

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-074**

**CHEMISTRY REVIEW(S)**

8/7/07

**TRADENAME  
(lanreotide)  
Injection**

**NDA 22-074**

**Division Director Review  
Chemistry, Manufacturing, and Controls**

**Applicant:** Beaufour Ipsen Pharma  
24 rue Erlanger  
75016 Paris  
France

**Indication:** Treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy

**Presentation:** TRADENAME is a prolonged-release formulation for subcutaneous injection. It is supplied in a single, sterile, pre-filled, ready-to-use, polypropylene syringe as one of three strengths, 60 mg, 90 mg, or 120 mg lanreotide. Each single-use syringe is fitted with a needle covered by a dry natural rubber sheath, sealed in a laminated pouch, and packed in a carton.

**EER Status:** Acceptable 30-JUL-2007

**Consults:** EA – Categorical exclusion granted under 21 CFR §25.31(b)  
Method Validation - Package will be sent to FDA laboratories.

**Original Submission:** 27-OCT-2006

**Post-Approval Agreements:** None

**Drug Substance:**

The drug substance lanreotide acetate, a new molecular entity (NME), is a synthetic cyclic octapeptide analogue of naturally-occurring somatostatin. The chemical name of lanreotide acetate is [cyclo S-S]-3-(2-naphthyl)-D-alanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-Valyl-L-cysteinyl-L-threoninamide, acetate salt. The molecular formula for the anhydrous free peptide is \_\_\_\_\_ with a molecular weight of 1096.34.

Lanreotide acetate is characterized as a \_\_\_\_\_

/ / / / / /

The structure of lanreotide was elucidated by a variety of analytical and spectrophotometric techniques, including amino acid analysis (AAA), amino acid sequencing, and mass spectrometry (MS).

Reference is made to DMF 8974 for information on the chemistry, manufacturing and controls of the drug substance. \_\_\_\_\_ is used to synthesize lanreotide. \_\_\_\_\_

\_\_\_\_\_ The information provided in this DMF was reviewed and found adequate to support the manufacturing of the drug substance.

The proposed release specifications include appearance, solubility, identification (MS and AAA), purity by high performance liquid chromatography (HPLC), peptide content by HPLC, \_\_\_\_\_, residual organic solvents by gas chromatography, individual peptide-related impurities and total peptide-related impurities by HPLC. The proposed regulatory methods have been validated. The five peptide-related impurities from the drug substance (three process impurities and two degradation impurities) have been isolated and characterized by amino acid analysis, mass spectrometry, and nuclear magnetic resonance (NMR). Reference standards for drug substance have been developed and characterized.

Stability data provided by the DMF holder support the proposed \_\_\_\_\_ retest period for the drug substance stored at  $5 \pm 3^\circ\text{C}$  or below. In practice, lanreotide acetate has been demonstrated to be stable for \_\_\_\_\_ at  $-20^\circ\text{C}$ , protected from light.

**Conclusion:** Drug substance is acceptable.

**Drug Product:**

TRADENAME is a prolonged-release formulation for deep subcutaneous injection containing the drug substance, lanreotide acetate, and water for injection USP. TRADENAME is provided in three strengths as sterile, ready-to-use, pre-filled syringes containing the same lanreotide supersaturated bulk solution at 24.6% w/w lanreotide peptide. The product is intended to deliver 60, 90 or 120 mg lanreotide.

TRADENAME is a \_\_\_\_\_

\_\_\_\_\_. The advantages of this new prolonged release formulation are (1) few preparation steps and product "ready-to-use"; (2) no excipients except water for injection USP; and (3) greater range of dose available to allow patient/disease indications to be varied.

The manufacturing process for TRADENAME is summarized as follows. \_\_\_\_\_



The proposed release specification includes appearance, identification (HPLC, UV), mean lanreotide concentration, mean lanreotide injectable dose, lanreotide injectable dose uniformity, lanreotide purity, pH, *in vitro* dissolution, bacterial endotoxins, and sterility. The proposed regulatory methods have been appropriately validated for their intended use.

The drug product contains two impurities \_\_\_\_\_ which were identified and characterized. One impurity \_\_\_\_\_, is a degradation product of a \_\_\_\_\_.

Based on data from nine primary stability batches and six supporting stability batches, the proposed expiration dating period of 24 months for drug product stored at 2° C to 8° C (36°F to 46°F) is recommended for TRADENAME.

**Conclusion:** Drug product is satisfactory.

**Additional Items:**

All associated Drug Master Files (DMFs) are adequate or the pertinent information has been adequately provided in the application.

The applicant submitted a methods validation package containing all relevant documentation (tests, methods, and acceptance criteria) for the control of the drug substance and the drug product. The method validation package will be sent to FDA laboratories.

**Overall Conclusion:**

From a CMC perspective, the application is recommended for **Approval**.

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

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Blair Fraser  
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8/7/07



CHEMISTRY REVIEW

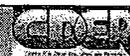


**NDA 22-074**

**SOMATULINE /  
(lanreotide) Injection**

**Beaufour Ipsen Pharma**

**Chien-Hua Niu, Ph.D.,  
ONDQA/DPMA-I/Branch-II**



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# Chemistry Review Data Sheet

1. NDA 22-074
2. REVIEW #: 2
3. REVIEW DATE: July 30, 2007
4. REVIEWER: Chien-Hua Niu, Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

Submission Type	Document Date
Amendment	22-JUN-2007
Amendment	11-JUL-2007

7. NAME & ADDRESS OF APPLICANT:

Name: Beaufour Ipsen Pharma  
24 rue Erlanger  
Address: 75016 Paris  
France  
Steven R. Scott  
Representative: Biomeasure Incorporated  
27 Maple Street  
Milford, MA 01757  
Telephone: (508)478-0144



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Somatuline— injection
- b) Non-Proprietary Name (USAN): Lanreotide acetate
- c) Code Name/# (ONDQA only): 108736-35-2 (CAS registry number)  
BN 52030  
BIM-23014C (DMF holder)
- d) Type/Submission Priority (ONDQA only):
  - Chem. Type:
  - Submission Priority: 1 S

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

10. PHARMACOL. CATEGORY: Hormone, somatostin analogue

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 60, 90, 120 mg

13. ROUTE OF ADMINISTRATION: Injection

14. Rx/OTC DISPENSED:  Rx  OTC

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

SPOTS product – Form Completed

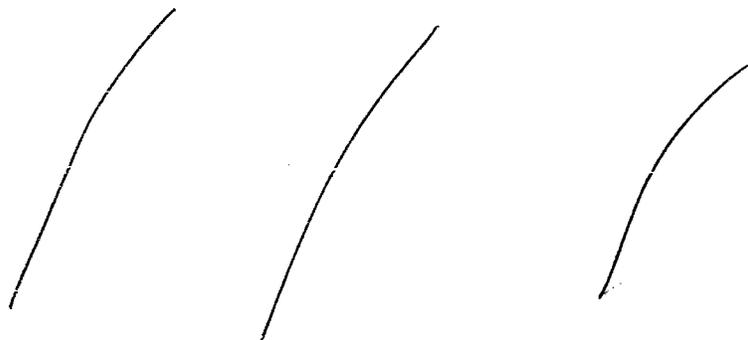
Not a SPOTS product

## Chemistry Review Data Sheet

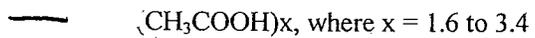
## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Lanreotide acetate

Structural Formula:



Molecular Formula:



Molecular Weight: 1096.34 (free base)



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
8974	II	Ipsen Manufacturing Ireland Ltd	Lanreotide	1	Adequate	06-FEB-2007	Review by Chien-hua Niu for NDA #22-074
	III			1	Adequate	15-SEP-2005	Reviewed by Elsbet Chikhale for NDA
					Adequate	14-NOV-2005	
	III			1	Adequate	25-FEB-2004	Reviewed by Suong Tran for NDA
	III			1	Adequate	29-APR-2007	Reviewed by Chien-hua Niu for NDA #22-074

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

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

#### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	53,993	Lanreotide used for treatment of acromegaly

**CHEMISTRY REVIEW**

## Chemistry Review Data Sheet

## 18. STATUS:

## ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Complete	7/13/2007	Dr. Jayabharathi Vaidyanathan
EES	Acceptable	7/30/2007	Office of Compliance
Pharm/Tox	N/A		Dr. Da-Lin Yao
Biopharm	N/A		Dr. Xiao-Xiong Wei
LNC	N/A		
Methods Validation	The method validation package will be sent to and validated by the FDA laboratories		Dr. Chien-Hua Niu
DMETS	Revision of the labels and labeling	11-JAN-07	Linda M. Wisniewski
EA	Categorical exclusion	02-MAY-07	Dr. Chien-Hua Niu
Microbiology	Pending		Dr. Robert Mello



REVIEW NOTE

# The Chemistry Review for NDA 22-074

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The application can be approved from chemistry point of view.

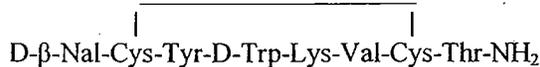
#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: None

### II. Summary of Chemistry Assessments

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

Somatuline (lanreotide) injection is utilized to treat acromegalic patients who have had an inadequate response to surgery and/or radiotherapy. The primary effect of lanreotide is a reduction of GH and/or IGF-1 levels enabling normalization of levels in acromegalic patients. [Note: SI stands for Sustained Injection]

**DRUG SUBSTANCE:** Lanreotide acetate is a synthetic octapeptide analogue of natural somatostatin with a prolonged half-life when compared to the parent compound. Lanreotide has a powerful inhibitory effect on growth hormone (GH) synthesis and reduces insulin-like growth factor (IGF-1). Therefore, lanreotide has been used for the treatment of carcinoid tumors and/or acromegaly. Lanreotide is an acetate salt of a synthetic 8 amino acids polypeptide (elemental composition, \_\_\_\_\_; molecular weight, 1096.34 Daltons). The amino acid sequence for lanreotide is presented below:



The structure of lanreotide was elucidated by a variety of analytical and spectrophotometric techniques, including amino acid analysis, amino acid sequencing, and mass spectrometry. The solubility of lanreotide \_\_\_\_\_

Lanreotide is manufactured by Ipsen Manufacturing Ireland Ltd (IMIL) (Blanchardstown, Dublin 15, Ireland) \_\_\_\_\_

## REVIEW NOTE

The proposed release specifications include appearance, solubility, identification (MS and AA analysis), purity, acetate content, residual organic solvent, individual peptide-related impurity and total peptide-related impurities. The proposed regulatory methods have been validated. The impurity and degradation profiles have been investigated. Reference standards for API have been developed and characterized.

Based on stability data from lots manufactured by Ipsen Manufacturing Ireland Ltd, lanreotide acetate is stable for at least 24 months when stored at 5°C.

**DRUG PRODUCT:** Somatuline is a prolonged-release formulation for deep subcutaneous injection containing the drug substance, lanreotide acetate, and water for injection. Somatuline SI is provided in three strengths as sterile, ready to use, pre-filled syringes containing the same lanreotide supersaturated bulk solution at 24.6% w/w lanreotide base. The product is intended to deliver 60, 90 or 120 mg lanreotide (potency is expressed as lanreotide base).

Somatuline SI is a

At high concentration of lanreotide acetate in water, the hydrated peptide will lead to the formation of a supersaturated solution with prolonged release properties. The main advantages of this new prolonged release formulation are (1) few preparation steps and product "ready to use", (2) no other excipients except water for injection, and (3) greater range of dose available to allow patient/disease indications to be varied.

Formulation development included the following areas:

- determination of target lanreotide serum levels
- selection of the appropriate peptide concentration and strength
- maximum daily dose
- mechanism of release
- overfill required by the injection device
- 
- dissolution test

The drug product is currently manufactured by Ipsen Pharma Biotch (83870 Signes, France). on the drug product is performed by

The manufacturing process for Somatuline is typical.



REVIEW NOTE

Somatuline 50, 90, and 120 mg is packaged in a sterile, single use, pre-filled polypropylene syringe fitted with a needle covered by a sheath. The 60 mg and 90 mg doses are provided in 1 mL syringes with a needle 1.5 mm in external diameter while the 120 mg dose is provided in 2 mL syringe with a needle 1.5 mm in external diameter. The secondary container closure components are functional pouch and a non-functional cardboard container.

The proposed release specifications included appearance, identification (HPLC, UV), mean lanreotide concentration, mean lanreotide injectable dose, lanreotide injectable dose uniformity, lanreotide purity, pH, in vitro dissolution, bacterial endotoxins, and sterility. The proposed regulatory methods have been validated.

For dissolution test, a specifically designed [redacted] has been developed [redacted] (see page 20 of this review). In vitro dissolution is performed by a modified method based upon the USP <711> and Ph.Eur.2.9.3 Apparatus 1. The amount of lanreotide released is established using [redacted] method. The factors might affect in vitro release and were investigated, including (1) dissolution medium, [redacted] (3) peptide concentration, (4) [redacted] and (5) stability of the drug product.

There are four impurities identified in Somatuline [redacted] Impurities [redacted], respectively. Their relative retention times (RRT) appear at [redacted] respectively. Impurity at [redacted] appears after [redacted], as a [redacted]. It has been identified as a [redacted]. Impurities eluted at RRT [redacted] have been identified to be [redacted]. Impurity at RRT [redacted] identified as [redacted] appears after [redacted] is a degradation product of [redacted].

Based on data from the [redacted] primary stability batches and [redacted] supporting stability batches, the following drug product attributes do not change as function of storage temperatures (5°C, and 25°C) or time (up to 24 months): appearance, lanreotide identification, mean lanreotide injectable dose, mean lanreotide concentration, lanreotide injectable dose uniformity, purity, pH, in vitro dissolution, bacterial endotoxins, and sterility. However, stability data also show that mean lanreotide concentration increases due to the water loss, but remains within the regulatory specification. Statistical analysis of stability data from samples stored at 5°C, an expiration dating period of 24 months is recommended for Somatuline [redacted].

The sponsor has cited a regulation [21 CFR 25.31(b)] to claim a categorical exclusion from filling an environmental assessment.



## REVIEW NOTE

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

Somatuline is sought for long-term treatment of acromegalic patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option. The goal of treatment in acromegaly is to reduce GH and IGF-1 levels to normal. Somatuline

The dose is started at 90 mg, every 4 weeks for 3 months. After 3 months, the dose maybe adapted based on GH and/or IGF-1 levels, and/or acromegaly symptoms.

Each dose should be administrated via the deep SC route in the superior external quadrant of the buttock.

Lanreotide was designated as an orphan drug on September 11, 2000 (Orphan Drug Application 00-1363).

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

This application can be **approved** from a CMC viewpoint. This recommendation is based upon several issues identified during the review. (1) General procedures for the synthesis of lanreotide are outlined in DMF #8974 (Ipsen Manufacturing Ireland Ltd.). All chemistry deficiencies have been properly addressed by the DMF holders as well as NDA applicant and found satisfactory. (2) Chemical structures of major impurities and degradation products are illustrated. (3) Stability data collected from primary stability batches indicate that no significant changes were observed in terms of appearance, lanreotide injectable dose, impurities, pH, *in vitro* dissolution, and sterility when stored at 2°C to 8°C for a period of up to 24 months. However, mean lanreotide concentration increases due to the water loss, but remains within the regulatory specification. (4) *In vitro* dissolution device utilized by the applicant clearly demonstrates that the proposed *in vitro* dissolution test can be considered as useful quality control test. (5) CGMP inspection of the manufacturing sites for the drug substance, the drug product as well as testing and packaging sites have been completed and found to be acceptable by the Office of Compliance (see the attached).

**III. Administrative****A. Reviewer's Signature****B. Endorsement Block**

Chemist Name/Date: Chien-Hua Niu, Ph.D./ONDQA/DPMA-I/Branch-II  
Chemistry Branch Chief: Name/Date: Ali Al Hakim, Ph.D., /ONDQA/DPMA-I/Branch-II

**C. CC Block**

Dr. Stephen K. Moore/Dr. Ali Al Hakim/ Dr. Blair Fraser  
Project Manager Name/Date: Jennifer Johnson

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Chien-Hua Niu  
8/7/2007 09:47:59 AM  
CHEMIST

Ali Al-Hakim  
8/7/2007 10:59:59 AM  
CHEMIST

8/2/07

**MEMORANDUM**

Date: August 2, 2007

From: Chien-Hua Niu, Ph.D. Chemistry Reviewer, ONDQA/DPMA-I/Branch-II)

Subject: Correction of A Statement in Chemistry Review #1 for NDA #22-074

To: NDA 22-074 File (Somatuline Injection)

Through Dr. Ali Al Hakim. Branch Chief, ONDQA/DPMA-I/Branch-II

On page 9 in Chemistry Review #1 for NDA #22-074, incorrect information was found in the following sentence: "Based on stability data from lots — lots manufactured by — and three lots manufactured by — , exenatide is stable for at least 24 months at -20°C protected from light."

The above sentence should be revised to read as "Based on stability data from — lots manufactured by Ipsen Manufacturing Ireland Ltd, lanreotide acetate is stable for at least 24 months when stored at 5°C."

cc: Org. NDA #22-074

Dr. Blair Fraser/Dr. Stephen K. Moore

Project Manager: Jennifer Johnson

NDA22074MEM1

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Chien-Hua Niu  
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Ali Al-Hakim  
8/2/2007 10:14:36 AM  
CHEMIST

5/15/07



CHEMISTRY REVIEW



**NDA 22-074**

**SOMATULINE AUTOGEL  
(lanreotide actate) Injection**

**Beaufour Ipsen Pharma**

**Chien-Hua Niu, Ph.D.,  
ONDQA/DNDC-II/HFD-510**



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II. DRUG PRODUCT	
III. LABELING & PACKAGE INSERT	
IV. Claim Of Categorical Exclusion	
V. List Of Deficiencies To Be Communicated	



# Chemistry Review Data Sheet

1. NDA 22-074
2. REVIEW #: 1
3. REVIEW DATE: May 10, 2007
4. REVIEWER: Chien-Hua Niu, Ph.D.
5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission Type	Document Date
Original	25-AUG-2006 (Pre-submission)
	27-OCT-2006 (Submission)

7. NAME & ADDRESS OF APPLICANT:

Name: Beaufour Ipsen Pharma  
24 rue Erlanger  
Address: 75016 Paris  
France  
Representative: Steven R. Scott  
Biomeasure Incorporated  
27 Maple Street  
Milford, MA 01757  
Telephone: (508)478-0144



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Somatuline Autogel Injection
- b) Non-Proprietary Name (USAN): Lanreotide acetate
- c) Code Name/# (ONDQA only): 108736-35-2 (CAS registry number)  
BN 52030  
BIM-23014C (DMF holder)
- d) Type/Submission Priority (ONDQA only):
  - Chem. Type:
  - Submission Priority: 1 S

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

10. PHARMACOL. CATEGORY: Hormone, somatostin analogue

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 60, 90, 120 mg

13. ROUTE OF ADMINISTRATION: Injection

14. Rx/OTC DISPENSED:  Rx  OTC

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

SPOTS product – Form Completed

Not a SPOTS product

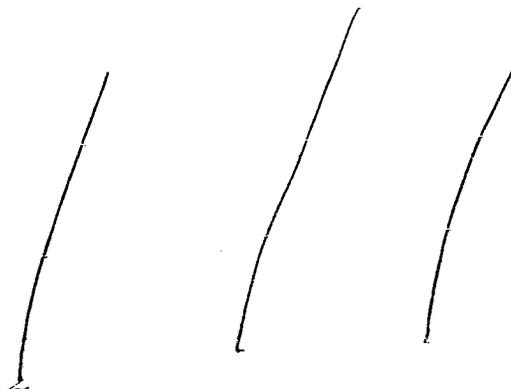


## Chemistry Review Data Sheet

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

Chemical Name: Lanreotide acetate

Structural Formula:



Molecular Formula:

 $(\text{CH}_3\text{COOH})_x$ , where  $x = 1.6$  to  $3.4$ 

Molecular Weight: 1096.34 (free base)



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
8974	II	Ipsen Manufacturing Ireland Ltd	Lanreotide	1	Adequate	06-FEB-2007	Review by Chien-hua Niu for NDA #22-074
	III			1	Adequate	15-SEP-2005	Reviewed by Elsbet Chikhale for NDA #
					Adequate	14-NOV-2005	
	III			1	Adequate	25-FEB-2004	Reviewed by Suong Tran for NDA #
	III			1	Adequate	29-APR-2007	Reviewed by Chien-hua Niu for NDA #

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

1 - DMF Reviewed.

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

2 - Type I DMF

3 - Reviewed previously and no revision since last review

4 - Sufficient information in application

5 - Authority to reference not granted

6 - DMF not available

7 - Other (explain under "Comments")

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

#### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	53,993	Lanreotide used for treatment of acromegaly



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### 18. STATUS:

#### ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Pending		Dr. Jayabharathi Vaidyanathan
EES	Pending		Office of Compliance
Pharm/Tox	Pending		Dr. Da-Lin Yao
Biopharm	Pending		Dr. Xiao-Xiong Wei
LNC	N/A		
Methods Validation	The method validation package will be sent to and validated by the FDA laboratories		Dr. Chien-Hua Niu
DMETS	Revision of the labels and labeling	11-JAN-07	Linda M. Wisniewski
EA	Categorical exclusion	02-MAY-07	Dr. Chien-Hua Niu
Microbiology	Pending		



## REVIEW NOTE

# The Chemistry Review for NDA 22-074

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The application can be approvable from chemistry point of view pending (1). Satisfactory responses from DMF holder and NDA applicant and (2) Acceptable cCMP inspection results of manufacturing sites for drug substance and drug product

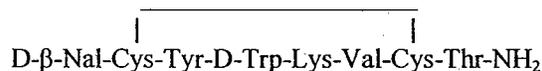
#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: None

### II. Summary of Chemistry Assessments

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

Somatuline Autogel (lanreotide acetated) injection is utilized to treat acromegalic patients who have had an inadequate response to surgery and/or radiotherapy. The primary effect of lanreotide is a reduction of GH and/or IGF-1 levels enabling normalization of levels in acromegalic patients.

**DRUG SUBSTANCE:** Lanreotide acetate is a synthetic octapeptide analogue of natural somatostatin with a prolonged half-life when compared to the parent compound. Lanreotide has a powerful inhibitory effect on growth hormone (GH) synthesis and reduces insulin-like growth factor (IGF-1). Therefore, lanreotide has been used for the treatment of carcinoid tumors and/or acromegaly. Lanreotide is an acetate salt of a synthetic 8 amino acids polypeptide (elemental composition, — molecular weight, 1096.34 Daltons). The amino acid sequence for lanreotide is presented below:



The structure of lanreotide was elucidated by a variety of analytical and spectrophotometric techniques, including amino acid analysis, amino acid sequencing, and mass spectrometry. The solubility of lanreotide

Lanreotide is manufactured by Ipsen Manufacturing Ireland Ltd (IMIL) (Balnchardstown, Dublin 15, Ireland).

**REVIEW NOTE**

The proposed release specifications include appearance, solubility, identification (MS and AA analysis), purity, peptide content, residual organic solvent, individual peptide-related impurity and total peptide-related impurities. The proposed regulatory methods have been validated. The impurity and degradation profiles have been investigated. Reference standards for API have been developed and characterized.

Based on stability data from lots manufactured by [redacted] and lots manufactured by [redacted], exenatide is stable for at least 24 months at -20°C protected from light.

**DRUG PRODUCT:** Lanreotide Autogel is a prolonged-release formulation for deep subcutaneous injection containing the drug substance, lanreotide acetate, and water for injection. Lanreotide Autogel is provided in three strengths as sterile, ready to use, pre-filled syringes containing the same lanreotide supersaturated bulk solution at 24.6% w/w lanreotide base. The product is intended to delivery 60, 90 or 120 mg lanreotide (potency is expressed as lanreotide base).

Lanreotide Autogel is a [redacted]

At high concentration of lanreotide acetate in water, the hydrated peptide will lead to the formation of a supersaturated solution with prolonged release properties. The main advantages of this new prolonged release formulation are (1) few preparation steps and product "ready to use", (2). no other excipients except water for injection, and (3). greater range of dose available to allow patient/disease indications to be varied.

Formulation development included the following areas:

- determination of target lanreotide serum levels
- selection of the appropriate peptide concentration and strength
- maximum daily dose
- mechanism of release
- overfill required by the injection device
- [redacted]
- dissolution test

The drug product is currently manufactured by Ipsen Pharma Biotch (83870 Signes, France). [redacted] on the drug product is performed by [redacted]

The manufacturing process for lanreotide Autogel is typical. [redacted]

REVIEW NOTE

Lanreotide Autogel 60, 90, and 120 mg is packaged in a sterile, single use, pre-filled polypropylene syringe fitted with a needle covered by a sheath. The 60 mg and 90 mg doses are provided in \_\_\_\_\_ mL syringes with a needle \_\_\_\_\_ in external diameter while the 120 mg dose is provided in \_\_\_\_\_ mL syringe with a needle \_\_\_\_\_ nm in external diameter. The secondary container closure components are functional pouch and a non-functional cardboard container.

The proposed release specifications included appearance, identification (HPLC, UV), mean lanreotide concentration, mean lanreotide injectable dose, lanreotide injectable dose uniformity, lanreotide purity, pH, *in vitro* dissolution, bacterial endotoxins, and sterility. The proposed regulatory methods have been validated.

For dissolution test, a specifically designed \_\_\_\_\_ has been developed to \_\_\_\_\_ (see page 20 of this review). *In vitro* dissolution is performed by a modified method based upon the USP <711> and Ph.Eur.2.9.3 Apparatus 1. The amount of lanreotide released is established using a \_\_\_\_\_ method. The factors might affect *in vitro* release and were investigated, including (1) dissolution medium, (2) \_\_\_\_\_ (3) peptide concentration, (4) \_\_\_\_\_ and (5) stability of the drug product.

There are four impurities identified in lanreotide Autogel: Impurities \_\_\_\_\_ respectively. Their relative retention times (RRT) appear at \_\_\_\_\_ respectively. Impurity at RRT \_\_\_\_\_ appears

\_\_\_\_\_ It has been identified as a \_\_\_\_\_ Impurity at RRT \_\_\_\_\_ identified as \_\_\_\_\_ appears \_\_\_\_\_ is a degradation product of \_\_\_\_\_

Based on data from the \_\_\_\_\_ primary stability batches and \_\_\_\_\_ supporting stability batches, the following drug product attributes do not change as function of storage temperatures (5°C, and 25°C) or time (up to 24 months): appearance, lanreotide identification, mean lanreotide injectable dose, mean lanreotide concentration, lanreotide injectable dose uniformity, purity, pH, *in vitro* dissolution, bacterial endotoxins, and sterility. However, stability data also show that mean lanreotide concentration increases due to the water loss, but remains within the regulatory specification. Statistical analysis of stability data from samples stored at 5°C, an expiration dating period of 24 months is recommended for lanreotide Autogel.

The sponsor has cited a regulation [21 CFR 25.31(b)] to claim a categorical exclusion from filling an environmental assessment.



## REVIEW NOTE

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

Somatuline Autogel is sought for long-term treatment of acromegalic patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option. The goal of treatment in acromegaly is to reduce GH and IGF-1 levels to normal. Somatuline Autogel

The dose is started at 90 mg, every 4 weeks for 3 months. After 3 months, the dose may be adapted based on GH and/or IGF-1 levels, and/or acromegaly symptoms.

Each dose should be administered via the deep SC route in the superior external quadrant of the buttock.

Lanreotide was designated as an orphan drug on September 11, 2000 (Orphan Drug Application 00-1363).

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

This application is **approvable** from a CMC viewpoint pending (1) satisfactory responses from DMF holders and NDA applicant and (2) acceptable results of cGMP inspection for the manufacturing sites of the drug substance and drug product. This recommendation is based upon several issues identified during the review. (1) General procedures for the synthesis of lanreotide are outlined in DMF #8974 (Ipsen Manufacturing Ireland Ltd.). All chemistry deficiencies have been addressed by the DMF holders and found satisfactory. (2) Chemical structures of major impurities and degradation products are illustrated. (3) Stability data collected from primary stability batches indicate that no significant changes were observed in terms of appearance, lanreotide injectable dose, impurities, pH, *in vitro* dissolution, and sterility when stored at 2°C to 8°C for a period of up to 24 months. However, mean lanreotide concentration increases due to the water loss, but remains within the regulatory specification. (4) *In vitro* dissolution device utilized by the applicant clearly demonstrates that the proposed *in vitro* dissolution test can be considered as useful quality control test.

**III. Administrative****A. Reviewer's Signature****B. Endorsement Block**

Chemist Name/Date: Chien-Hua Niu, Ph.D./ONDQA/DPMA-I/Branch-I  
Chemistry Division Director Name/Date: Blair Fraser, Ph.D., /ONDQA/DPMA-I/

**C. CC Block**

Dr. Blair Fraser/Dr. Stephen K. Moore  
Project Manager Name/Date: Jennifer Johnson

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Chien-Hua Niu  
5/14/2007 03:57:02 PM  
CHEMIST

Blair Fraser  
5/15/2007 05:14:35 AM  
CHEMIST  
IR Letter comments

12/13/06

**INITIAL QUALITY ASSESSMENT**  
**Office of New Drug Quality Assessment**  
**Division of Metabolism and Endocrinology Products**  
**NDA 22-074**

**Applicant:** Beaufour Ipsen Pharma  
24 rue Erlanger  
75016 Paris  
France

U.S. Agent: Biomeasure Incorporated  
27 Maple Street  
Milford, MA 01757.  
Contact: Steven R. Scott (tel. 508-478-0144)

**Submission date:** Pre-submission: Letter date 25-AUG-2006 (Stamp date: 28-AUG-2006)  
Submission: Letter date 27-OCT-2006 (Stamp date: 30-OCT-2006)

**Proprietary Name:** Somatuline® Autogel®

**Established Name:** Lanreotide acetate injection

**Legal basis for Submission:** 505(b)(1)

**Pharmacological Category:** Somatostatin analogue

**Dosage Form:** Injection

**Strength/Potency:** 60, 90 and 120 mg

**Route of Administration:** Deep subcutaneous injection

**Related/Supporting Documents:** IND# 53,993; DMF# \_\_\_\_\_ DMF# \_\_\_\_\_ DMF# 8974 and DMF# \_\_\_\_\_

**Drug Substance:** Lanreotide is synthetic cyclic peptide of eight amino acid residues. Lanreotide has a disulphide bridge and D-tryptophan, in the ring, which stabilize the molecule. It is an analogue of natural somatostatin. Lanreotide is a new chemical entity (NCE). (see IQA Notes for additional information).

**Drug Product:** Somatuline® Autogel® (lanreotide acetate) injection consist of a sterile pre-filled syringe containing lanreotide acetate gel in strengths are 60 mg, 90 mg and 120 mg. The formulation consists only of lanreotide and water for injection. (see IQA Notes for additional information).

**Description of How the Drug Product is Intended to be Used:** The clinical indication(s) being sought is long-term treatment of acromegalic patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option. The goal of treatment in acromegaly is to reduce GH and IGF-II levels to normal. Somatuline Autogel \_\_\_\_\_ Lanreotide was designated as an orphan drug on September 11, 2000 (Orphan Drug Application 00-1363). The dose is started at 90 mg, every 4 weeks for 3 months. After 3 months, the dose may be adapted based on GH, and/or IGF-I levels, and/or acromegaly symptoms.

**Pre-submission CMC issues and/or agreements:** Investigational studies were performed under Ipsen Biotech's IND 53,993 for I \_\_\_\_\_ Initially, the product was developed as an immediate release formulation then as a micro-particle formulation consisting of' \_\_\_\_\_ The micro-particles were manufactured

6 / / / / / / / / /

Subsequently, a new Somatuline Autogel formulation was developed. This manufacturing process for the new formulation does not use \_\_\_\_\_ A Pre-NDA meeting pertaining to the Somatuline Autogel was held on 06-JUL-2004. Included in the discussion was a novel in vitro release test involving ar \_\_\_\_\_ The Agency agreed that although the approach was novel it was acceptable. The Agency recommended using both clinical and commercial batches to set the specifications for the in vitro release test. The Agency agreed that physicochemical characterization was acceptable to demonstrate comparability, however, a bioequivalence study may also be needed. \_\_\_\_\_ of the pre-filled syringes was also discussed. The Agency requested inclusion of information on the effect of the \_\_\_\_\_ The Agency indicated that the proposed physicochemical characterization and quality control testing appeared acceptable. A change in the manufacturing site for investigational drug product from Ipsen, Dreux, France to Ipsen, Pharma Biotech, Signes, France for commercialization was also discussed.

**Recommendations:**

Time goals:

- Initial Quality Assessment in DFS: 21-DEC-2006
- Chemistry filing memo in DFS: 21-DEC-2006
- Filing date "Day 60": 29-DEC-2006
- Filing review issues "Day 74": 07-JAN-2007
- Chemistry Review (DR/IR) letter: TBD
- Mid-cycle meeting "Month 5": TBD
- Final Chemistry Review "Month 8" in DFS: 23-AUG-2007
- PDUFA date: 30-AUG-2007

Filability: Acceptable for filing from CMC perspective.

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		CFNs. pending for Ipsen Manufacturing Ireland Ltd.,
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		
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		
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		
15	Is a separate microbiological section included?	X		

Comment: The application was submitted in paper and electronic copies, however, the CMC section is paper only. A conventional CMC summary is included in the application.

Drug Master Files (DMF):

DMF	TYPE	HOLDER	ITEM REFERENCED	Letter of Authorization (LOA)	PREVIOUS REVIEW(S)	Recommendation
	III			30-AUG-2005	DMF previously reviewed 29-AUG-2005 (Adequate).	Review not needed.
					DMF previously reviewed 14-NOV-2005. (Adequate).	Review not needed.
	III			31-AUG-2005	DMF previously reviewed 25-FEB-2004 (Adequate).	Review not needed.
8974	II	Ipsen Manufacturing Ireland, Ltd.	Lanreotide drug substance	24-JUL-2006	DMF previously reviewed 26-JAN-1996 (Inadequate).	Review needed.
	III			06-AUG-2005	DMF previously reviewed 30-AUG-2001 (Adequate for	Review needed.

Consults:

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm/ClinPharm	To be assessed by Biopharm/ClinPharm reviewer.
CDRH	Not Applicable.
EA	Claim for Categorical Exclusion (< 1 PPB). To be assessed by Primary Reviewer.
EES	EER sent to Office of Compliance on 22-NOV-2006.
OSE/DMETS	Labeling consult request sent by DMEP on 12-SEP-2006.
Methods Validation	Validation may be requested of FDA labs after test methods are finalized.
Microbiology	Microbiology consult request sent by DMEP 01-SEP-2006.
Pharm/Tox	To be assessed by Pharm/Tox reviewer.

Recommendation for Primary Reviewer(s): Dr. Chien-Hua Niu is recommended as the primary reviewer.

Identification of Critical CMC Review Issues: See IQA notes and list of critical CMC review issues.

**Endorsement block (see appended electronic signature page):**

Stephen Moore, Ph.D., Pharmaceutical Assessment Lead (PAL), Branch II/DPA I/ONDQA

Init. by: Blair Fraser, Ph.D., Division Director, Branch II/DPA I/ONDQA

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Stephen Moore  
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Blair Fraser  
12/13/2006 05:20:39 AM  
CHEMIST