) (Valtropin™) drug substance is derived from the yeast *Saccharomyces cerevisiae* by recombinant DNA technology.

b(4)

Somatropin is a single-chain protein of 191 amino acids, including four cysteine residues present as two intra-chain disulfides. Somatropin is produced by recombinant DNA technology from yeast *Saccharomyces cerevisiae*. Methionyl recombinant human growth hormone (met-rhGH of 192 amino acids) is expressed from the yeast cells, folded into its native three-dimensional structure, and its N-terminal methionine residue is cleaved to yield mature rhGH of 191 amino acids during subsequent purification steps. The primary and secondary structures of somatropin are identical to pituitary-derived human growth hormone.

18 months of real-time stability data have been provided in the NDA for Valtropin™ drug substance manufactured using the proposed commercial manufacturing process. LG Life Sciences will update these stability data via the annual report through the planned 3 years of stability. Based on the supporting stability data and the similarity of the developmental manufacturing processes to the proposed commercial process, it is reasonable to grant a shelf life of 3 years for the Valtropin™ drug substance.

The recommended storage condition of the drug substance is at ——————; or alternatively, -25 °C when required, for up to 3 years. b(4)

The recommended storage condition of drug substance at 5°C is no more than three weeks.

The Valtropin™ drug substance may undergo a maximum of 6 freeze/thaws cycles

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

Pediatric Patients

- Valtropin™ is indicated for the ——————————————— b(4)
- Valtropin™ is indicated for the ——————————————— (TS).

Adult Patients

- [redacted]

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable (AE) from a CMC viewpoint. This recommendation is based upon the evaluation of the relevant drug product manufacturing, characterization and stability data provided in this 505(b)(1) application. These data are substantial, detailed and acceptable. The applicant has demonstrated lot-to-lot consistency in the manufacture and quality of the drug product. The CGMP facility inspections, Microbiological and Labeling evaluations are pending.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

John C. Hill, Ph.D., Review Chemist: Same data as electronic review.
Blair A. Fraser, Ph.D., Branch Chief, Same data as electronic review.

C. CC Block

Jena M. Weber, Regulatory Health Project Manager, Same data as electronic review.

19 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

John C. Hill
6/27/2006 11:14:12 AM
CHEMIST

Blair Fraser
6/27/2006 12:01:07 PM
CHEMIST

NDA 21-905

Valtropin™ (somatropin)

LG Life Sciences, Ltd.

John C. Hill, Ph.D.
ONDQA/DPA I/DMEDP/HFD-510

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-905

2. REVIEW #1

3. REVIEW DATE: 10-MAR-2006

4. REVIEWER: John C. Hill, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA Filing	01-DEC-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	LG Life Sciences, Ltd Youn Sung Choo and/or Hyi-Jeong Ji.
Address:	20, Yoido-dong Youngdungpo-gu Seoul 150-721, Korea Tel: 822-3773-0693 Fax: 822-785-0324
Representative:	PAREXEL International (US Agent) Bruce Babbitt and/or Hoss Dowlat and/or Alberto Grignolo 200 West Street Waltham, MA 02451-1163 Tel: 781-434-4057 Fax: 978-848-2221

Chemistry Review Data Sheet

Telephone: Noted above

8. DRUG PRODUCT NAME/CODE/TYPE:

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

- Chem. Type: 3
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Hormone Replacement

11. DOSAGE FORM: Lyophilized Powder

12. STRENGTH/POTENCY: 5 mg (15 IU) in 1.5 ml

13. ROUTE OF ADMINISTRATION: Subcutaneous Injection

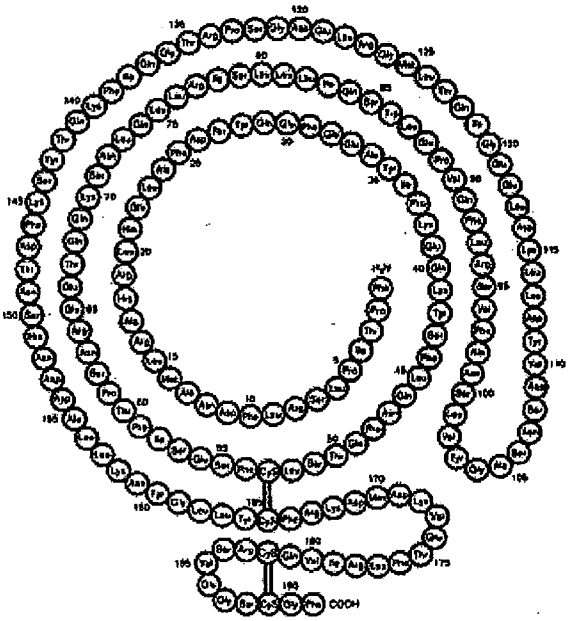
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

Chemistry Review Data Sheet



Amino acid sequence of human growth hormone

Chemical Formula: $C_{990}H_{1528}N_{262}O_{300}S_7$
Molecular Weight: 22,125.19 Daltons (22.12519 kDa)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
					Adequate	24-FEB-2003	LOA 27-APR-2005
					Adequate	9-AUG-2005	LOA 15-SEP-2005

b(4)

	Adequate	Acceptable DMF for sterile manufacturing facility	LOA 24-APR-2005
	Adequate	15-SEP-2000 24-FEB-2003 3-MAY-2000 19-FEB-2000	LOA 15-SEP-2005

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 – [redacted]
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")

b(4)

[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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	IND 62,376	
IND	IND 69,726	

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	EER was drafted on 14-DEC-2005. Waiting for Compliance's datbase entry of a new facility (in ———, before sending the EER to Compliance.		John Hill, Ph.D.
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Not Required		John C. Hill, Ph.D.
DMETS	Labeling consult request will be sent.		
OPDRA			
EA	To be done		John C. Hill, Ph.d.
Microbiology	Consult request will be sent for the review of 1) microbiology controls proposed for the drug substance, drug product, and diluent, 2) sterilization and aseptic processing validation for the drug product and diluent, and 3) antimicrobial effectiveness in the reconstituted multi-dose product.		

b(4)

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

Chemistry Review Data Sheet

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 21-905

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC viewpoint this NDA is approvable (AE). The outstanding issues are:

1.) Acceptable responses to CMC review deficiencies,
2.) Acceptable CGMP status for pending pre-approval establishment inspections.

Based on the provided Valtropin™ drug substance stability data, the following drug substance storage, expiry and use conditions are approved:

1. Valtropin™ drug substance may be stored for up to 36 months at [redacted] or alternatively, -25 °C when required. b(4)
2. Valtropin™ drug substance may be stored for up to 3 weeks at 5°C.
3. The Valtropin™ drug substance may undergo a maximum of 6 freeze/thaws cycles.

Based on the provided Valtropin™ drug product stability data, the following drug product storage, expiry and use conditions are approved:

1. Lyophilized Valtropin™ drug product may be stored at 2-8°C for up to 36 months with an excursion to 25°C for up to 2 weeks.
2. Reconstituted Valtropin™ drug product is stable for up to 21 days at 2°C - 8°C, and can be taken out daily for up to five minutes
3. The pre-filled solvent syringe may be stored for up to 30 months at 5±3°C

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

1. LG Life Sciences agrees to enroll [redacted] lot of Valtropin™ drug substance annually into the ongoing stability program. Stability data will be updated in the annual report. b(4)
2. LG Life Sciences agrees to enroll [redacted] lot of Valtropin™ drug product annually into the ongoing stability program. Stability data will be updated in the annual report.

II. Summary of Chemistry Assessments

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

Drug Product

Executive Summary Section

The Valtropin™ drug product powder is presented in a 5 cc/13 mm vial which is closed with a bromobutyl stopper/closure with a [redacted]. The rubber stopper is covered with an aluminum overseal and a polypropylene flip-off cap.

The solvent co-product is presented in a [redacted], glass syringe with [redacted] and rubber tip cap. b(4)

[redacted]

Valtropin™ is manufactured from somatropin drug substance that is compounded with excipients as a solution and meets USP sterility testing. The compounded solution is aseptically filled into vials, vacuum lyophilized under a controlled environment and the vials are stoppered under a positive pressure of sterile nitrogen. b

The Valtropin™ drug product formulation is based on the known formulation of the majority of somatropin preparations. The active principle, recombinant human growth hormone (rhGH) is [redacted] with glycine; a [redacted] mannitol) is included fo [redacted] b(4)
The formulation is also buffered with [redacted], which is consistent with all the somatropin products except for Saizen® which is an exception because it is [redacted]. The composition of the Valtropin™ drug product is summarized in the following table:

Table 3.2.P.1-1: Composition

Name of Ingredient	Unit and/or Percentage	Function	Reference to Standard
Active ingredient			
Somatropin	5 mg	Active ingredient	Current USP*
Other ingredients			
Glycine	10 mg	[redacted]	USP/Ph. Eur.
Mannitol	45 mg		USP/Ph. Eur.
Sodium phosphate monobasic [redacted]	0.22 mg		USP
Sodium phosphate dibasic [redacted]	2.98 mg		USP
Water for injection	to 2 ml	[redacted]	USP/Ph. Eur.

* Complies with USP plus additional specifications that are Ph. Eur. conforming
1N Sodium hydroxide and 1N hydrochloric acid are used to adjust pH

[redacted] b(4)

The solvent copackaged with the lyophilized drug product, consisting of water for injection (WFI) containing 0.3% metacresol as an antimicrobial agent, is presented in a 1.5 ml glass pre-filled syringe, The composition of the diluent is provided in the following tables:

Table 3.2.P.1-1: Composition of a single pre-filled syringe (1.5 mL) of the solvent (0.3%)[1)]

Ingredient	Unit	Function	Reference to Standard
m-Cresol		Preservative	Ph. Eur.[2)]
Water for Injections		Solvent	Ph. Eur./USP

b(4)

[1)] Conforms to USP. Prior to 2005 was tested against in house specifications, which were tighter than Ph. Eur.

Table 3.2.P.1-2: Composition of the solvent per mL (0.3%)

Ingredient	Unit	Function	Reference to Standard
m-Cresol		Preservative	Ph. Eur.
Water for Injections		Solvent	Ph. Eur./USP

b(4)

This solvent is similar to that used with other somatropin products, but omits glycerine (Humatrope®), mannitol (Genotropin®) or benzyl alcohol (Nutropin® and Norditropin®).

The reconstitution of a Valtropin™ vial with the full contents of a 1.5 ml solvent syringe results in a final product concentration of 3.33 mg/ml. When Valtropin™ is reconstituted with 1.5 ml of solvent, osmolalities of approximately /kg are obtained, which is close to the ideal tonicity of 240 to 340 mOsm/kg, falling within the physiologically desired range. The reconstituted Valtropin™ is then used as a multidose product for repeat use.

b(4)

Drug Substance

Somatropin (rDNA origin) (Valtropin™) drug substance is derived from the yeast *Saccharomyces cerevisiae* by recombinant DNA technology. Poly(A) mRNAs were isolated from human pituitaries, where human growth hormone (hGH) is secreted. The

b(4)

Consequently, the bulk drug substance was produced through a series of

Somatropin is a single-chain protein of 191 amino acids, including four cysteine residues present as two intra-chain disulfides. Somatropin is produced by recombinant DNA technology from yeast *Saccharomyces cerevisiae*. Methionyl recombinant human growth hormone (met-rhGH of 192 amino acids) is expressed from the yeast cells, folded into its native three-dimensional structure, and its N-terminal methionine residue is cleaved to yield mature rhGH of 191 amino acids during subsequent purification steps. The primary and secondary structures of somatropin are identical to pituitary-derived human growth hormone.

18 months of real-time stability data have been provided in the NDA for Valtropin™ drug substance manufactured using the proposed commercial manufacturing process. LG Life Sciences will update these stability data via the annual report through the planned 3 years of stability. Based on the supporting stability data and the similarity of the developmental manufacturing processes to the proposed commercial process, it is reasonable to grant a shelf life of 3 years for the Valtropin™ drug substance.

The recommended storage condition of the drug substance is at [redacted], or alternatively, -25 °C when required, for up to 3 years. b(4)

The recommended storage condition of drug substance at 5°C is no more than three weeks.

The Valtropin™ drug substance may undergo a maximum of 6 freeze/thaws cycles

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

Pediatric Patients

- Valtropin™ is indicated for the [redacted] b(4)
- Valtropin™ is indicated for the [redacted]

Adult Patients

[redacted] b(4)

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable (AE) from a CMC viewpoint. This recommendation is based upon the evaluation of the relevant drug product manufacturing, characterization and stability data provided in this 505(b)(1) application. These data are substantial, detailed and acceptable. The applicant has demonstrated lot-to-lot consistency in the manufacture and quality of the drug product. However, certain CMC deficiencies remain be addressed. The CGMP facility inspections are pending.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

John C. Hill, Ph.D., Review Chemist: Same data as electronic review.
Blair A. Fraser, Ph.D., Branch Chief, Same data as electronic review.

C. CC Block

Jena M. Weber, Regulatory Health Project Manager, Same data as electronic review.

185 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

John C. Hill
4/10/2006 01:22:10 PM
CHEMIST

Blair Fraser
4/10/2006 01:27:00 PM
CHEMIST

Appears This Way
On Original

CHEMISTRY NDA FILEABILITY CHECKLIST

NDA: 21-905
Applicant: LG Life Sciences
Stamp Date: 01-DEC-2005
PDUFA Date: 01-OCT-2005

Proposed Proprietary Name: Valtropin™
Established Name: [somatropin (rDNA origin) for injection]

IS THE CMC SECTION OF APPLICATION FILEABLE? Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		All facilities are listed.
6	Has an environmental assessment report or categorical exclusion been provided?	X		Exclusion request is included.
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Have stability data and analysis been provided to support the requested expiration date?	X		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		No information was requested.
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		In section 3.2.P.5.3.
15	Is a separate microbiological section included?	X		Sections are included.

This memo accompanies the Initial Quality Assessment (already filed in DFS).

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

/s/

Suong Tran
1/20/2006 11:29:44 AM
CHEMIST

no filing issue

Blair Fraser
1/20/2006 11:53:03 AM
CHEMIST