

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-505

CHEMISTRY REVIEW(S)

The sponsor has updated the Drug Substance Specifications to include a specification limit for purity assessment and Identification by Peptide Mapping. This is in response to the Agency's email request sent to the sponsor by PM J. Johnson on Nov 6, 2009.

No Action is Indicated.

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/s/

JOSEPH M LEGINUS
11/04/2010

On 9 June 2010, FDA emailed a request for information (not from CMC) requesting information on a) needles as part of the Egrifta kit, and b) volume of sterile water for injection in the 10 mL diluent vials.

CMC-relevant information provided in the applicant's response is the volume of sterile water for injection in the 10 mL diluent vials is 10 mL.

No action is indicated.

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/s/

JOSEPH M LEGINUS
10/20/2010

MEMORANDUM

Date: 08-Aug-2010

From: Joseph Leginus, Review Chemist, Branch VII/ONDQA

To: NDA 22-505, EGRIFTA™ (tesamorelin for injection)

Through: Ali Al-Hakim, Branch Chief, Branch VII//ONDQA

Subject: Post Approval Stability Protocol

Background:

- A final recommendation for Approval was made from the standpoint of chemistry, manufacturing and controls for NDA 22-505 in a Memorandum of 29-Jun-2010 concurred with by Branch Chief, A. Al-Hakim.
- On 02-Aug-2010, the sponsor submitted an unsolicited amendment to NDA 22-505 regarding a revised drug product stability protocol.
- The stability protocol for the post-approval commercial batches is unchanged from that of the long-term registration stability studies, with the exception of the addition of a bioactivity test and a testing time point at 30 months.
- A final stability time point of 36 months for the drug product remains unchanged.

Conclusion:

- The updated stability protocol is acceptable and does not affect the original recommendation for Approval of NDA 22-505 from a CMC perspective.

Joseph Leginus, Ph.D.
Review Chemist

Ali Al-Hakim, Ph.D.
Branch VII Chief, ONDQA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22505	ORIG-1	THERATECHNOLOGIES INC	Egrifta

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/s/

JOSEPH M LEGINUS
08/05/2010

ALI H AL HAKIM
08/05/2010

MEMORANDUM

Date: 29-Jun-2010

From: Joseph Leginus, Review Chemist, Branch VII/ONDQA

To: NDA 22-505, EGRIFTA™ (tesamorelin for injection)

Through: Ali Al-Hakim, Branch Chief, Branch VII//ONDQA

Subject: Approval Recommendation

Background:

- The sponsor has submitted satisfactory responses (see Quality Reviews: 14-Dec-2009 and 22-Jan-2010) to the deficiencies delineated in the List of Deficiencies and Information Request (in the CMC Review #1: 21-Oct-2009).
- Acceptable cGMP recommendations have been received from the Office of Compliance for each of the seven manufacturing and testing facilities. An Overall Compliance recommendation of Acceptable was provided on 23-Jun-2009.
- A recommendation for approval from a microbiology quality standpoint has been provided (see Product Quality Microbiology Review: 11-Jun-2010).

Conclusion:

- With no outstanding quality issues, a final recommendation for Approval is made from the standpoint of chemistry, manufacturing and controls for NDA 22-505.

Joseph Leginus, Ph.D.
Review Chemist

Ali Al-Hakim, Ph.D.
Branch VII Chief, ONDQA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22505	ORIG-1	THERATECHNOLOGIES INC	Egrifta

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/s/

JOSEPH M LEGINUS
06/29/2010

ALI H AL HAKIM
06/29/2010

This amendment contains the following information on the bioassay used to measure activity of the drug product, EGRIFTA:

- a) Revised specifications to include proposed limits for bioactivity of the drug product.
- b) Description of the bioassay method.
- c) Description of the bioassay method validation and validation report.
- d) Revised Justification of Specifications to include rationale for the proposed limits for bioactivity of the drug product.
- e) Updated protocol to include testing of bioactivity during stability assessment of the drug product.

Adequate information is contained in the above items regarding the bioassay method for the drug product. No Action Indicated.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22505	ORIG-1	THERATECHNOLOGIES INC	Egrifta

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/s/

JOSEPH M LEGINUS
06/04/2010

The sponsor (Theratechnologies) intends to replace the bioidentity test for Egrifta drug product with a new, validated bioassay, which was started on 3/25/2010. Following completion of the validation report, they propose to amend the drug product release specifications to include limits of bioactivity using the new, validated bioassay.

Information in this amendment will not be reviewed at this time because the information is incomplete (validation study is not yet completed for the proposed bioassay test) and because this information was unsolicited by FDA. No Action Indicated.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22505

ORIG-1

THERATECHNOLO
GIES INC

Egrifta

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/s/

JOSEPH M LEGINUS

05/10/2010

Egriffta™
(Tesamorelin for injection)
NDA 22-505

**Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls**

Applicant: TheraTechnologies
2310 Alfred-Nobel Blvd.
Montreal, Quebec, Canada, H4S 2B4

Indication: Tesamorelin acetate is a synthetic analogue of human hypothalamic Growth Hormone-Releasing Factor (hGRF) indicated to induce and maintain a reduction of excess abdominal fat in HIV-infected patients with lipodystrophy.

Presentation: EGRIFTA is a white to off-white, sterile, lyophilized powder contained in a 3 mL clear glass vial with grey stoppers and green, plastic flip off caps with aluminum seals. Each vial contains (b) (4) tesamorelin free base equivalent to (b) (4). A 30-day supply of vials is packed in an opaque cardboard box containing 2 carton trays (30 vials per tray), 30 vials of reconstitution diluent (Sterile Water for Injection, USP), and 3 foam dividers (bottom, between carton trays and on top). Also provided in the patient kits are 30 disposable syringes and needles sufficient for a 30 day supply.

The recommended dose of EGRIFTA of 2 mg in 2 mL requires reconstitution of 2 vials of drug product using one 2.2 mL volume of Sterile Water for Injection from a single use 10 mL vial. Immediately after reconstitution, 2 mL of the 1mg/mL solution (pH ~ 6) is injected subcutaneously by the patient, preferably into the abdomen.

EER Status: Recommendation Acceptable (23-Jun-2009)

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

Original Submission: 29-May-2009

Post-Approval CMC Commitments: None

Drug Substance:

Tesamorelin acetate is a synthetic analog of human GRF (Growth Releasing Factor) comprised of the 44 amino acid sequence of human GRF. Tesamorelin acetate is made by attaching a hexenoyl moiety, a C6 chain with a double bond at position 3, to the tyrosine residue at the N-

Drug Product:

EGRIFTA™ (tesamorelin for injection) is a white to off-white, sterile, lyophilized powder with mannitol, USP as the only excipient (55 mg per vial). No preservatives are used in the formulation.

The drug product is manufactured and packaged by (b) (4) The manufacturing process includes (b) (4)



The drug product is packaged in a stoppered 3 mL clear glass vial, placed in an opaque carton and co-packaged in a kit that includes disposable syringes, disposable needles and reconstitution diluent. The diluent is Sterile Water for Injection, USP, an approved product of NDA 18-801. Each vial contains the overfill amount of 0.1 mg tesamorelin to ensure the drawing of 1.0 mL (for an actual dose of 1.0 mg) from each reconstituted vial.

The release specifications include appearance, identity (HPLC), assay (HPLC), individual and total impurities (HPLC), content uniformity, water content, sterility, bacterial endotoxin, reconstitution time, completeness and clarity of solution, pH, osmolality and particulate matter. The proposed regulatory methods have been validated. The drug product is photo labile and the primary container (clear glass vial) does not provide adequate protection from exposure to light. However, the secondary packaging (opaque carton) adequately protects the drug product from degradation due to light.

A precise correlation between tesamorelin acetate bioactivity and assay by HPLC could not be established due to high variability in the cell-based bioassay. However, verification of biological activity of the drug product through the use of bio-identity testing supports the use of assay by HPLC as a reliable method for assessing tesamorelin biological activity. A test for bio-identity is included in the drug product specifications.

24 months of real-time stability data have been provided for three drug product registration batches manufactured using the proposed commercial manufacturing process. Additionally, real-time stability data for three validation batches is available through 18 months. The in-use stability evaluation was performed 2 hours after reconstitution of the drug product at room temperature. This supports the recommended use of the product immediately following reconstitution. Based on the supporting stability data and the similarity of the developmental manufacturing process to the proposed commercial process, a shelf life of 24 months at 2° – 8°C is granted for the drug product. The label includes a statement to protect from light.

Conclusion: The drug product is acceptable pending no microbiology issues pertaining to sterility assurance.

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.

Overall Conclusion:

From a CMC perspective, the application is recommended for approval pending satisfactory microbiology evaluation pertaining to sterility assurance.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22505	ORIG-1	THERATECHNOLOGIES INC	Egrifta

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/s/

CHRISTINE M MOORE
02/26/2010

NDA 22-505

**EGRIFTA™
(tesamorelin for injection)**

Theratechnologies, Inc.

**Joseph Leginus, PhD
Division of Pre-Marketing Assessment I, Branch II, ONDQA**

**For the Division of
Metabolism and Endocrinology Products**

CHEMISTRY REVIEW #3

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Chemistry Review Data Sheet

1. NDA 22-505
2. REVIEW #: 3
3. REVIEW DATE: 22-Jan-2010
4. REVIEWER: Joseph Leginus, PhD
5. PREVIOUS DOCUMENTS:

Previous Documents

Original NDA
NDA Amendment

Document Date

29-May-2009
30-Nov-2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

NDA Amendment

Document Date

20-Jan-2010

7. NAME & ADDRESS OF APPLICANT:

Name: Theratechnologies, Inc.
Address: 2310 Alfred-Nobel Blvd. Montreal, Quebec, Canada,
H4S 2B4
Representative: Nadine Bouchard, Director, Compliance and Associate
Regulatory Affairs
Telephone: 514-336-7800

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: EGRIFTA™
- b) Non-Proprietary Name (USAN): Tesamorelin acetate
- c) Code Name/# (ONDC only): CAS No.: 901758-09-6; TH9507 (Theratechnologies).
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: Standard

Chemistry Review Data Sheet

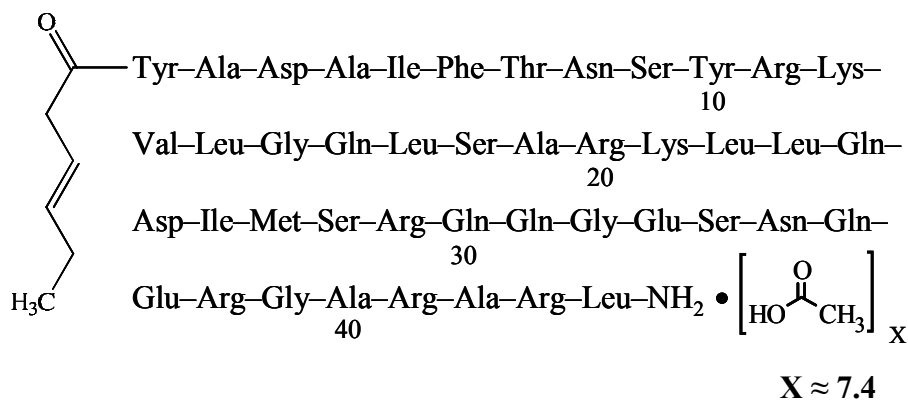
9. LEGAL BASIS FOR SUBMISSION: This NDA is submitted as a 505(b)(1) application.
10. PHARMACOL. CATEGORY:
 Tesamorelin acetate is a synthetic analogue of human hypothalamic Growth Hormone-Releasing Factor (hGRF) indicated to induce and maintain a reduction of excess abdominal fat in HIV-infected patients with lipodystrophy.
11. DOSAGE FORM: Lyophilized Powder for Injection
12. STRENGTH/POTENCY:
 1 mg (to be constituted in Sterile Water for Injection at 1 mg/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:

USAN: Tesamorelin acetate

Molecular Formula: $C_{221}H_{366}N_{72}O_{67}S \cdot x C_2H_4O_2$ ($x \approx 7.4$)

Molecular Weight: 5135.86 (free base)

Structural Formula:



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code ¹	Status ²	Date Review Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	20-Aug-2009	Reviewed by J. Leginus
	III			1	Adequate	05-Nov-2007	Reviewed by M. Stevens-Riley
	III			1	Adequate	22-Apr-2009	Reviewed by S. Chatterjee
	III			1	Adequate	24-Feb-2009	Reviewed by C. Evans
	V						See Microbiology Review

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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	61,226	TH9507; N-(trans-3-Hexenoyl)-Human Growth Hormone Releasing Factor (1-44) Acetate
NDA	18-801	Sterile Water for Injection, USP, in Plastic Vials. A letter of authorization is provided from Hospira Inc.

Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable. An Overall Compliance recommendation of Acceptable was provided on 23-Jun-2009.	23-Jun-2009	N/A
Pharm/Tox	A request for the safety evaluation of impurities was made. Impurities have been qualified at proposed acceptable levels.	08-Oct-2009	Lauren Murphree-Mihalcik
Biopharm	Not applicable. This is an injectable product, and the commercial formulation was used in Phase 3 studies.		
Methods Validation	Validation may be requested of FDA labs after test methods are finalized.		
EA	Conducted by CMC reviewer. Granting the categorical exclusion as per 21 CFR 25.31(b).	10/14/2009	Joseph Leginus
Microbiology	Review of 1) microbiology controls proposed for the drug product, and 2) sterilization and (b) (4) processing validation for the drug product.	Pending ¹	Steve Fong

¹An addendum will be submitted to document Microbiology's final recommendation.

19. ORDER OF REVIEW: N/A

Executive Summary Section

The Chemistry Review for NDA 22-505

See Chemistry Review #2 (14-Dec-2009) for details on The Executive Summary for NDA 22-505, which has not changed since that time. NDA 22-505 remains recommended for Approval from the standpoint of chemistry, manufacturing and controls.

4 pages withheld in full immediately after this page as (b)(4) CCI/TS.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22505	ORIG-1	THERATECHNOLOGIES INC	Egrifta

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/s/

JOSEPH M LEGINUS
01/22/2010

PRASAD PERI
01/22/2010
I concur

NDA 22-505

**EGRIFTA™
(tesamorelin for injection)**

Theratechnologies, Inc.

**Joseph Leginus, PhD
Division of Pre-Marketing Assessment I, Branch II, ONDQA**

**For the Division of
Metabolism and Endocrinology Products**

CHEMISTRY REVIEW #2

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Chemistry Review Data Sheet

1. NDA 22-505
2. REVIEW #: 2
3. REVIEW DATE: 14-Dec-2009
4. REVIEWER: Joseph Leginus, PhD
5. PREVIOUS DOCUMENTS:

Previous Documents

Original NDA

Document Date

29-May-2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

NDA Amendment

Document Date

30-Nov-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Theratechnologies, Inc.
Address: 2310 Alfred-Nobel Blvd. Montreal, Quebec, Canada,
H4S 2B4
Representative: Nadine Bouchard, Director, Compliance and Associate
Regulatory Affairs
Telephone: 514-336-7800

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- c) Code Name/# (ONDC only): CAS No.: 901758-09-6; TH9507 (Theratechnologies).
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Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

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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
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NDA	18-801	Sterile Water for Injection, USP, in Plastic Vials. A letter of authorization is provided from Hospira Inc.

Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable. An Overall Compliance recommendation of Acceptable was provided on 23-Jun-2009.	23-Jun-2009	N/A
Pharm/Tox	A request for the safety evaluation of impurities was made. Impurities have been qualified at proposed acceptable levels.	08-Oct-2009	Lauren Murphree-Mihalcik
Biopharm	Not applicable. This is an injectable product, and the commercial formulation was used in Phase 3 studies.		
Methods Validation	Validation may be requested of FDA labs after test methods are finalized.		
EA	Conducted by CMC reviewer. Granting the categorical exclusion as per 21 CFR 25.31(b).	10/14/2009	Joseph Leginus
Microbiology	Review of 1) microbiology controls proposed for the drug product, and 2) sterilization and (b) (4) processing validation for the drug product.	Pending ¹	Steve Fong

¹An addendum will be submitted to document Microbiology's final recommendation.

19. ORDER OF REVIEW: N/A

Executive Summary Section

(MALDI-TOF MS), circular dichroism (CD) and peptide mapping. [REDACTED] (b) (4)

The proposed release specifications include appearance, solubility, identification (HPLC), amino acid analysis, mass spectral analysis, acetate content (HPLC), water content, specific rotation, residual organic solvents, peptide content, individual and total peptide related impurities (HPLC), mass balance, bioburden and endotoxin. Reference standards for the drug substance have been developed and characterized.

Although robust bioactivity was observed in the bioassay for tesamorelin acetate, high variability in the test results precluded it from being an acceptable method for determining the relative potency of the tesamorelin primary reference standard. As a result, a bio-identity test was established to ensure bioactivity of the drug substance. The bio-identity test uses the upper and lower values obtained from the tesamorelin bioactivity assays as limits for its acceptance criteria.

Impurities generated during the synthesis and storage of the drug substance are classified based on their HPLC elution position relative to the drug substance (RRT). One process related impurity [REDACTED] (b) (4) and one degradant [REDACTED] (b) (4) are identified in the drug substance specifications. Each impurity has been adequately qualified at its respective proposed acceptable limit.

DRUG PRODUCT

EGRIFTA™ (tesamorelin for injection), with the dosage strength of 1 mg per vial, is a white to off-white, sterile, lyophilized powder (total content per vial including an overfill: [REDACTED] (b) (4) tesamorelin free base equivalent to [REDACTED] (b) (4) per vial¹) with mannitol, USP as the only excipient (55 mg per vial). The drug product is packaged in a stoppered 3 mL clear glass vial, placed in an opaque carton and co-packaged in a kit that includes disposable syringes, disposable needles and reconstitution diluent. The diluent is Sterile Water for Injection, USP, an approved product of NDA 18-801. Each vial contains the overfill amount of 0.1 mg tesamorelin to ensure the drawing of 1.0 mL (for an actual dose of 1.0 mg) from each reconstituted vial. The recommended 2 mg dose requires reconstitution of 2 vials of drug product using one 2.2 mL volume of Sterile Water for Injection from a single use 10 mL vial. Immediately after reconstitution, 2 mL of the 1 mg/mL solution (pH ~ 6) is injected subcutaneously by the patient. No preservatives are added given that the reconstituted product is indicated for immediate single-use injection.

The manufacturing process for the drug product involves [REDACTED] (b) (4)

¹ Communicated by the sponsor in a 12/3/09 email to PM, J. Johnson, "1 mg tesamorelin free base is equivalent to 1.1 mg tesamorelin acetate."

Executive Summary Section

(b) (4)

The proposed release specifications include appearance, identity (HPLC), assay (HPLC), individual and total impurities (HPLC), content uniformity, water content, sterility, bacterial endotoxin, reconstitution time, completeness and clarity of solution, pH, osmolality and particulate matter. The proposed regulatory methods have been validated.

A precise correlation between tesamorelin acetate bioactivity and assay by HPLC could not be established due to high variability in the cell-based bioassay. However, verification of biological activity of the drug product through the use of bio-identity testing supports the use of assay by HPLC as a reliable method for assessing tesamorelin biological activity. A test for bio-identity has been added to the drug product specifications.

The drug product is photo labile and the primary container (clear glass vial) does not provide adequate protection from exposure to light. However, the secondary packaging (opaque carton) adequately protects the drug product from degradation due to light.

24 months of real-time stability data have been provided for three drug product registration batches manufactured using the proposed commercial manufacturing process. Additionally, real-time stability data for three validation batches is available through 18 months. Theratechnologies will update these stability data via annual reports through the planned 3 years of stability testing. The in-use stability evaluation was performed 2 hours after reconstitution of the drug product at room temperature. This supports the recommended use of the product immediately following reconstitution. Based on the supporting stability data and the similarity of the developmental manufacturing process to the proposed commercial process, a shelf life of 24 months at 2° – 8°C is granted for the drug product.

Theratechnologies requested a categorical exclusion from submitting an environmental assessment for the drug product based on the regulations in 21 CFR, part 25, section 25.31(b). The request is granted.

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

EGRIFTA™ (tesamorelin for injection) is indicated to induce and maintain a reduction of excess abdominal fat in HIV-infected patients with lipodystrophy, a common complication with HIV patients taking protease inhibitor drugs. The recommended dose of EGRIFTA is 2 mg in 2 mL injected subcutaneously once a day, preferably in the abdomen. The 2 mg dose requires reconstitution of 2 vials of drug product using one 2.2 mL volume of Sterile Water for Injection from a single use 10 mL vial. EGRIFTA is available in a package containing 60 vials of EGRIFTA, 30 vials of reconstitution diluent (Sterile Water for Injection, USP), and 30 disposable syringes and needles sufficient for a

Executive Summary Section

30 day supply. The drug product will be labeled for long term storage (up to two years) at refrigerated (2° - 8°C) conditions and recommended for use immediately after reconstitution.

C. Basis for Approvability or Not-Approval Recommendation

Recommendation of the application is **approval** from a CMC perspective.

This is a 505(b)(1) application where the drug substance, tesamorelin acetate, is a New Molecular Entity (NME). The IND for tesamorelin acetate (61,226) was received on 10/16/2001. An EOP2 meeting was not requested by the sponsor, however, a Guidance meeting (at which issues typically discussed during an EOP2 meeting were discussed) was held on 12/3/2007. A pre-NDA meeting was held on 9/19/2008.

The drug substance (tesamorelin acetate) will be manufactured for commercial use by (b) (4) located in (b) (4) with most of the CMC parameters provided in the (b) (4) DMF No. (b) (4). A copy of the letter of authorization to reference DMF (b) (4) has been provided. The DMF was reviewed and found to be adequate. Two impurities have been identified in the drug substance (b) (4) and each has been adequately qualified at its respective proposed acceptable limit based on non-clinical toxicology studies.

The drug product, EGRIFTA™ (tesamorelin for injection) is manufactured by (b) (4) located in (b) (4) as a sterile, lyophilized powder comprised of tesamorelin acetate and mannitol, USP. It is intended for immediate subcutaneous injection following reconstitution with Sterile Water for Injection, USP. No preservatives are added given that the reconstituted product is indicated for single-use injection.

EGRIFTA was found to be photosensitive, therefore, vials containing lyophilized drug product are immediately labeled and placed in secondary containers, which provide adequate protection from light. A label statement will be added to protect the drug product from light.

No additional impurities have been imparted to the drug product during its manufacture or found during stability testing.

Based on the supporting stability data, a shelf life of 24 months at 2° – 8°C is granted for EGRIFTA.

Acceptable cGMP recommendations have been received from the Office of Compliance for each of the seven manufacturing and testing facilities. An Overall Compliance recommendation of Acceptable was provided on 23-Jun-2009.

Executive Summary Section

III. Administrative

- A. Reviewer's Signature:** in DAARTS
- B. Endorsement Block:** in DAARTS
- C. CC Block:** in DAARTS

5 pages withheld in full immediately after this page as (b)(4) CCI/TS.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22505	ORIG-1	THE RATECHNOLOGIES INC	TESAMORELIN ACETATE

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/s/

JOSEPH M LEGINUS
12/15/2009

PRASAD PERI
12/16/2009
I concur

On Nov 30, 2009, Theratechnologies submitted a complete response to the CMC request for information dated Nov 6, 2009 resulting from Chemistry Review #1. The deficiencies, Theratechnologies' responses and review comments will be provided in Chemistry Review #2.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22505

ORIG-1

THERATECHNOLO
GIES INC

TESAMORELIN ACETATE

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/s/

JOSEPH M LEGINUS

12/11/2009

NDA 22-505

**EGRIFTA™
(tesamorelin acetate for injection)**

Theratechnologies, Inc.

**Joseph Leginus, PhD
Division of Pre-Marketing Assessment I, Branch II, ONDQA**

**For the Division of
Metabolism and Endocrinology Products**

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Chemistry Review Data Sheet

1. NDA 22-505
2. REVIEW #: 1
3. REVIEW DATE: 21-Oct-2009
4. REVIEWER: Joseph Leginus, PhD
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original NDA

29-May-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Theratechnologies, Inc.
Address:	2310 Alfred-Nobel Blvd. Montreal, Quebec, Canada, H4S 2B4
Representative:	Nadine Bouchard, Director, Compliance and Associate Regulatory Affairs
Telephone:	514-336-7800

8. DRUG PRODUCT NAME/CODE/TYPE:

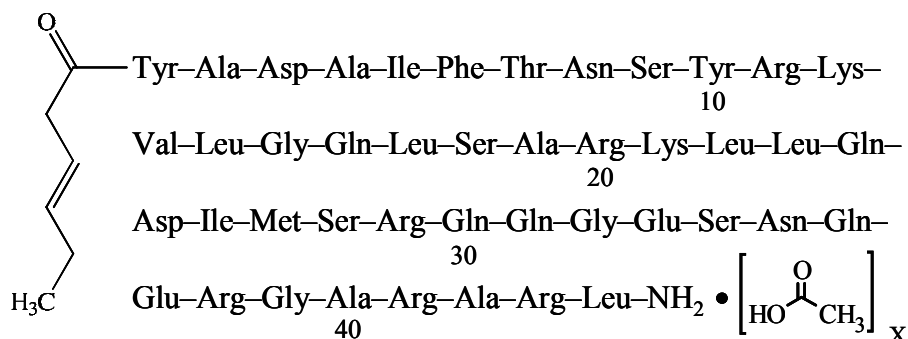
- a) Proprietary Name: EGRIFTA™
- b) Non-Proprietary Name (USAN): Tesamorelin acetate
- c) Code Name/# (ONDC only): CAS No.: 901758-09-6; TH9507 (Theratechnologies).
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: Standard

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: This NDA is submitted as a 505(b)(1) application.
10. PHARMACOL. CATEGORY:
Tesamorelin acetate is a synthetic analogue of human hypothalamic Growth Hormone-Releasing Factor (hGRF) indicated to induce and maintain a reduction of excess abdominal fat in HIV-infected patients with lipodystrophy.
11. DOSAGE FORM: Lyophilized Powder for Injection
12. STRENGTH/POTENCY:
1 mg (to be constituted in Sterile Water for Injection at 1 mg/mL)
13. ROUTE OF ADMINISTRATION: Subcutaneous Injection
14. Rx/OTC DISPENSED: Rx OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):
 SPOTS product – Form Completed
 Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

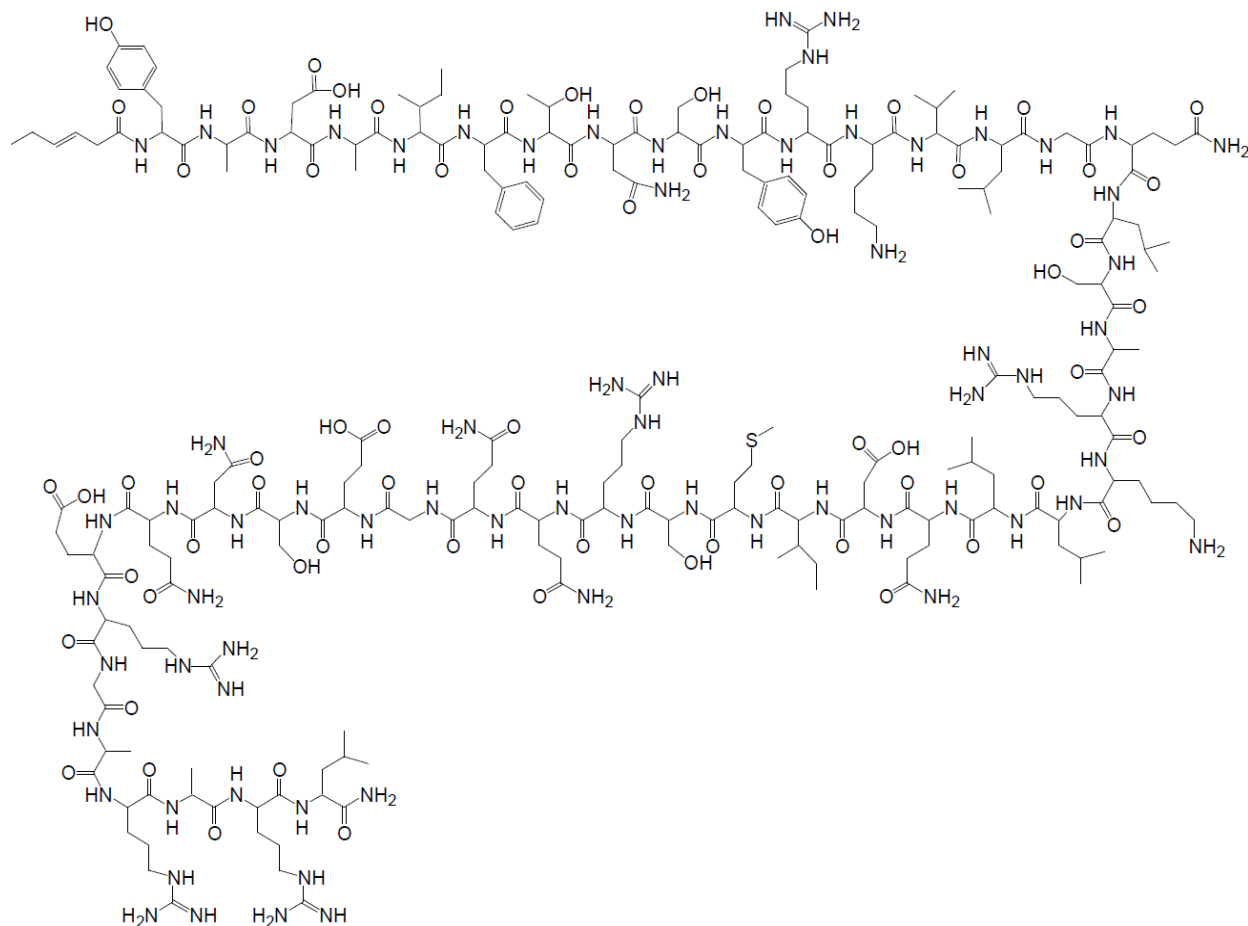
Chemical Name: *L-Leucinamide, N-[(3E)-1-oxo-3-hexenyl]-L-tyrosyl-L-alanyl-L- α -aspartyl-L-alanyl-L-isoleucyl-L-phenylalanyl-L-threonyl-L-asparaginyl-L-seryl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucylglycyl-L-glutamyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutamyl-L- α -aspartyl-L-isoleucyl-L-methionyl-L-seryl-L-arginyl-L-glutamyl-L-glutamylglycyl-L- α -glutamyl-L-seryl-L-asparaginyl-L-glutamyl-L- α -glutamyl-L-arginylglycyl-L-alanyl-L-arginyl-L-alanyl-L-arginyl-, acetate*

Structural Formula:



Chemistry Review Data Sheet

Chemical Structure (free base):

Molecular Formula: $C_{221}H_{366}N_{72}O_{67}S \cdot x C_2H_4O_2$

Molecular Weight: 5135.86 (free base)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code ¹	Status ²	Date Review Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	20-Aug-2009	Reviewed by J. Leginus
	III			1	Adequate	05-Nov-2007	Reviewed by M. Stevens-Riley
	III			1	Adequate	22-Apr-2009	Reviewed by

Chemistry Review Data Sheet

		LOA Date: 10-Apr-2009				S. Chatterjee
(b) (4)	III	(b) (4)	1	Adequate	24-Feb-2009	Reviewed by C. Evans
	V					See Microbiology Review

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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	61,226	TH9507; N-(trans-3-Hexenoyl)-Human Growth Hormone Releasing Factor (1-44) Acetate
NDA	18-801	Sterile Water for Injection, USP, in Plastic Vials. A letter of authorization is provided from Hospira Inc.

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable. An Overall Compliance recommendation of Acceptable was provided on 23-Jun-2009.	23-Jun-2009	N/A
Pharm/Tox	A request for the safety evaluation of impurities was made. Impurities have been qualified at proposed acceptable levels.	08-Oct-2009	Lauren Murphree-Mihalcik
Biopharm	Not applicable. This is an injectable product, and the commercial formulation was used in Phase 3 studies.		
Methods Validation	Validation may be requested of FDA labs after test methods are finalized.		

Chemistry Review Data Sheet

EA	Conducted by CMC reviewer. Granting the categorical exclusion as per 21 CFR 25.31(b).	10/14/2009	Joseph Leginus
Microbiology	Review of 1) microbiology controls proposed for the drug product, and 2) sterilization and (b) (4) processing validation for the drug product.	Pending	Steve Fong

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 22-505

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 22-505 is recommended for an Approvable action from the standpoint of chemistry, manufacturing and controls pending a satisfactory response to the deficiencies delineated in the List of Deficiencies and Information Request (in the CMC review for NDA 22-505). Acceptable cGMP recommendations have been received from the Office of Compliance for each of the seven manufacturing and testing facilities. An Overall Compliance recommendation of Acceptable was provided on 23-Jun-2009.

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

Not applicable.

II. Summary of Chemistry Assessments

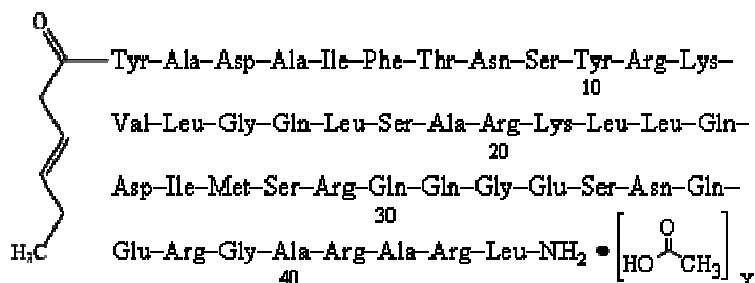
A. Description of the Drug Product(s) and Drug Substance(s)

DRUG SUBSTANCE

Information for the drug substance is provided in the (b) (4) DMF (b) (4), which was reviewed (J. Leginus, 20-Aug-2009) and found to be adequate. The drug substance will be manufactured, tested for release and stability, and packaged at (b) (4). A copy of the letter of authorization to reference DMF (b) (4) has been provided. Supplementary information on the drug substance has been provided by the applicant.

Tesamorelin acetate is a synthetic analog of human GRF (Growth Releasing Factor) comprised of the 44 amino acid sequence of human GRF. Tesamorelin acetate is made by attaching a hexenoyl moiety, a C6 chain with a double bond at position 3, to the tyrosine residue at the N-terminal part of the molecule. It is isolated as a white to off-white amorphous powder. The molecular formula of tesamorelin acetate is $C_{221}H_{366}N_{72}O_{67}S \cdot x C_2H_4O_2$ (x not provided) and its molecular weight (free base) is 5135.9 Daltons. The structural formula of tesamorelin acetate is presented below:

Executive Summary Section



The structure of tesamorelin acetate was elucidated by a variety of analytical and spectrophotometric techniques, including amino acid analysis, mass spectrometry (MALDI-TOF MS), circular dichroism (CD) and peptide mapping. (b) (4)

The proposed release specifications include appearance, solubility, identification (HPLC), amino acid analysis, mass spectral analysis, acetate content (HPLC), water content, specific rotation, residual organic solvents, peptide content, individual and total peptide related impurities (HPLC), mass balance, bioburden and endotoxin. Reference standards for the drug substance have been developed and characterized.

Although robust bioactivity was observed in the bioassay for tesamorelin acetate, high variability in the test results precluded it from being an acceptable method for determining the relative potency of the tesamorelin primary reference standard. As a result, a bioidentity test was established to ensure bioactivity of the drug substance. The bioidentity test uses the upper and lower values obtained from the tesamorelin bioactivity assays as limits for its acceptance criteria.

Impurities generated during the synthesis and storage of the drug substance are classified based on their HPLC elution position relative to the drug substance (RRT). One process related impurity (b) (4) and one degradant (b) (4) are identified in the drug substance specifications. Each impurity has been adequately qualified at its respective proposed acceptable limit.

DRUG PRODUCT

EGRIFTA™ (tesamorelin acetate for injection) is a white to off-white, sterile, lyophilized powder (1.1 mg tesamorelin acetate per vial) with mannitol, USP as the only excipient (55 mg per vial). The drug product is packaged in a stoppered 3 mL clear glass vial, placed in an opaque carton and co-packaged in a kit that includes disposable syringes, disposable needles and reconstitution diluent. The diluent is Sterile Water for Injection, USP, an approved product of NDA 18-801. Each vial contains an overfill amount of 0.1 mg tesamorelin acetate to ensure the drawing of 1.0 mL (for an actual dose of 1.0 mg) from each reconstituted vial. The recommended 2 mg dose requires reconstitution of 2

Executive Summary Section

vials of drug product using 2.2 mL Sterile Water for Injection from a single use 10 mL vial. Immediately after reconstitution, 2 mL of the 1 mg/mL solution (pH ~ 6) is injected subcutaneously by the patient. No preservatives are added given that the reconstituted product is indicated for single-use injection.

The manufacturing process for the drug product involves

(b) (4)

The proposed release specifications include appearance, identity (HPLC), assay (HPLC), individual and total impurities (HPLC), content uniformity, water content, sterility, bacterial endotoxin, reconstitution time, completeness and clarity of solution, pH, osmolality and particulate matter. The proposed regulatory methods have been validated. A request has been made to add a test for bioidentity to the drug product specifications.

A precise correlation between tesamorelin acetate bioactivity and assay by HPLC could not be established due to high variability in the cell-based bioassay. However, verification of biological activity of the drug product through the use of bioidentity testing supports the use of assay by HPLC as a reliable method for assessing tesamorelin acetate biological activity.

The drug product is photo labile and the primary container (clear glass vial) does not provide adequate protection from exposure to light. However, the secondary packaging (opaque carton) adequately protects the drug product from degradation due to light.

24 months of real-time stability data have been provided in the NDA for one drug product registration batch manufactured using the proposed commercial manufacturing process. (Real time stability data for two additional registration batches is available through 18 and 12 months, respectively). Theratechnologies will update these stability data via annual reports through the planned 3 years of stability. The in-use stability evaluation was performed 2 hours after reconstitution of the drug product at room temperature. This supports the recommended use of the product immediately following reconstitution. Based on the supporting stability data and the similarity of the developmental manufacturing processes to the proposed commercial process, a shelf life of 24 months at 2° – 8°C is granted for the drug product.

Theratechnologies requested a categorical exclusion from submitting an environmental assessment for the drug product based on the regulations in 21 CFR, part 25, section 25.31(b). The request is granted.

Executive Summary Section

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

EGRIFTA™ is indicated to induce and maintain a reduction of excess abdominal fat in HIV-infected patients with lipodystrophy, a common complication with HIV patients taking protease inhibitor drugs. The recommended dose of EGRIFTA is 2 mg in 2 mL injected subcutaneously once a day, preferably in the abdomen. The 2 mg dose requires reconstitution of 2 vials of drug product using 2.2 mL Sterile Water for Injection from a single use 10 mL vial. EGRIFTA is available in a package containing 60 vials of EGRIFTA, 30 vials of reconstitution diluent (Sterile Water for Injection, USP), and 30 disposable syringes and needles sufficient for a 30 day supply. The drug product will be labeled for long term storage (up to two years) at refrigerated (2° - 8°C) conditions and recommended for use immediately after reconstitution.

C. Basis for Approvability or Not-Approval Recommendation

The application is approvable from a CMC perspective pending satisfactory responses to the deficiencies identified in the review. Acceptable cGMP recommendations have been received from the Office of Compliance for each of the seven manufacturing and testing facilities. An Overall Compliance recommendation of Acceptable was provided on 23-Jun-2009.

This is a 505(b)(1) application where the drug substance, tesamorelin acetate, is a New Molecular Entity (NME). The IND for tesamorelin acetate (61,226) was received on 10/16/2001. An EOP2 meeting was not requested by the sponsor, however, a Guidance meeting (at which issues typically discussed during an EOP2 meeting were discussed) was held on 12/3/2007. A pre-NDA meeting was held on 9/19/2008.

The drug substance (tesamorelin acetate) will be manufactured for commercial use by (b) (4) located in (b) (4) with most of the CMC parameters provided in the (b) (4). A copy of the letter of authorization to reference DMF (b) (4) has been provided. The DMF was reviewed and found to be adequate. Two impurities have been identified in the drug substance (b) (4) and each has been adequately qualified at its respective proposed acceptable limit.

The drug product, EGRIFTA™ (tesamorelin acetate for injection) is manufactured by (b) (4), located in (b) (4) as a sterile, lyophilized powder comprised of tesamorelin acetate and mannitol, USP. It is intended for immediate subcutaneous injection following reconstitution with Sterile Water for Injection, USP. No preservatives are added given that the reconstituted product is indicated for single-use injection.

EGRIFTA was found to be photosensitive, therefore, vials containing lyophilized drug product are immediately labeled and placed in secondary containers, which provide adequate protection from light. A label statement will be added to protect the drug product from light.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22505

ORIG-1

THERATECHNOLO
GIES INC

TESAMORELIN ACETATE

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/s/

JOSEPH M LEGINUS
10/21/2009

PRASAD PERI
10/21/2009



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 9/23/2009

From: Susan Kirshner

Subject: NDA 22-505 and IND 61,226 Immunogenicity IR responses

Product: Egrifta (GHRH)

Sponsor: Theratechnologies

Recommendations:

The Sponsor adequately answered all our questions. We have no follow-up questions. The assays are acceptable.

Review:

This submission is a response to information requested by the Agency in a letter dated June 22, 2009 regarding the Sponsor's NAb assays.

FDA Question 1:

Provide data supporting the selection of (b) (4) Tesamorelin or rGRF as the stimulatory dose. The Agency recommends that the stimulatory dose selected should be between 40 – 70% of the maximum response of the linear portion of the dose-response curve for the cells. Alternative choices may be appropriate but should be supported by a strong scientific rationale and appropriate data.

The Sponsor responded that the stimulatory dose was selected to be (b) (4) of the maximum stimulatory dose in the linear range of the dose response curve (see figure below).

Figure 1

Tesamorelin (TH9507) Dose Response Curve in CRL and HIV Pool of Human Serum Diluted 1/25



The Agency generally recommends that the stimulatory dose fall within 40 – 70% of the maximum stimulatory dose of the linear portion of the dose response curve. Nevertheless up to (b) (4) of the maximum dose generally allows for adequate buffering between the non-linear portion of the dose response curve and assay variability. Therefore the Sponsor selection of the stimulatory dose is appropriate.

FDA question 2

With regard to the NAb assay negative cut-off determinations (for “potentially positive results”), provide the data and formulas used for your determination of the cut-off values (either the NCO factors or the serum source correction factors).

The Sponsor provided the requested data in the NDA submission. I briefly reviewed the data and they fulfill the requirements for using (b) (4). Therefore the Sponsor’s approach is appropriate and they have satisfied this request.

FDA Question 3:

Provide the expected concentration of (b) (4)

The expected range of concentrations for (b) (4)

The Table below shows the accuracy of the cAMP detection assay across a range of cAMP concentrations. As can be seen the accuracy of the cAMP assay is acceptable (87 – 97%) within the expected concentration of cAMP that will be generated in the cell based assay. Our request from the Sponsor is satisfied.

Table 2 Linearity of Dilution of the Immunoassay for the Quantitative Determination of cAMP

Sample ID	Theoretical undiluted concentration (pmol/mL)	cAMP concentration (mean result of duplicate reported) (pmol/mL) Val 11 A					
		Dilution (Fold)	1/Dilution	Theoretical concentration (pmol/mL)*	Back-calculated concentration (pmol/mL)	Corrected concentration (pmol/mL)	Recovery (%)
linearity of dilution 1 ^a	1250.00	1.0	1.000000	1250.00	726.22	726.2	58.1
linearity of dilution 2 ^a	1250.00	2.0	0.500000	625.00	538.76	1077.52	86.2
linearity of dilution 3 ^a	1250.00	4.0	0.250000	312.50	338.85	1355.40	108.4
linearity of dilution 4	1250.00	8.0	0.125000	156.25	151.79	1214.32	97.1
linearity of dilution 5	1250.00	16.0	0.062500	78.13	67.96	1087.36	87.0
linearity of dilution 6	1250.00	32.0	0.031250	39.06	30.67	981.44	78.5
linearity of dilution 7	1250.00	64.0	0.015625	19.53	20.43	1307.52	104.6
linearity of dilution 8	1250.00	128.0	0.007813	9.77	9.90	1267.20	101.4
linearity of dilution 9	1250.00	256.0	0.003906	4.88	5.86	1500.16	120.0
linearity of dilution 10 ^b	1250.00	512.0	0.001953	2.44	2.76	1413.12	113.0
linearity of dilution 11 ^b	1250.00	1024.0	0.000977	1.22	1.29	1320.96	105.7
Overall Mean							98.10
SD							14.430
CV (%)							14.7
n							6

a = result > ULOQ (240.00 pmol/mL) therefore, result were not included in calculations

b = The validated STD curve range is 240 - 3.5 pmol/mL, therefore those results were not included in calculation

Recovery = (Corrected concentration/theoretical undiluted concentration) × 100

* Please note that a cAMP stock with a concentration of 30.000 pmol/mL was used to prepare the 1250 pmol/mL dilution that was used for the serial dilutions.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22505

ORIG-1

THERATECHNOLO
GIES INC

TESAMORELIN ACETATE

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/s/

SUSAN L KIRSHNER

09/23/2009

Initial Quality Assessment
ONDQA Pre-Marketing Assessment Division 1

Division of Metabolism and Endocrinology Products

NDA: 22-505

Applicant: Theratechnologies, Inc.

Stamp Date: 29-MAY-2009

PDUFA Date: 29-MAR-2010

Proposed Proprietary Name: EGRIFTA

Established Name: Tesamorelin acetate for injection

Dosage form and strength: Powder for injection, 1 mg

Route of Administration: injection

Indications: To induce and maintain a reduction of excess abdominal fat in HIV-infected patients with lipodystrophy

CMC Lead: Su (Suong) Tran, Branch II/DPA I/ONDQA

ONDQA Fileability: Yes

Comments for 74-Day Letter: Yes, on the last page.

Initial Quality Assessment
ONDQA Pre-Marketing Assessment Division 1

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharmaceutics	Not Applicable
CDRH or CBER	Not Applicable
EA	Categorical exclusion request will be assessed by Primary Reviewer.
EES	EER was sent to Office of Compliance on 18-JUN-2009.
OSE	Labeling consult request will be sent as part of DMEP's request.
Methods Validation	Validation may be requested of FDA labs after test methods are finalized.
Microbiology	Review of 1) microbiology controls proposed for the drug substance and drug product, and 2) sterilization and (b) (4) processing validation for the drug product.
Pharm/Tox	A consult review will be requested for the qualification of specified peptide impurities/degradants with limits higher than 1.0%.

Summary: [See the discussion in Critical Issues later in this review.]

This is an electronic NDA, filed as a 505(b)(1) application. The associated IND is IND 61226.

The drug substance tesamorelin acetate is a New Molecular Entity (NME) and a synthetic 44-amino acid peptide. It differs from the natural human growth releasing factor, hGRF (1-44), by the addition of a trans-3-hexenoic acid group at one end. The chemical modification extends the in vivo half life of the molecule.

The drug product is a sterile lyophilized powder (1 mg tesamorelin per vial) with mannitol as the only excipient (55 mg per vial). The proposed labeling states "1.1 mg" as the dosage strength to include the overfill amount of 0.1 mg (see Critical Issues later in the review).

The drug product is packaged in a stoppered glass vial and co-packaged in a kit that includes the diluent, disposable syringes, and disposable needles. The diluent is Sterile Water for Injection, USP, an approved product of NDA 18-801 (different applicant: Hospira). Each 2 mg dose requires reconstitution of 2 vials of drug product. Immediately after reconstitution, the 1 mg/mL solution is administered subcutaneously.

Maximum daily dose is 2 mg tesamorelin.

Initial Quality Assessment
ONDQA Pre-Marketing Assessment Division 1

CRITICAL ISSUES

Has all information requested during the IND phases, and at the pre-NDA meetings been included?

Yes. The NDA includes some information as requested by FDA during the IND development. There is no item-by-item response to FDA's comments, which makes it difficult to assess in the limited time allotted for this filing memo/IQA whether the applicant has provided a satisfactory response to each question.

The primary reviewer will assess the information in the NDA and decide whether issues previously raised have been satisfactorily addressed.

Consults and CMC-related reviews:

- The Microbiology Team will review 1) microbiology controls proposed for the drug substance and drug product, and 2) sterilization and (b) (4) processing validation for the drug product.

Critical issues: To be discussed in the following sections.

Initial Quality Assessment
ONDQA Pre-Marketing Assessment Division 1

Drug substance:

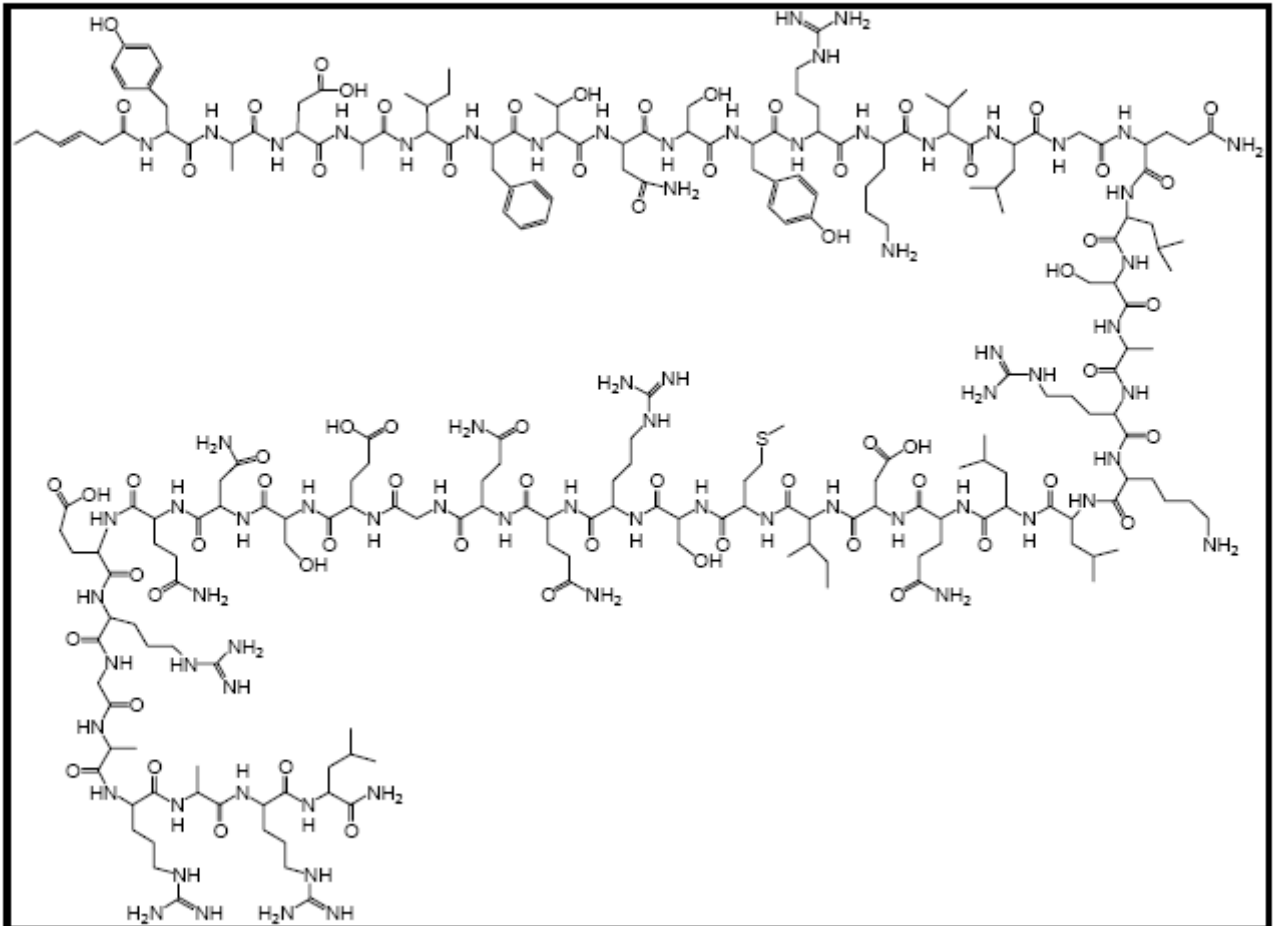
The drug substance tesamorelin is a synthetic 44-amino acid peptide. Its structure is that of the natural human growth releasing factor, hGRF (1-44), with the addition of a trans-3-hexenoic acid group at one end.

N-[trans-3-Hexenoyl]-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu-NH₂. x AcOH

Molecular Formula: C₂₂₁H₃₆₆N₇₂O₆₇S. x C₂H₄O₂

Molecular weight: 5135.9 (free base)

Tesamorelin Chemical Structure:



Initial Quality Assessment
ONDQA Pre-Marketing Assessment Division 1

Reference is made to the DMF (b) (4) (holder: (b) (4)) for all CMC information on the drug substance.

The NDA provides some information on the drug substance such as characterization results, general properties, and regulatory specification.

Critical Issues:

No specific comment regarding the CMC information on the drug substance can be discussed in this review because the information is in a DMF. The following issues will be evaluated by the primary reviewer as part of the NDA review:

- **Drug substance specification.** The drug substance specification is copied on pages 16-17 of this review. Testing as per specification is conducted by the manufacturer of the peptide, (b) (4)



- **Peptide mapping.** Tesamorelin is a 44-amino acid peptide. Peptide mapping is commonly included in the drug substance specification as an identity test. The reviewer will determine whether this test should be added to the specification based on all pertinent characterization information.

Initial Quality Assessment
 ONDQA Pre-Marketing Assessment Division 1

Drug product

Maximum daily dose is 2 mg tesamorelin.

Tesamorelin¹, sterile lyophilized powder, 1.1 mg/vial is available as a single unit dose for reconstitution with 1.1 mL of Sterile Water for Injection USP for a final concentration of 1 mg/mL.

1.1. Composition of the dosage form:

Component	Quantity (mg/vial)	Function	% Of the total unit weight*
N-[trans-3-Hexenoyl]-Human Growth Hormone-Releasing Factor (1-44) Acetate, In-house	1.1**	Active Pharmaceutical Ingredient	0.1
Mannitol USP	55 mg	Bulking agent	(b) (4)
Water for injection USP***	-----	Solvent	-----
(b) (4)	-----	(b) (4)	-----
(b) (4)	-----	(b) (4)	-----
(b) (4)	-----	(b) (4)	-----

* Based on a theoretical unit filling weight of 1.1 g

** This weight is corrected for peptide content

(b) (4)

Critical Issues:

- **Complete drug product.** The drug product consists of the tesamorelin formulation and the co-packaged diluent, which is the approved Sterile Water for Injection of NDA 18-801 (different applicant: Hospira). The primary chemist will review the complete CMC documentation for the tesamorelin formulation. No review of the diluent should be necessary because this is an approved product (letter of authorization from Hospira is included in the NDA).
- **Dosage strength and established name.** The proposed labeling states “1.1 mg” as the dosage strength to include the overfill amount of 0.1 mg. It is not clear whether the “1.1 mg” amount denotes the free base or the salt form of the peptide. The proposed dosage strength is not acceptable because it should not include the overfill amount. For injectables, USP <1151> recommends a 10% amount in excess of the labeled fill. Therefore, the labeled strength should not include the overfill and should be revised to state “1 mg”.

Initial Quality Assessment
ONDQA Pre-Marketing Assessment Division 1

- **Overfill.** The primary reviewer will confirm that this additional amount is adequately justified by data, that it is used to compensate for lost drug in the vial, syringe, and needle and not for stability problems.

Manufacturing process of the drug product

The manufacturing process consists of the bulk formulation (preparation of the drug solution with mannitol), sterile filtration, (b) (4) filling of vials and lyophilization. The flow diagram is copied on page 19 of this review. (b) (4)

Critical Issues:

- **Comparability of the product used in the clinical studies, stability studies, and commercial product.** There is no change in the formulation or manufacturing process used for the Phase 3 clinical batches, registration/stability batches, and validation (commercial) batches.

1 page withheld in full immediately after this page as (b)(4) CCI/TS.

Initial Quality Assessment
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Container closure systems for product distribution

The drug product is packaged in 3 mL, 13 mm neck, USP type I (b) (4) clear glass vials that are (b) (4). The vials are stoppered with (b) (4) 13 mm grey (b) (4) lyophilisation stoppers. The stoppers are capped with 13 mm, plastic flip off caps with aluminum seals.

Company Name	Address	Packaging Component	File # (DMF or 510K)
(b) (4)			

Critical Issues:

- **Leachables and extractables.** The drug product dosage form is a powder, the primary container is a Type I USP glass vial, and the product is administered immediately after reconstitution. Therefore, the risk of leachable formation is very low. The applicant states that the rubber stopper complies with USP requirements for elastomeric closures and was tested as per USP <381> and <87>. The reviewer will evaluate all available data to confirm that the stopper poses low risk of leachable contamination.

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Stability of the drug product

The NDA includes stability data for the following batches, all batches having the same formulation, manufactured at the commercial (b) (4) site at the commercial scale of (b) (4) (except for the clinical batch 5D407 at (b) (4) scale), and packaged in the commercial container closure system. Samples were stored at -20 °C as well as at 5 °C. In addition, 6-month accelerated data at 25 °C/60% RH were also obtained. The stability testing includes appearance, water content, identity, pH, completeness and clarity of solution, assay, related substances, particulate matter, and sterility.

Table 1: Summary of tesamorelin batches used in formal stability studies

Drug Product Lot Number	Drug substance Lot Number	Batch Type	Batch Size	Data Available to Date with method MOA 600490C ¹
5D407	FHEXGRF0201	Selected Clinical	(b) (4)	36-month only
5F682	FHEXGRF0201	Selected Clinical		36-month only
5F644	FHEXGRF0201	Selected Clinical		36-month only
6M434	FHEXGRF0201 FHEXGRF0401 FHEXGRF0501	Registration		12, 18 and 24 months
7B144	FHEXGRF0401	Registration		9, 12 and 18 months
7E530	FHEXGRF0401 FHEXGRF0501	Registration		9 and 12 months
8A050	FHEXGRF0601	Validation		0, 1, 3, 6, 9 and 12 months
8B148	FHEXGRF0601	Validation		0, 1, 3, 6 and 9 months
8C273	FHEXGRF0501 FHEXGRF0601	Validation		0, 1, 3, 6 and 9 months

¹ MOA 600490 version C is equivalent to MOA 600490 version D presented in section 3.2.P.5.2

Other stability data in the NDA are for photostability and temperature cycling (from -20 °C to 5 °C to 40 °C to 20 °C).

The applicant requests an expiry of 24 months at 2-8 °C.

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Critical Issues:

- **Co-packaging of the tesamorelin formulation and diluent: expiration dating period and storage conditions.** The reviewer will make sure that the expiration date of the co-packaged kit that includes both tesamorelin and Sterile Water for Injection will be the expiration date of the component with the nearest expiry.
- **In-use (reconstitution) stability.** No in-use stability study was conducted. The drug product will be administered immediately after the powder and diluent are mixed to constitute the solution. The labeling should indicate clearly that this product is for immediate use upon reconstitution.

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Supporting NDA or IND:

IND 61226 (same sponsor)

NDA 18-801 Sterile Water for Injection: A letter of authorization is provided from Hospira Inc.

Supporting DMF:

DMF	TYPE	HOLDER	ITEM REFERENCED	LOA
(b) (4)	II			x
	III			x
	III			x
	III			x
	V			X
	V			X

* DMFs (b) (4) and (b) (4) are type V DMFs. Both support the manufacture of the drug product. It is not clear what information is being referenced (no referenced item in the LOAs) because the NDA includes detailed information and all data on the manufacture and controls of the drug product.

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GMP facilities: EER was sent to the Office of Compliance on 18-JUN-2009. The list of facilities was in the 17-JUN-2009 amendment as per this reviewer's request to the applicant.

Tesamorelin Drug Substance is manufactured, labeled, packaged, released and placed on stability testing by:



The following contract laboratories are used by (b) (4) for release testing of tesamorelin acetate:

1. Mass Spectral Analysis



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2. Bioburden



3. Bacterial Endotoxin



4. Peptide Content by Elemental Analysis



5. Sequence Analysis by electrospray ionization and mass spectrometry



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Tesamorelin Drug Product is manufactured, labeled, packaged, released and placed on stability testing by:



Subcontracted Activities: Testing for osmolality in the finished product is sub-contracted to following laboratory facility:



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CHEMISTRY NDA FILEABILITY CHECKLIST

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.

	Content Parameter	Yes	No	Comment
1	Is the section legible, organized, indexed, and paginated adequately?	x		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	x		
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?	x		
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	x		Exclusion request per 21 CFR 25.31 is included.
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	x		
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	x		
7	If applicable, has all information requested during the IND phases and at the pre-NDA meetings been included?	x		
8	Have draft container labels and package insert been provided?	x		
9	Have all DMF References been identified?	x		
10	Is information on the investigational formulations included?	x		
11	Is information on the methods validation included?	x		
12	If applicable, is documentation on the sterilization process validation included?			See Microbiologist's filing memo.

74-Day Letter – Draft Comment to the Applicant:

The proposed labeling states “1.1 mg” as the dosage strength to include the overfill amount of 0.1 mg. The proposed dosage strength is not acceptable because it should not include the overfill amount. Revise the dosage strength to state “1 mg”. In addition, clarify whether the dosage strength denotes the free base or the salt form of the peptide because the established name of the product should correlate with the dosage strength (1 mg tesamorelin or 1 mg tesamorelin acetate).

**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
7/16/2009 02:14:00 PM
CHEMIST

Ali Al-Hakim
7/16/2009 02:24:23 PM
CHEMIST