

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203696Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: December 11, 2012

From: Zhengfang Ge, Ph. D.

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
New Drug Quality Assessment Division II
ONDQA

To: CMC Review #1 of NDA 203696

Subject: Final Recommendation

The CMC review #1 has noted the following two pending issues:

1. Final "Acceptable" recommendation from the Office of Compliance was not issued.
2. Label/labeling issues were not resolved.

And because of these deficiencies, in the CMC Review #1, this NDA was not recommended for approval from the ONDQA perspective.

On December 6, 2012, the Office of Compliance issued the "Acceptable" recommendation for the facilities involved in the NDA (see the **Attachment 1**).

On December 11, 2012, the applicant provided the revised label and labeling via e-mail and they are revised satisfactorily from the ONDQA perspective (see the **Attachment 2**).

Recommendation:

This NDA is **now** recommended for **Approval** from the ONDQA perspective.

Attachment 1:

EES report

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:	NDA 203696/000	Sponsor:	ABBOTT ENDOCRINE
Org. Code:	580		200 ABBOTT PARK RD D-PA77/AP30-1NE
Priority:	4		ABBOTT PARK, IL 600646157
Stamp Date:	15-FEB-2012	Brand Name:	leuprolide acetate for depot suspension
PDUFA Date:	15-DEC-2012	Estab. Name:	leuprolide acetate for depot suspension and norethindrone acetate tablets
Action Goal:		Generic Name:	
District Goal:	16-OCT-2012	Product Number; Dosage Form; Ingredient; Strengths	
			001; INJECTION; LEUPROLIDE ACETATE; 3.75MG/1VIL
			001; INJECTION; NORETHINDRONE ACETATE; 5MG
			002; INJECTION; LEUPROLIDE ACETATE; 11.25MG/1VIL
			002; INJECTION; NORETHINDRONE ACETATE; 5MG
FDA Contacts:	R. MCKNIGHT	Project Manager	3017961765
	Z. GE	Review Chemist	3017961358
	D. CHRISTNER	Team Leader	3017961341

Overall Recommendation:	ACCEPTABLE	on 06-DEC-2012	by T. GOOEN	(HFD-320)	3017963257
	PENDING	on 13-SEP-2012	by EES_PROD		
	PENDING	on 19-MAR-2012	by EES_PROD		
	PENDING	on 19-MAR-2012	by EES_PROD		

Attachment 2

Final Labels

1) Drug Product Cartons:

In the cover letter, the applicant noted that “The Lot Number and Expiration Date statements are not included in our proposed labeling, as they will be applied to the Lupaneta Pack cartons [REDACTED] (b) (4) Therefore, the proposed carton is acceptable





2) Container Labels for Norethindrone Acetate Tablets :

NDC 0074-1049-02

**NORETHINDRONE
ACETATE TABLETS USP**

5 mg

ORALLY ACTIVE PROGESTIN

Rx Only 30 Tablets

NOT FOR INDIVIDUAL SALE.
NORETHINDRONE ACETATE IS A
COMPONENT OF LUPANETA PACK
COPACKAGED KIT (NDC 0074-1052-05)

Each tablet contains 5 mg norethindrone acetate USP.

Take 5 mg (one tablet) by mouth once daily for 1 month. See Package Insert for full prescribing information.

Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature].

Dispense in well-closed containers.

Manufactured by:
Glenmark Generics Ltd,
Colvale-Bardéz, Goa 403513, India.
60/DRUGS/785

Manufactured for:
Abbott Laboratories
North Chicago, IL 60064
Product of The Netherlands

Lot No.:
Exp.:

DN2424V5

NDC 0074-1049-04

**NORETHINDRONE
ACETATE TABLETS USP**

5 mg

ORALLY ACTIVE PROGESTIN

Rx Only 90 Tablets

NOT FOR INDIVIDUAL SALE.
NORETHINDRONE ACETATE IS A
COMPONENT OF LUPANETA PACK
COPACKAGED KIT (NDC 0074-1053-05)

Each tablet contains 5 mg norethindrone acetate USP.

Take 5mg (1 tablet) by mouth once daily for 3 months. See Package Insert for full prescribing information.

Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature].

Dispense in well-closed containers.

Manufactured by:
Glenmark Generics Ltd,
Colvale-Bardéz, Goa 403513, India.
60/DRUGS/785

Manufactured for:
Abbott Laboratories
North Chicago, IL 60064
Product of The Netherlands

Lot No.:
Exp.:

DN2426V5

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

/s/

ZHENGFANG GE
12/12/2012

MOO JHONG RHEE
12/12/2012
Chief, Branch IV

NDA 203696

Trade Name

(leuprolide acetate for depot suspension and norethindrone acetate tablets) kit

3.75 mg (or 11.25mg) / 5 mg

Abbott Endocrine Inc

Zhengfang Ge, Ph.D.

Branch IV

Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

For

Division of Reproductive and Urologic Drugs

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	8
I. Recommendations	8
A. Recommendation and Conclusion on Approvability	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments.....	8
A. Description of the Drug Product(s) and Drug Substance(s)	8
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Not-Approval Recommendation.....	9
III. Administrative.....	9
A. Reviewer's Signature.....	9
B. Endorsement Block.....	9
C. CC Block.....	9
Chemistry Assessment	10
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	10
S DRUG SUBSTANCE [Leuprolide acetate and norethindrone acetate]	10
P DRUG PRODUCT [Co-packaged Lupron Depot Suspension and Norethindrone Acetate Tablets]	12
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	16
A. Labeling & Package Insert	16
III. List Of Deficiencies	24

Chemistry Review Data Sheet

1. NDA 203696
2. REVIEW #: 1
3. REVIEW DATE: October 2, 2012
4. REVIEWER: Zhengfang Ge, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

ANDA 91090

NDA 20011

NDA 20708

Document Date30 and 90 count bottles approved on
17-Jan-2012

Approved on 22-Oct-1990

Approved on 7-Mar-1997

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Amendment

Document Date

15-Feb-2012

14-June-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Abbott Endocrine Inc

200 Abbott Park Rd

Address: D-PA77/AP30-1NE

Abbott Park, IL 60064-6157

Representative: Jean M Conaway

Chemistry Review Data Sheet

Telephone: 847-935-6244

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Trade Name
- b) Non-Proprietary Name (USAN): Leuprolide acetate for depot suspension and norethindrone acetate tablets kit
- c) Code Name/# (ONDQA only): TAP-144 and ABT-818
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 4
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH). Norethindrone acetate is a synthetic, orally active progestin. Treatment of endometriosis with add-back therapy

11. DOSAGE FORM: Injection and Oral tablets (co-packaged kit)

12. STRENGTH/POTENCY: 3.75mg injection/5mg tablets and 11.25mg injection/5mg tablets

13. ROUTE OF ADMINISTRATION: injection and oral

14. Rx/OTC DISPENSED: Rx OTC

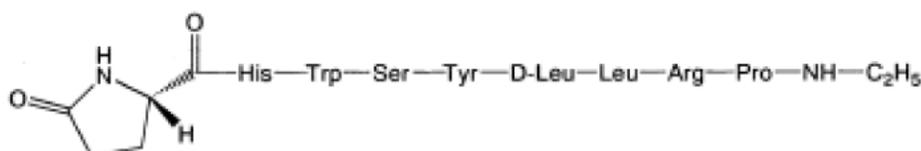
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

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

Leuprolide Acetate

Chemical Name: 5-Oxo- L-prolyl- L- histidyl- L-tryptophyl- L-seryl- L-tyrosyl- D- leucyl- L-leucyl- L-arginyl- N-ethyl- L-prolinamide (salt)

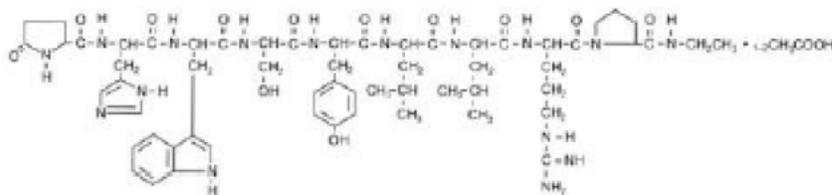
USAN: Leuprolide acetate

IUPAC Name (for the free base): *N*-[1-[[1-[[1-[[1-[[1-[[1-[[5-(diaminomethylideneamino)-1-[2-(ethylcarbamoyl)pyrrolidin-1-yl]-1-oxopentan-2-yl]carbamoyl]-3-methylbutyl]carbamoyl]-3-methylbutyl]carbamoyl]-2-(4-hydroxyphenyl)ethyl]carbamoyl]-2-hydroxyethyl]carbamoyl]-2-(1*H*-indol-3-yl)ethyl]carbamoyl]-2-(3*H*-imidazol-4-yl)ethyl]-5-oxopyrrolidine-2-carboxamide

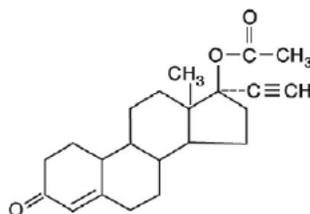
CAS: 74381-53-6

Molecular formula: $C_{59}H_{84}N_{16}O_{12} \cdot (C_2H_4O_2)_n, n=1 \text{ or } 2$

Molecular weight: 1269.45

Leuprolide Acetate**Norethindrone acetate**

Chemistry Review Data Sheet



Chemical Name: 17-hydroxy-19-nor-17 α -pregn-4-en-20-yn-3-one acetate

CAS: 38673-38-0

Molecular formula: C₂₂H₂₈O₃

Molecular weight: 340.45

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)	7	N/A	07-Aug-1995	The DMF was reviewed for NDA 20-011. Updates thereafter are mainly for LOAs and manufacturing process which is also referenced by approved NDA 20-011.
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	20-May-2011	S. Zimmerman
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	01-Jun-2011	S. Dhanesar

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
None		

Chemistry Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	pending		
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMEPA	N/A		
EA	N/A		
Microbiology	N/A		

The Chemistry Review for NDA 203696

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

However, the Office of Compliance has *not* issued an overall “Acceptable” recommendation.

Labeling issues also have *not* been resolved as of this review.

Therefore, from the ONDQA perspective, this NDA is *not* recommended for “Approval” in its present form per 21CFR 314.125(b)(6),(13) until all the pending issues are resolved.

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)

Abbot Endocrine Inc. proposed, in this NDA, co-packaged kits of approved drug products, leuprolide acetate for depot suspension and norethindrone acetate (NETA) tablets with two package configurations: 1) 1 month package of LUPRON DEPOT 3.75 mg and Norethindrone acetate 5 mg (30 tablets); 2) 3 month package of LUPRON DEPOT 11.25 mg and Norethindrone acetate 5 mg (90 tablets).

The applicant cross-referenced NDA 20011 for the CMC information of Lupron Depot 3.75 mg and NDA 20708 for the Lupron Depot 11.25 mg. Abbot Endocrine Inc. is the holder of both NDA 20-011 and NDA 20708. In addition, the applicant cross-referenced NDA 19-010, also owned by Abbott Endocrine Inc, for the CMC information of the drug substance leuprolide acetate.

Norethindrone acetate tablets 5 mg (30 tablets and 90 tablets per bottle) co-packaged in the proposed drug products are generic drug supplied by Glenmark, ANDA 91090. ANDA 91090 was approved on Jan 17, 2012. LOA for ANDA 91-090 is provided in this NDA.

Inspection for the manufacturing facilities of the drug substances and drug products has been requested through EES and currently pending recommendation from OC.

Chemistry Assessment Section

The drug product labeling is based on integrating approved labels for leuprolide acetate injection and norethindrone acetate tablets. Deficiencies on the co-packaging carton label have been identified as outlined in section III. List of Deficiencies, and will be communicated to the applicant during the labeling review.

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

The co-packaged products is indicated for:

- Initial management of the painful symptoms of endometriosis
- Management of recurrence of symptoms

1 month package of LUPRON DEPOT 3.75 mg and Norethindrone acetate 5 mg (30 tablets):

LUPRON DEPOT 3.75 mg for 1-month administration given as a single intramuscular injection every 4 weeks

Norethindrone acetate 5 mg tablets should be taken orally once per day for 4 weeks

3 month package of LUPRON DEPOT 11.25 mg and Norethindrone acetate 5 mg (90 tablets):

LUPRON DEPOT 11.25 mg for 3-month administration given as a single intramuscular injection every 3 months

Norethindrone acetate 5 mg tablets should be taken orally once per for 3 months

C. Basis for Not-Approval Recommendation

21CFR314.125(b)(13)

- The overall “Acceptable” recommendation has *not* been issued from the Office of Compliance.

21CFR 314.125(b)(6)

- Labeling issues are *not* resolved (see the **List of Deficiencies** on p. 24)

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

Zhengfang Ge, Ph.D.
Reviewer/ONDQA

Moo-Jhong Rhee, Ph.D.
Branch Chief/ONDQA

C. CC Block

Donna Christner

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/s/

ZHENGFANG GE
10/02/2012

MOO JHONG RHEE
10/02/2012
Chief, Branch IV

Initial Quality Assessment
Branch IV
Division of New Drug Quality Assessment II

OND Division: Division of Reproductive and Urologic Products
NDA: 203696
Applicant: Abbott Laboratories
Stamp Date: 15-Feb-2012
PDUFA Date: 15-Dec-2012
Trademark: TBD
Established Name: Leuprolide acetate for depot suspension and norethindrone acetate tablets kit
Dosage Form: Injection and Oral tablets copackaged kit
Route of Administration: Co-packaged depot suspension and oral tablets
Indication: Endometriosis with add back therapy

CMC Lead: Donna F. Christner, Ph.D.

	YES	NO
ONDQA Fileability:	X	<input type="checkbox"/>
Comments for 74-Day Letter	<input type="checkbox"/>	X

Summary and Critical Issues:

A. Summary

Abbott Laboratories has submitted this NDA to seek to co-package two approved drug products in a kit. Lupron Depot has been previously approved for use in combination with norethindrone acetate. All CMC information is provided in the cross-referenced applications for approved products. The only information provided in Module 3 is the manufacturing site information to allow submission of EES for this NDA.

B. Critical issues for review

Labeling will require review. EES has been submitted.

C. Comments for 74-Day Letter

There are no comments to be conveyed at this time.

D. Recommendation:

This NDA is fileable from a CMC perspective. Zhengfang Ge is the primary reviewer.

REGULATORY BRIEFING RECOMMENDATION: Branch-level.

Donna F. Christner, Ph.D.

NDA Number: 203696 Type: 5

Established/Proper Name:
Leuprolide acetate for depot suspension and norethindrone acetate tablets kit

Applicant: Abbott Labs

Letter Date: 15-Feb-2012

Stamp Date: 15-Feb-2012

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		<ul style="list-style-type: none"> • LOA to Cross-reference Glenmark ANDA 91090 for NETA tablets • Cross-reference to DMF (b)(4) for NETA • Reference to NDAs 19-010, (b)(4) and 20-708 for Leuprolide Acetate
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		<ul style="list-style-type: none"> • LOA to Cross-reference Glenmark ANDA 91090 for NETA tablets • Cross-reference to DMF (b)(4) for NETA Reference to NDAs 19-010, (b)(4) and 20-708 for Leuprolide Acetate
3.	Are all the pages in the CMC section legible?	X		<ul style="list-style-type: none"> • LOA to Cross-reference Glenmark ANDA 91090 for NETA tablets • Cross-reference to DMF (b)(4) for NETA Reference to NDAs 19-010, (b)(4) and 20-708 for Leuprolide Acetate
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		<ul style="list-style-type: none"> • LOA to Cross-reference Glenmark ANDA 91090 for NETA tablets • Cross-reference to DMF (b)(4) for NETA Reference to NDAs 19-010, (b)(4) and 20-708 for Leuprolide Acetate

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		See attachment to 356h

6.	<p>For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.</p>		X	N/A
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		See attachment to 356h

8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		See attachment to 356h
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		See attachment to 356h
10.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p>	X		See attachment to 356h

- If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Request for categorical exclusion provided

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		Cross-reference to DMF (b)(4) for NETA Reference to NDA 19-010 for Leuprolide Acetate
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Cross-reference to DMF (b)(4) for NETA Reference to NDA 19-010 for Leuprolide Acetate
14.	Does the section contain information regarding the characterization of the DS?	X		Cross-reference to DMF (b)(4) for NETA Reference to NDA 19-010 for Leuprolide Acetate
15.	Does the section contain controls for the DS?	X		Cross-reference to DMF (b)(4) for NETA Reference to NDA 19-010 for Leuprolide Acetate
16.	Has stability data and analysis been provided for the drug substance?	X		Cross-reference to DMF (b)(4) for NETA Reference to NDA 19-010 for Leuprolide Acetate
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	Not a filing issue
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	Not a filing issue

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		<ul style="list-style-type: none"> • LOA to Cross-reference Glenmark ANDA 91090 for NETA tablets • Cross-reference to NDAs (b)(4) and 20-708 provided in Module 1, Section 1.2 “Notes to Reviewer-Leuprolide acetate CMC”
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		<ul style="list-style-type: none"> • LOA to Cross-reference Glenmark ANDA 91090 for NETA tablets • Cross-reference to NDAs (b)(4) and 20-708 provided in Module 1, Section 1.2 “Notes to Reviewer-Leuprolide acetate CMC”
21.	Is there a batch production record and a proposed master batch record?	X		<ul style="list-style-type: none"> • LOA to Cross-reference Glenmark ANDA 91090 for NETA tablets • Cross-reference to NDAs (b)(4) and 20-708 provided in Module 1, Section 1.2 “Notes to Reviewer-Leuprolide acetate CMC”
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		<ul style="list-style-type: none"> • LOA to Cross-reference Glenmark ANDA 91090 for NETA tablets • Cross-reference to NDAs (b)(4) and 20-708 provided in Module 1, Section 1.2 “Notes to Reviewer-Leuprolide acetate CMC”
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		<ul style="list-style-type: none"> • LOA to Cross-reference Glenmark ANDA 91090 for NETA tablets • Cross-reference to NDAs (b)(4) and 20-708 provided in Module 1, Section 1.2 “Notes to Reviewer-Leuprolide acetate CMC”
25.	Does the section contain controls of the final drug product?	X		<ul style="list-style-type: none"> • LOA to Cross-reference Glenmark ANDA 91090 for NETA tablets • Cross-reference to NDAs (b)(4) and 20-708 provided in Module 1, Section 1.2 “Notes to Reviewer-Leuprolide acetate CMC”
26.	Has stability data and analysis been provided to support the requested expiration date?	X		<ul style="list-style-type: none"> • LOA to Cross-reference Glenmark ANDA 91090 for NETA tablets • Cross-reference to NDAs (b)(4) and 20-708 provided in Module 1, Section 1.2 “Notes to Reviewer-Leuprolide acetate CMC”
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	Not a filing issue
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	Not a filing issue

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		<ul style="list-style-type: none"> • LOA to Cross-reference Glenmark ANDA 91090 for NETA tablets • Cross-reference to NDAs (b)(4) and 20-708 provided in Module 1, Section 1.2 "Notes to Reviewer-Leuprolide acetate CMC"

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	N/A

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	(b)(4)	LOA DATE	COMMENTS
(b)(4)	II	(b)(4)	(b)(4)	25-Jan-2012	ADEQUATE on 07-Aug-1995. Updates submitted.
(b)(4)	IV	(b)(4)	(b)(4)	03-Feb-2012	No review found. Excipients not typically reviewed.
(b)(4)	II	(b)(4)	(b)(4)	25-Jan-2012	ADEQUATE on 20-May-2011. Updates submitted
(b)(4)	IV	(b)(4)	(b)(4)	03-Feb-2012	No review found. Excipients not typically reviewed
(b)(4)	III	(b)(4)	(b)(4)	24-Jan-2012	ADEQUATE on 26-Apr-2002. Updates since that time.
(b)(4)	III	(b)(4)	(b)(4)	23-Jan-2012	ADEQUATE on 25-Jan-2012.
(b)(4)	III	(b)(4)	(b)(4)	15-Dec-2011	No review found
(b)(4)	III	(b)(4)	(b)(4)	07-Dec-2011	ADEQUATE on 16-Jun-2011
(b)(4)	III	(b)(4)	(b)(4)	05-Dec-2011	ADEQUATE on 07-Jul-2010
(b)(4)	III	(b)(4)	(b)(4)	06-Dec-2011	ADEQUATE on 07-Jul-2010

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	02-Dec-2011	ADEQUATE on 21-Jan-2011
(b) (4)	III	(b) (4)		06-Dec-2011	ADEQUATE on 09-Jun-2003
(b) (4)	III	(b) (4)		05-Dec-2011	Deemed INADEQUATE on 13-Apr-2009. However, comments not sent to holder. Currently used for ANDA 91090
(b) (4)	III	(b) (4)		06-Dec-2011	No review found. However, currently used for ANDA 91090.
(b) (4)	III	(b) (4)		03-Dec-2011	No review found. However, currently used for ANDA 91090. See ONDC Policies on (b) (4)
(b) (4)	II	(b) (4)		07-Feb-2012	ADEQUATE on 01-Jun-2011
ANDA 91090	ANDA	Glenmark		Norethindrone Acetate Tablets, USP, 5 mg	03-Feb-2012
(b) (4)	MAF	(b) (4)	(b) (4)	06-Nov-2008	APPROVED in NDA 19943_SCS-019 dated 18-Sep-2002

(b) (4)

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		Bar codes should be added on the labels of the individual component of the kit (Lupron syringe and NETA tablet bottle)

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?			

{See appended electronic signature page}

Donna F. Christner, Ph.D.
 CMC Lead
 Division of New Drug Quality Assessment II
 Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
 Chief, Branch IV
 Division of New Drug Quality Assessment II
 Office of New Drug Quality Assessment

Date

Attachment A: Nanotechnology product evaluating questions:

1, This review contains new information added to the table below: _____ Yes; ___ x ___ No Review date: <u>29-Feb-2012</u>
2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.) Yes _____; No _____; Maybe (please specify) _____
3 a) What nanomaterial is included in the product? (Examples of this are listed as search terms in Attachment B.) _____
3 b) What is the source of the nanomaterial? _____
4) Is the nanomaterial a reformulation of a previously approved product? Yes _____ No _____
5) What is the nanomaterial functionality? Carrier _____; Excipient _____; Packaging _____ API _____; Other _____
6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble (e.g., gold nanoparticle) in an aqueous environment? Soluble _____; Insoluble _____
7) Was particle size or size range of the nanomaterial included in the application? Yes _____ (Complete 8); No _____ (go to 9).
8) What is the reported particle size? Mean particle size _____; Size range distribution _____; Other _____
9) Please indicate the reason(s) why the particle size or size range was not provided: _____ _____
10, What other properties of the nanoparticle were reported in the application (See Attachment E)? _____
11) List all methods used to characterize the nanomaterial? _____ _____

REVIEW NOTES

Abbott Laboratories has submitted this NDA to seek to co-package two approved drug products in a kit. Lupron Depot has been previously approved for use in combination with norethindrone acetate.

All CMC information is provided in the following cross-referenced applications. The only information provided in Module 3 is the manufacturing site information to allow submission of EES for this NDA.

1.4.4 Cross Reference to Other Applications

The following applications are referenced within this NDA 203696 in support of:

- leuprolide acetate for depot suspension 3.75mg for 1-month administration and norethindrone acetate 5 mg tablets kit
- leuprolide acetate for depot suspension 11.25mg for 3-month administration and norethindrone acetate 5mg tablets kit.

Lupron Active Applications Owned by Abbott Endocrine Inc.

- NDA 20-011 for Lupron Depot (leuprolide acetate for depot suspension) 3.75 mg for 1-month administration (clinical)
- NDA 20-708 for Lupron Depot (leuprolide acetate for depot suspension) 11.25 mg for 3-month administration (clinical)
- NDA 19-010 for Lupron Injection (leuprolide acetate) (nonclinical, API CMC)
- NDA 19-943 for Lupron Depot (leuprolide acetate for depot suspension) 3.75 mg for 1-month administration (nonclinical)
- NDA 19-732 for Lupron Depot (leuprolide acetate for depot suspension) 7.5 mg for 1-month administration (CMC, nonclinical)
- NDA 20-517 for Lupron Depot (leuprolide acetate for depot suspension) 22.5 mg, 30 mg, and 45 mg for 3-month, 4-month and 6-month administration, respectively (CMC)
- IND 27,350 Lupron Depot (leuprolide acetate for depot suspension) (clinical)

Lupron Letter of Authorizations (LOA) and/or DMF applications

-  (b) (4)
-
-
-
-
-
-
-

Norethindrone Acetate 5mg tablets Letter of Authorizations (LOA) and/or DMF applications

- [ANDA 091090 for norethindrone acetate 5mg tablets \(Glenmark\) ANDA 091090 Letter of Authorization](#)



The following CMC-related advice was provided by the FDA prior to submission of the NDA:

Correspondence dated 23-Mar-2011:

The sponsor was advised that since clinical studies were performed in support of the add-back therapy and were approved in the previous Lupron NDA, that no clinical studies would be

necessary for the co-packaging NDA. The sponsor was advised that the storage statement for the co-packaged configuration would need to be the more restrictive of the two storage statements for the approved products. Therefore, the storage statement should be the same as approved for Lupron and read:

"Store at 25°C (77°F); excursions permitted 15-30°C (59-86°F) (See USP Controlled Room Temperature)"

Meeting held 10-Nov-2011

For CMC, the sponsor was advised that it was acceptable to cross-reference the majority of the CMC information from the previously approved applications. They were requested to submit the following information to the new NDA:

- A list of all manufacturing facilities
- DMF Letters of Authorization written to the new NDA
- Specific cross-references to the most current information in the approved applications

The sponsor was also requested to submit general information on the drug substance and drug product to the new NDA and not only by cross-reference.

***Comment:** The requested information is provided in the NOTES TO REVIEWER section of the NDA. Information is adequate to allow review.*

As part of the co-packaging configuration, the NETA tablets would need to be provided in a 30-count and 90-count bottle, which was not an approved configuration for the proposed NETA tablets marketed by Glenmark. The sponsor requested that the ANDA supplement be submitted concurrently with the NDA, with the hopes that both would be approved at the same time. The sponsor was advised that it would be better for the ANDA supplement to be submitted first to allow adequate time for an action to be taken on the ANDA supplement. OGD committed to expedite the review of the ANDA supplement.

Approval letter for ANDA 91090/S-002 30- and 90-count bottles

The CBE-30 for addition of the 30- and 90-count bottle configurations was approved on 17-Jan-2012.

***Comment:** The requested information is provided in NDA. Information is adequate to allow review.*

LABELING

Draft labeling is provided.

***Comment:** Information is adequate to allow review.*

MANUFACTURERS

Establishment Information for Leuprolide acetate Drug Substance

The leuprolide acetate drug substance is manufactured, packaged, and tested at:
 Takeda Pharmaceutical Company Limited
 4720 Takeda Mitsui, Hikari
 Yamaguchi 743-8502, Japan

Facility Establishment Identifier (FEI): 3002808306

For leuprolide acetate drug substance information, please refer to NDA 19-010.

Establishment Information for Norethindrone acetate Drug Substance



Establishment Information for Leuprolide acetate for depot suspension and norethindrone acetate tablet co-packaged kit

Facility Location	DMF Number	Manufacture & Packaging	Analytical Testing
Takeda Pharmaceutical Company Limited 4720 Takeda, Mitsui, Hikari Yamaguchi 743-8502, Japan Facility Establishment Identifier (FEI): 3002808306	(b) (4)	X ¹	X ¹
Takeda Pharmaceutical Company Limited 17-85, Jusohonmachi 2-chome Yodogawa-ku Osaka 532-8686, Japan Facility Establishment Identifier (FEI): 3002808311	(b) (4)	X ¹	X ¹
Glenmark Generics Limited Plot No. S-7, Colvale Industrial Estate Colvale-Bardéz Goa - 403 513 India Registration Number (CFN): 3004672766	N/A	X ²	X ²
Abbott Laboratories 100 & 200 Abbott Park Road Abbott Park, IL 60064, USA Facility Establishment Identifier (FEI): 1415939	N/A	X ³	

1. Leuprolide acetate for depot suspension
 2. Norethindrone acetate tablets
 3. Secondary packaging of Leuprolide acetate depot for suspension and norethindrone acetate tablet co-packaged kit
 N/A - Not Applicable

Comment: Sites were submitted to EES on 19-Mar-2012. As of 10-Apr-2012, the Takeda sites in Yamaguchi and Osaka, Japan are ASSIGNED INSPECTION TO IB. All other sites are ACCEPTABLE based on profile.

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

/s/

DONNA F CHRISTNER
04/13/2012

MOO JHONG RHEE
04/13/2012
Chief, Branch IV