

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20-866**

**CHEMISTRY REVIEW(S)**

NDA 20-866  
Cycloset™ (Bromocriptine Mesylate) 0.8 mg Tablets

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

Original Submission: August 22, 1997

Applicant: VeroScience, LLC  
1334 Main Road  
Tiverton, RI 02878

Indication: Hyperglycemia (Adjunct to diet to improve glycemic control in patients with NIDDM whose hyperglycemia cannot be managed by diet alone)

Presentation: The drug product is supplied in 200 and 600 count tablets packaged into \_\_\_\_\_ HDPE bottles respectively. Bottles will have a tamper-evident seal and a \_\_\_\_\_ with \_\_\_\_\_ and \_\_\_\_\_

b(4)

EER Status: Acceptable

Consult:	EA:	Acceptable (categorical exclusion provided in the NDA)
	Pharm/Tox:	Acceptable
	Biopharm:	Acceptable
	Methods Validation:	Acceptable
	Microbiology:	N/A

**Drug Substance**

Bromocriptine Mesylate (structure shown below) has six stereogenic centers at positions C-5, C-8, C-2', C-5', C-11' and C-12'. The absolute stereochemistry 5*R*, 8*R*, 2'*R*, 5'*S*, 11'*S*, 12'*S*, is produced with a fix stereochemistry by the natural configuration  $\alpha$ -ergocryptine obtained by fermentation. Bromidation at the C-2 position of  $\alpha$ -ergocryptine does not involve the stereogenic centers present in the molecule.

b(4)

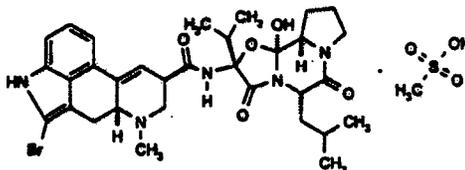
Chemical structure, chemical name, molecular formula and molecular weight are provided below.

**Bromocriptine Mesylate**

$C_{12}H_{16}BrN_5O_5 \cdot CH_3SO_3$   
MW = 654.60 + 96.12 = 750.72  
CAS 22260-51-1

CAS 25260-03-3 (Bromocriptine)

(5*S*)-2-Bromo-12'-hydroxy-2'-(1-methylethyl)-5'-(2-methylpropyl)-ergotaman-3',6',18'-trione monomethanesulfonate (salt)  
Ergotam-17',27',30'-trione, 2-bromo-1'-hydroxy-19'-(1-methyl-ethyl)-28'-(2-methylpropyl)-, monomethanesulfonate (salt) [IUPAC]



Chemistry, Manufacture and Controls information for the drug substance is referred to \_\_\_\_\_ proprietary Type II Drug Master File (DMF) \_\_\_\_\_ DMF \_\_\_\_\_ has been reviewed and its current CMC status is adequate.

b(4)

Bromocriptine mesylate is a white to off white powder (no polymorphs) very sensitive to light with a melting point range between 192 – 196 °C. Its pKa value, measured in water at 25 °C, is 4.9. It is practically insoluble in water, freely soluble in methanol, soluble in ethanol, and sparingly soluble in dichloromethane.

b(4)

Bromocriptine mesylate is manufactured by \_\_\_\_\_

b(4)

The drug substance is packaged in a \_\_\_\_\_ and stored between \_\_\_\_\_  
The retest period of \_\_\_\_\_ at reduced temperature conditions (5 °C ± 3 °C) is fully supported by the stability data.

b(4)

#### Conclusion

Drug substance: The drug substance is satisfactory.

#### Drug Product

The drug product, Cycloset™ (Bromocriptine Mesylate) 0.8 mg Tablets, is an immediate release white round shaped tablet (flat faced beveled edge) with one side debossed "C" and the other debossed "9".

The manufacturing process includes \_\_\_\_\_

b(4)

The in process control for the \_\_\_\_\_ for the \_\_\_\_\_ step, \_\_\_\_\_ in process controls include tablet thickness, weight, hardness and friability.

The drug product is available as 0.8 mg strength tablets. Each table contains \_\_\_\_\_ of bromocriptine mesylate (equivalent to 0.8 mg bromocriptine \_\_\_\_\_). Excipients include \_\_\_\_\_ mg of corn starch \_\_\_\_\_ of citric acid \_\_\_\_\_ of lactose \_\_\_\_\_ of colloidal silicon dioxide \_\_\_\_\_ of magnesium stearate \_\_\_\_\_. The total weight of the tablet is \_\_\_\_\_. All excipients meet compendial requirements.

b(4)

Specifications include appearance (visual), identification (UV and HPLC), Assay by HPLC (bromocriptine \_\_\_\_\_), Purity (bromocriptinine NMT \_\_\_\_\_ any other individual impurity NMT \_\_\_\_\_ and the total impurity content NMT \_\_\_\_\_), dosage uniformity (USP <905>), and dissolution ( \_\_\_\_\_ % at 30 minutes; USP Dissolution Test 2: 0.1 N HCl, 500 mL, apparatus 2, 50 rpm). Cycloset (bromocriptine mesylate) tablets are supplied in 200 and 600 count tablets packaged into \_\_\_\_\_, HDPE bottles respectively.

b(4)

b(4)

The applicant provided stability data from 3 registration batches manufactured by Patheon Pharmaceutical Inc, which includes stability data up to 9 months at room temperature and up to 6 months at 40 °C. In addition, supportive stability data from tablets manufactured by Geneva Pharmaceuticals stored at 25-30 °C/ Ambient RH and 30 °C/60 % RH for periods up to 36 months (6 lots) and by Pliva dd stored at room temperature for up to 24 months (1 lot) were also provided.

Based on stability data, an expiration dating of 18 months at recommended storage conditions "20-25 °C (66-77 °F) in a tight, light resistant container", is granted for the drug product.

**Conclusion**

**Drug product:** The drug product is satisfactory.

**Overall Conclusion:**

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

Ali Al-Hakim, Ph.D.  
Branch Chief, Branch II  
DPA I/ONDQA

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this page is the manifestation of the electronic signature.**

/s/

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Ali Al-Hakim  
10/31/2008 03:32:06 PM  
CHEMIST

**NDA 20-866**

**Cycloset™ (Bromocriptine Mesylate) 0.8 mg Tablets**

**VeroScience, LLC**

**Xavier Ysern, PhD ONDQA/ DPA I/ Branch II**

**NDA Clinical Division DMEP**

# CHEMISTRY REVIEW

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See CMC Review # 7	
<b>III. List of Deficiencies To Be Communicated</b>	<b>(There are no deficiencies to be communicated.)</b>

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

### Chemistry Review Data Sheet

1. **NDA #:** 20-866  
2. **REVIEW #:** 8  
3. **REVIEW DATE:** 14-Oct-2008  
4. **REVIEWER:** Xavier Ysern, PhD

5. **PREVIOUS DOCUMENTS:**

<u>Previous Documents</u>	<u>Document Date</u>
Original:	22-Aug-1997
Amendments:	19-Dec-1997
	31-Mar-1998
	08-Apr-1998
	14-Aug-1998
	02-Oct-1998
	09-Nov-1998
	20-Nov-1998
	23-Nov-1998
	13-Apr-2008

6. **SUBMISSION(S) BEING REVIEWED:**

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment 38	09-Oct-2008 (labeling)
Amendment 39	10-Oct-2008

1. **NAME & ADDRESS OF APPLICANT:**

Name: VeroScience, LLC  
Address: 1334 Main Road  
Tiverton, RI 02878  
Representative: Anthony H. Cincotta, PhD  
President and CSO  
Telephone: 617 966 8413

8. **DRUG PRODUCT NAME/CODE/TYPE:**

- a) Proprietary Name: Cycloset™  
b) Non-Proprietary Name (USAN): Bromocryptine Mesylate Tablets  
c) Code Name/# (ONDC only):  
d) Chem. Type/Submission Priority (ONDC only):  
    • Chem. Type: 3  
    • Submission Priority: S

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

10. **PHARMACOL. CATEGORY:** Hypoglycemic agent.

11. **DOSAGE FORM:** Tablet

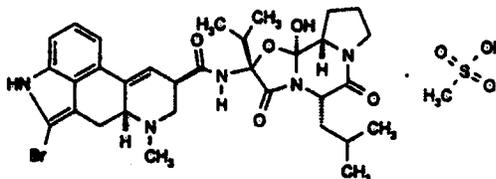
# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

12. **STRENGTH/POTENCY:** 0.8 mg
13. **ROUTE OF ADMINISTRATION:** Oral
14. **Rx/OTC DISPENSED:** Rx
15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):** Not a SPOTS product
16. **CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

Bromocriptine Mesylate

$C_{22}H_{40}BrN_5O_5 \cdot CH_3SO_3$   
 MW = 654.60 + 96.12 = 750.72  
 CAS 22260-51-1  
 CAS 25260-03-3 (Bromocriptine)



(5'-2-Bromo-12'-hydroxy-2'-(1-methyl-ethyl)-5'-(2-methylpropyl)-ergotaman-3',6',18'-trione monomethanesulfonate (salt)  
 Ergotam-17',27',30'-trione, 2-bromo-1'-hydroxy-19'-(1-methyl-ethyl)-28'-(2-methylpropyl)-, monomethanesulfonate (salt) [IUPAC]

17. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

DMF #	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	LOA date/ COMMENTS
Type II				Adequate	22-Aug-2008	15-Jan-2008
Type III				Adequate		24-Jan-2008
				Adequate		04-Feb-2008
				Adequate		22-Jan-2008
				Adequate		22-Jan-2008
				Adequate		24-Jan-2008
				Adequate		01-Feb-2008

<sup>1</sup> Action codes for DMF Table: 1 - DMF Reviewed.  
 Other codes indicate why the DMF was not reviewed, as follows:  
 2 - Type I DMF  
 3 - Reviewed previously and no revision since last review  
 4 - Sufficient information in application  
 5 - Authority to reference not granted  
 6 - DMF not available  
 7 - Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
--	--	--

18. **STATUS:**

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer
Biometrics	N.A.		
EPS	Acceptable	01-Oct-2008	Office of Compliance
Pharm/Tox	--		
Biopharm	--		
LNC	--		
Methods Validation	Revalidation by Agency laboratories not recommended		Part of this review
Labeling (OSE)	Labeling issues still under review (multi disciplinary approach)		
EA	Acceptable		Part of this review
Microbiology	--		

b(4)

## CHEMISTRY REVIEW

### The Executive Summary

#### I. Recommendations

##### A. Recommendation and Conclusion on Approvability

From the CMC point of view, the application is recommended for approval. Based on the submitted stability data, an expiry date of 18 months is granted under the recommended storage conditions: "Store and dispense at: 20-25 °C (66-77 °F) in a tight, light resistant container. See USP Controlled Room Temperature."

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

None.

#### II. Summary of Chemistry Assessments

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

###### Drug Substance

The drug substance is the mesylate salt of the active component bromocriptine. The applicant, VeroScience, LLC, obtains the drug substance from \_\_\_\_\_ Chemistry, Manufacture and Controls' (CMC) information is referred to \_\_\_\_\_ proprietary Type II Drug Master File (DMF). \_\_\_\_\_ DMF \_\_\_\_\_ has been reviewed and its current CMC status is adequate.

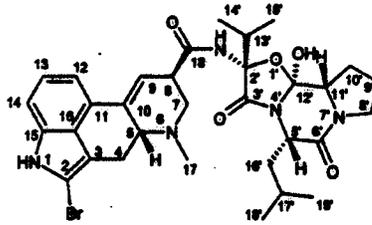
Bromocriptine mesylate is a white to off white powder (no polymorphs) very sensitive to light with a melting point range between 192 – 196 °C. Its pKa value, measured in water at 25 °C, is 4.9. It is practically insoluble in water, freely soluble in methanol, soluble in ethanol, and sparingly soluble in dichloromethane. Regarding its biological activity, bromocriptine is a prolactin inhibitor and a D2 dopamine receptor agonist. [FDA removed the indication for prevention of lactation in 1995, because of concerns with respect to an increased risk of heart attack, seizure and stroke. The indications for the treatment of acromegaly and Parkinson's disease are still in use.]

Bromocriptine mesylate is manufactured by \_\_\_\_\_

b(4)

Bromocriptine free base (structure shown below) has six stereogenic centers at positions C-5, C-8, C-2', C-5', C-11' and C-12'. The absolute stereochemistry 5*R*, 8*R*, 2'*R*, 5'*S*, 11'*S*, 12'*S*, is produced with a fix stereochemistry by the natural configuration  $\alpha$ -ergocryptine obtained by fermentation. Bromination at the C-2 position of  $\alpha$ -ergocryptine does not involve the stereogenic centers present in the molecule.

## CHEMISTRY REVIEW



Bromocriptine mesylate manufactured and supplied by \_\_\_\_\_ complies with the USP bromocriptine mesylate monograph.

The drug substance is packaged in a \_\_\_\_\_ and stored between \_\_\_\_\_ (the retest period of \_\_\_\_\_ at reduced temperature conditions ( $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ ) is fully supported by the stability data.

### Drug Product

The drug product, Cycloset™ (Bromocriptine Mesylate) 0.8 mg Tablets, is an immediate release white round shaped tablet (flat faced beveled edge) with one side debossed "C" and the other debossed "9".

ErgoScience Corp. (Ergo), the original Sponsor of IND 34,661 and NDA 20-866, utilized Geneva Pharmaceuticals Inc. to manufacture the Cycloset™ product (originally called Ergoset) for clinical studies in NDA 20-866 filed on August 18, 1997. Upon transfer of ErgoScience ownership of the IND and NDA to Pliva d.d. (PLIVA), in November, 2003, PLIVA became the new manufacturer of Cycloset™ for ongoing clinical studies. In May 2006, the ownership of IND 34,661 and NDA 20-866 for Cycloset™ (bromocriptine mesylate) tablets was transferred from PLIVA to VeroScience LLC (VeroScience). PLIVA does not longer manufacture drug product and a new contract manufacturer, Patheon Pharmaceuticals Inc. (Patheon), manufactures the drug product.

The manufacturing process by Patheon does not differ appreciably from the manufacturing process carried out by Geneva Pharmaceuticals and by PLIVA. The manufacturing process is conventional for a solid dosage form. It includes:

\_\_\_\_\_ The in process control for the \_\_\_\_\_ are \_\_\_\_\_ in process controls include tablet thickness, weight, hardness and friability.

The drug product is available as 0.8 mg strength tablets. Each table contains \_\_\_\_\_ of bromocriptine mesylate (equivalent to 0.8 mg bromocriptine) \_\_\_\_\_ of corn starch \_\_\_\_\_ of citric acid \_\_\_\_\_ of lactose \_\_\_\_\_ of colloidal silicon dioxide \_\_\_\_\_ of magnesium stearate. The total weight of the tablet is \_\_\_\_\_. All excipients meet compendial requirements.

Drug product specifications comply with USP monograph for Bromocriptine Mesylate Tablets with the exception of the allowed content for bromocriptinine. Bromocriptinine, the enimer of bromocriptine at C-3 and the main degradation product of bromocriptine, is not more than (NMT) \_\_\_\_\_ instead of NMT 3.0 % by USP. Specifications include appearance (visual), identification (UV and HPLC), Assay by HPLC (bromocriptine free base \_\_\_\_\_), Purity (bromocriptinine NMT \_\_\_\_\_), any other individual impurity NMT \_\_\_\_\_ and the total impurity content NMT \_\_\_\_\_, dosage uniformity (USP <905>), and dissolution (Q \_\_\_\_\_ at 30 minutes; USP Dissolution Test 2: 0.1 N HCl, 500 mL, apparatus 2, 50 rpm).

Cycloset (bromocriptine mesylate) tablets are supplied in 200 and 600 count tablets packaged into \_\_\_\_\_ HDPE bottles respectively. Also, a lower count of 21 tablets, packaged into \_\_\_\_\_ HDPE bottles

## CHEMISTRY REVIEW

are distributed as courtesy or professional samples. All bottles will have a tamper-evident seal and a HDPE with \_\_\_\_\_ and \_\_\_\_\_

b(4)

Primary stability data from 3 registration batches manufactured by Patheon Pharmaceutical Inc, includes stability data up to 9 months at room temperature and up to 6 months at 40 °C. Supportive stability data includes data from tablets manufactured by Geneva Pharmaceuticals stored at 25-30 °C/ Ambient RH and 30 °C/60 % RH for periods up to 36 months (6 lots) and by Pliva dd stored at room temperature for up to 24 months (1 lot). The expiration dating of 18 months requested by applicant, under the recommended storage conditions "20-25 °C (66-77 °F) in a tight, light resistant container", is fully supported by the stability data.

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

Cycloset Tablets are indicated as an adjunct to diet and exercise to improve glycaemic control (hyperglycemia) in patients with type 2 diabetes mellitus. The drug product is intended to be used orally. The recommended dose is 1.6 to 4.8 mg once daily, to be taken within two hours after waking in the morning as monotherapy or as combination therapy (see package insert for details).

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

Adequate CMC information has been submitted to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP) manufactured and packaged in accordance with the procedures and recommendations given in the original submission and pertinent amendments. All pending issues: (1) acceptability of the impurity content for the bromocriptinine impurity in the drug product of NMT \_\_\_\_\_, (see Dr. Gemma Kuijpers' Pharmacology Review), and (2) acceptable recommendation for the manufacturing facilities by the Office of Compliance (EER Summary report attached), have been satisfactorily resolved. Based on the evaluation of the provided CMC information, from the chemistry viewpoint this NDA can be approved.

b(4)

## III. Administrative

### A. Reviewer's Signature

Xavier Ysern, PhD Review Chemist/ ONDAQ/ DPA I/ Branch II

### B. Endorsement Block

Al Al-Hakim Branch Chief/ ONDAQ/ DPA I/ Branch II

### C. CC Block

Jana Weber Project Manager/ ONE/ DME

ATTACHED:  
EER Summary Report (2 pages)

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**CHEMISTRY REVIEW**

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FDA CDER EES

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**ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

Application : NDA 20866/000  
Org Code : 510  
Priority : 3S

Sponsor: VEROSCIENCE  
1334 MAIN RD  
TIVERTON, RI 02878

Stamp Date : 22-AUG-1997  
PDUFA Date : 13-OCT-2008  
Action Goal :  
District Goal : 22-APR-1998

Brand Name : ERGOSET(BROMOCRIPTINE  
MESYLATE)TABS 0.8  
Estab. Name:  
Generic Name: BROMOCRIPTINE MESYLATE  
Dosage Form: (TABLET)  
Strength : 0.8 MG

FDA Contacts: X. YSERN Review Chemist 301-796-2410

Overall Recommendation: ACCEPTABLE on 01-OCT-2008 by S. FERGUSON (HFD-322) 301-796-3247  
WITHHOLD on 09-OCT-2002 by S. FERGUSON (HFD-322) 301-796-3247  
ACCEPTABLE on 30-NOV-1998 by DAMBROGIOJ  
WITHHOLD on 28-OCT-1998 by DAMBROGIOJ  
WITHHOLD on 24-AUG-1998 by DAMBROGIOJ

Establishment : \_\_\_\_\_ FEI : \_\_\_\_\_ b(4)

DMF No: 6737

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : \_\_\_\_\_ OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 01-MAY-08 b(4)  
Decision : ACCEPTABLE  
Reason : BASED ON PROFILE

Establishment : CFN : 1510437 FEI : 1510437  
PATHEON PHARMACEUTICALS INC  
2110 E GALBRAITH RD  
CINCINNATI, OH 452371625

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE RELEASE TESTER  
FINISHED DOSAGE STABILITY TESTER

Profile : TCM OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 19-MAY-08  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : \_\_\_\_\_ FEI : \_\_\_\_\_ b(4)

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18-SEP-2008

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

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b(4)

DMF No: 6955

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER  
Profile : OAI Status: NONE  
Last Milestone : OC RECOMMENDATION  
Milestone Date : 01-MAY-08  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

Establishment : CFN \_\_\_\_\_ FEI: \_\_\_\_\_ b(4)

DMF No: \_\_\_\_\_ AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER  
Profile : TCM OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 05-MAY-08  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

Establishment : CFN \_\_\_\_\_ FEI: \_\_\_\_\_ b(4)

DMF No: \_\_\_\_\_ AADA:

Responsibilities: FINISHED DOSAGE PACKAGER  
Profile : TCM OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 01-MAY-08  
Decision : ACCEPTABLE  
Reason : BASED ON PROFILE

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/s/

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Xavier Ysern  
10/15/2008 01:14:29 PM  
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Blair Fraser  
10/15/2008 01:15:20 PM  
CHEMIST

**NDA 20-866**

**Cycloset™ (Bromocriptine Mesylate) 0.8 mg Tablets**

**VeroScience, LLC**

**Xavier Ysern, PhD ONDQA/ DPA I/ Branch II**

**NDA Clinical Division DMEP**

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**CHEMISTRY REVIEW****Chemistry Review Data Sheet****Chemistry Review Data Sheet**

1. **NDA #:** 20-866  
2. **REVIEW #:** 7  
3. **REVIEW DATE:** 25-Sep-2008  
4. **REVIEWER:** Xavier Ysern, PhD

**5. PREVIOUS DOCUMENTS:**

<u>Previous Documents</u>	<u>Document Date</u>
Original:	22-Aug-1997
Amendments:	19-Dec-1997
	31-Mar-1998
	08-Apr-1998
	14-Aug-1998
	02-Oct-1998
	09-Nov-1998
	20-Nov-1998
	23-Nov-1998

**6. SUBMISSION(S) BEING REVIEWED:**

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment 29	13-Apr-2008

**1. NAME & ADDRESS OF APPLICANT:**

Name: VeroScience, LLC  
Address: 1334 Main Road  
Tiverton, RI 02878  
Representative: Anthony H. Cincotta, PhD  
President and CSO  
Telephone: 401 816 0525

**8. DRUG PRODUCT NAME/CODE/TYPE:**

- a) **Proprietary Name:** Cycloset™  
b) **Non-Proprietary Name (USAN):** Bromocryptine Mesylate Tablets  
c) **Code Name/# (ONDC only):**  
d) **Chem. Type/Submission Priority (ONDC only):**  
• **Chem. Type:** 3  
• **Submission Priority:** S

**9. LEGAL BASIS FOR SUBMISSION:** 505(b) (1)**10. PHARMACOL. CATEGORY:** Hypoglycemic agent.**11. DOSAGE FORM:** Tablet**12. STRENGTH/POTENCY:** 0.8 mg

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

13. ROUTE OF ADMINISTRATION: Oral

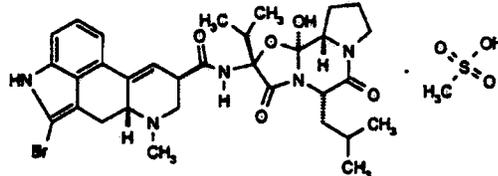
14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): Not a SPOTS product

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

Bromocriptine Mesylate

$C_{32}H_{40}BrN_5O_5 \cdot CH_4SO_3$   
 MW = 654.60 + 96.12 = 750.72  
 CAS 22260-51-1  
 CAS 25260-03-3 (Bromocriptine)



(5<sup>'</sup>)-2-Bromo-12'-hydroxy-2'-(1-methylethyl)-5'-(2-methylpropyl)-ergotaman-3',6',18'-trione monomethanesulfonate (salt)  
 Ergotam-17',27',30'-trione, 2-bromo-1'-hydroxy-19'-(1-methyl-ethyl)-28'-(2-methylpropyl)-, monomethanesulfonate (salt) [IUPAC]

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	LOA date/ COMMENTS
Type II			1	Adequate	22-Aug-2008	15-Jan-2008
Type III				Adequate		24-Jan-2008
				Adequate		04-Feb-2008
				Adequate		22-Jan-2008
				Adequate		22-Jan-2008
				Adequate		24-Jan-2008
				Adequate		01-Feb-2008

<sup>1</sup>Action codes for DMF Table: 1 - DMF Reviewed.

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

- 2 - Type I DMF
- 3 - Reviewed previously and no revision since last review
- 4 - Sufficient information in application
- 5 - Authority to reference not granted
- 6 - DMF not available
- 7 - Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
--	--	--

18. STATUS:

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer
Biometrics	N.A.		
EES	Pending		
Pharm/Tox	--		
Biopharm	--		
LNC	--		
Methods Validation	Revalidation by Agency laboratories not recommended		Part of this review
Labeling (OSE)	Labelling issues still under review (multi disciplinary approach)		
EA	Acceptable		Part of this review
Microbiology	--		

b(4)

# CHEMISTRY REVIEW

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From the CMC point of view, the application is recommended for approval pending: (1) an agreement for the acceptability of the impurity content of the bromocriptinine impurity in the drug product of NMT \_\_\_\_\_ by the pharmacology and medical review disciplines, and (2) an acceptable recommendation for the manufacturing facilities by the Office of Compliance. Based on the submitted stability data, an expiry date of 18 months is granted under the recommended storage conditions: "Store and dispense at: 20-25 °C (66-77 °F) in a tight, light resistant container. See USP Controlled Room Temperature]." b(4)

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

None.

### II. Summary of Chemistry Assessments

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

##### Drug Substance

The drug substance is the mesylate salt of the active component bromocriptine. The applicant, VeroScience, LLC, obtains the drug substance from \_\_\_\_\_ Chemistry, Manufacture and Controls' (CMC) information is referred to \_\_\_\_\_ proprietary Type II Drug Master File (DMF) \_\_\_\_\_ DMF \_\_\_\_\_ has been reviewed and its current CMC status is adequate. b(4)

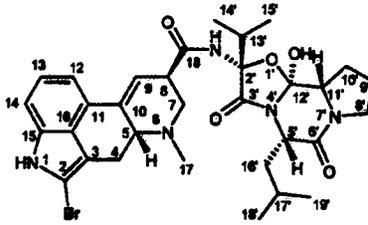
Bromocriptine mesylate is a white to off white powder (no polymorphs) very sensitive to light with a melting point range between 192 - 196 °C. Its pKa value, measured in water at 25 °C, is 4.9. \_\_\_\_\_ b(4)

Regarding its biological activity, bromocriptine is a prolactin inhibitor and a D2 dopamine receptor agonist. [FDA removed the indication for prevention of lactation in 1995, because of concerns with respect to an increased risk of heart attack, seizure and stroke. The indications for the treatment of acromegaly and Parkinson's disease are still in use.]

Bromocriptine mesylate is manufactured by \_\_\_\_\_ b(4)

Bromocriptine \_\_\_\_\_ (structure shown below) has \_\_\_\_\_ b(4)

**CHEMISTRY REVIEW**



Bromocriptine mesylate manufactured and supplied by \_\_\_\_\_ complies with the USP bromocriptine mesylate monograph. b(4)

The drug substance is packaged in a \_\_\_\_\_ and stored between \_\_\_\_\_ the retest period of \_\_\_\_\_ at reduced temperature conditions ( $5\text{ }^{\circ}\text{C} \pm 3\text{ }^{\circ}\text{C}$ ) is fully supported by the stability data. b(4)

**Drug Product**

The drug product, Cycloset™ (Bromocriptine Mesylate) 0.8 mg Tablets, is an immediate release white round shaped tablet (flat faced beveled edge) with one side debossed "C" and the other debossed "9".

ErgoScience Corp. (Ergo), the original Sponsor of IND 34,661 and NDA 20-866, utilized Geneva Pharmaceuticals Inc. to manufacture the Cycloset™ product (originally called Ergoset) for clinical studies in NDA 20-866 filed on August 18, 1997. Upon transfer of ErgoScience ownership of the IND and NDA to Pliva d.d. (PLIVA), in November, 2003, PLIVA became the new manufacturer of Cycloset™ for ongoing clinical studies. In May 2006, the ownership of IND 34,661 and NDA 20-866 for Cycloset™ (bromocriptine mesylate) tablets was transferred from PLIVA to VeroScience LLC (VeroScience). PLIVA does not longer manufacture drug product and a new contract manufacturer, Patheon Pharmaceuticals Inc. (Patheon), manufactures the drug product.

The manufacturing process by Patheon does not differ appreciably from the manufacturing process carried out by Geneva Pharmaceuticals and by PLIVA. The manufacturing process is conventional for a solid dosage form. It includes \_\_\_\_\_ b(4)

\_\_\_\_\_ The in process control for the \_\_\_\_\_ for the \_\_\_\_\_ step \_\_\_\_\_, in process controls include tablet thickness, weight, hardness and friability.

The drug product is available as 0.8 mg strength tablets. Each table contains \_\_\_\_\_ of bromocriptine mesylate (equivalent to 0.8 mg bromocriptine \_\_\_\_\_ of citric acid \_\_\_\_\_ of lactose \_\_\_\_\_ of colloidal silicon dioxide \_\_\_\_\_ and \_\_\_\_\_ of magnesium stearate \_\_\_\_\_ The total weight of the tablet is \_\_\_\_\_ All excipients meet compendial requirements. b(4)

Drug product specifications comply with USP monograph for Bromocriptine Mesylate Tablets with the exception of the allowed content for bromocriptinine. Bromocriptinine, the enantiomer of bromocriptine at C-8 and the main degradation product of bromocriptine, is not more than (NMT) \_\_\_\_\_ instead of NMT \_\_\_\_\_ by USP. Specifications include appearance (visual), identification (UV and HPLC), Assay by HPLC (bromocriptine \_\_\_\_\_ Purity (bromocriptinine NMT \_\_\_\_\_ any other individual impurity NMT \_\_\_\_\_ and the total impurity content NMT \_\_\_\_\_ dosage uniformity (USP <905>), and dissolution (Q \_\_\_\_\_ 30 minutes; USP Dissolution Test 2: 0.1 N HCl, 500 mL, apparatus 2, 50 rpm). b(4)

Cycloset (bromocriptine mesylate) tablets are supplied in 200 and 600 count tablets packaged into \_\_\_\_\_ HDPE bottles respectively. Also, a lower count of 21 tablets, packaged into \_\_\_\_\_ HDPE bottles are distributed as courtesy or professional samples. All bottles will have a tamper-evident seal and a HDPE canister with \_\_\_\_\_ b(4)

## CHEMISTRY REVIEW

Primary stability data from 3 registration batches manufactured by Patheon Pharmaceutical Inc, includes stability data up to 9 months at room temperature and up to 6 months at 40 °C. Supportive stability data includes data from tablets manufactured by Geneva Pharmaceuticals stored at 25-30 °C/ Ambient RH and 30 °C/60 % RH for periods up to 36 months (6 lots) and by Pliva dd stored at room temperature for up to 24 months (1 lot). The expiration dating of 18 months requested by applicant, under the recommended storage conditions "20-25 °C (66-77 °F) in a tight, light resistant container", is fully supported by the stability data.

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

Cycloset Tablets are indicated as an adjunct to diet and exercise to improve glycemic control (hyperglycemia) in patients with type 2 diabetes mellitus. The drug product is intended to be used orally. The recommended dose is 1.6 to 4.8 mg once daily, to be taken within two hours after waking in the morning as monotherapy or as combination therapy (see package insert for details).

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

Adequate CMC information has been submitted to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP) manufactured and packaged in accordance with the procedures and recommendations given in the original submission and pertinent amendments. Based on the evaluation of the provided CMC information, from the chemistry viewpoint this NDA can be approved pending an acceptable recommendation of the cGMP status of the manufacturing facilities by the Office of Compliance.

## III. Administrative

### A. Reviewer's Signature

Xavier Ysern, PhD      Review Chemist/ ONDAQ/ DPA I/ Branch II

### B. Endorsement Block

Al Al-Hakim              Branch Chief/ ONDAQ/ DPA I/ Branch II

### C. CC Block

Jena Weber              Project Manager/ OND/ DMEP

24 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

**CHEMISTRY REVIEW**

□(s)P□&k4S□&17.27c66F 18-SEP-2008

FDA CDER EES

Page 1 of 2

**ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

Application : NDA 20866/000  
Org Code : 510  
Priority : 3S

Sponsor: VEROSCIENCE  
1334 MAIN RD  
TIVERTON, RI 02878

Stamp Date : 22-AUG-1997  
PDUFA Date : 15-OCT-2008  
Action Goal :  
District Goal: 22-APR-1998

Brand Name : ERGOSET(BROMOCRIPTINE  
MESYLATE)TABS 0.8  
Estab. Name:  
Generic Name: BROMOCRIPTINE MESYLATE  
Dosage Form: (TABLET)  
Strength : 0.8 MG

FDA Contacts: X. YSERN Review Chemist 301-796-2410

Overall Recommendation: WITHHOLD on 09-OCT-2002by S. FERGUSON(HFD-322) 301-796-3247  
ACCEPTABLE on 30-NOV-1998by DAMBROGIOJ  
WITHHOLD on 28-OCT-1998by DAMBROGIOJ  
WITHHOLD on 24-AUG-1998by DAMBROGIOJ

Establishment : CFN \_\_\_\_\_ FEI \_\_\_\_\_ b(4)

DMF No: 6737 AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : \_\_\_\_\_ OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 01-MAY-08  
Decision : ACCEPTABLE  
Reason : BASED ON PROFILE

Establishment : CFN : 1510437 FEI : 1510437  
PATHEON PHARMACEUTICALS INC  
2110 E GALBRAITH RD  
CINCINNATI, OH 452371625

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE RELEASE TESTER  
FINISHED DOSAGE STABILITY TESTER

Profile : TCM OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 19-MAY-08  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : \_\_\_\_\_ FEI : \_\_\_\_\_ b(4)

**CHEMISTRY REVIEW**

18-SEP-2008

FDA CDER EES

Page 2 of 2

**ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

DMF No: 6955

AADA:

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**  
Profile : \_\_\_\_\_ OAI Status: NONE  
Last Milestone: **SUBMITTED TO DO**  
Milestone Date: **01-MAY-08**  
:  
:

b(4)

---

Establishment : CFN: \_\_\_\_\_ FEI: \_\_\_\_\_  
[ ]  
DMF No: \_\_\_\_\_ AADA:  
Responsibilities: **FINISHED DOSAGE MANUFACTURER**  
Profile : **TCM** OAI Status: NONE  
Last Milestone: **OC RECOMMENDATION**  
Milestone Date: **05-MAY-08**  
Decision : **ACCEPTABLE**  
Reason : **DISTRICT RECOMMENDATION**

b(4)

---

Establishment : CFN: \_\_\_\_\_ FEI: \_\_\_\_\_  
[ ]  
DMF No: \_\_\_\_\_ AADA:  
Responsibilities: **FINISHED DOSAGE PACKAGER**  
Profile : **TCM** OAI Status: NONE  
Last Milestone: **OC RECOMMENDATION**  
Milestone Date: **01-MAY-08**  
Decision : **ACCEPTABLE**  
Reason : **BASED ON PROFILE**

b(4)

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

/s/

-----  
Xavier Ysern  
10/6/2008 10:58:06 AM  
CHEMIST

Ali Al-Hakim  
10/6/2008 11:03:42 AM  
CHEMIST



FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Application: NDA 20866/000 Priority: 3S Org Code: 510  
 Stamp: 22-AUG-1997 Regulatory Due: 22-NOV-1998 Action Goal: District Goal: 22-APR-1998  
 Applicant: ERGO Brand Name: ERGOSET(BROMOCRIPTINE MESYLATE)TABS 0.8  
 100 1ST AVE 4TH FL Established Name:  
 CHARLESTOWN, MA 021292051 Generic Name: BROMOCRIPTINE MESYLATE  
 Dosage Form: TAB (TABLET)  
 Strength: 0.8, \_\_\_\_\_MG b(4)

FDA Contacts: X. YERN (HFD-510) 301-827-6430 , Review Chemist

Overall Recommendation:

ACCEPTABLE on 30-NOV-1998 by J. D AMBROGIO (HFD-324) 301-827-0062  
 WITHHOLD on 28-OCT-1998 by J. D AMBROGIO (HFD-324) 301-827-0062  
 WITHHOLD on 24-AUG-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: \_\_\_\_\_ DMF No: \_\_\_\_\_  
 \_\_\_\_\_ AADA No: b(4)

Profile: \_\_\_\_\_ OAI Status: NONE Responsibilities: DRUG SUBSTANCE MANUFACTURER b(4)  
 Last Milestone: OC RECOMMENDATION  
 Milestone Date: 28-APR-1998  
 Decision: ACCEPTABLE  
 Reason: DISTRICT RECOMMENDATION

Establishment: 1717759 DMF No:  
 GENEVA PHARMACEUTICALS INC AADA No:  
 2555 WEST MIDWAY BLVD  
 BROOMFIELD, CO 80038

Profile: TCM OAI Status: NONE Responsibilities: FINISHED DOSAGE MANUFACTURER  
 Last Milestone: OC RECOMMENDATION  
 Milestone Date: 30-NOV-1998  
 Decision: ACCEPTABLE  
 Reason: DISTRICT RECOMMENDATION

Establishment: \_\_\_\_\_ DMF No: \_\_\_\_\_ b(4)  
 \_\_\_\_\_ AADA No: b(4)

Profile: CFN OAI Status: NONE Responsibilities: DRUG SUBSTANCE MANUFACTURER  
 Last Milestone: OC RECOMMENDATION  
 Milestone Date: 28-OCT-1998





FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Application: NDA 20866/090  
Stamp: 22-AUG-1997 Regulatory Due: 22-NOV-1998  
Applicant: ERGO  
100 1ST AVE 4TH FL  
CHARLESTOWN, MA 021292051

Priority: 3S  
Action Goal:  
Brand Name: ERGOSET(BROMOCRIPTINE  
MESYLATE)TABS 0.8  
Established Name:  
Generic Name: BROMOCRIPTINE MESYLATE  
Dosage Form: TAB (TABLET)  
Strength: 0.8 MG b(4)

Org Code: 510

District Goal: 22-APR-1998

FDA Contacts: X. YSERN (HFD-510) 301-827-6430 , Review Chemist

Overall Recommendation:

WITHHOLD on 28-OCT-1998 by J. D AMBROGIO (HFD-324) 301-827-0062  
WITHHOLD on 24-AUG-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

DMF No: \_\_\_\_\_  
AADA No: b(4)

Profile: CSN OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 28-APR-1998  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE  
MANUFACTURER

Establishment: 1717759  
GENEVA PHARMACEUTICALS INC  
2555 WEST MIDWAY BLVD  
BROOMFIELD, CO 80038

DMF No:  
AADA No:

Profile: TCM OAI Status: NONE  
Last Milestone: ASSIGNED INSPECTION TO IB  
Milestone Date: 13-NOV-1998

Responsibilities: FINISHED DOSAGE  
MANUFACTURER

Establishment: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

DMF No: \_\_\_\_\_  
AADA No: b(4)

Profile: \_\_\_\_\_ OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 28-OCT-1998  
Decision: ACCEPTABLE

Responsibilities: DRUG SUBSTANCE  
MANUFACTURER b(4)

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Reason: **FIRM RESPONSE TO DEFIC. ADEQ**

Establishment: \_\_\_\_\_

DMF No:

AADA No:

b(4)

Profile: TCM

OAI Status: NONE

Responsibilities: **FINISHED DOSAGE PACKAGER**

Last Milestone: **OC RECOMMENDATION**

Milestone Date: **23-DEC-1997**

Decision: **ACCEPTABLE**

Reason: **DISTRICT RECOMMENDATION**

Printed by Xavier Ysern  
**Electronic Mail Message**

**Date:** 16-Nov-1998 04:01pm  
**From:** wsherer  
wsherer@ora.fda.gov  
**Dept:**  
**Tel No:**

**Subject: Re: NDA 20-866**

Some months ago we attempted to conduct an inspection with respect to this NDA. However, the firm was not ready for inspection and we recommended withholding the application pending re-inspection. The firm is now ready for inspection and we will begin the inspection Nov 18, 1998. We may have some idea of what the firm's compliance status is after three days, but since November 22 is a Sunday, I do not think it is realistic to believe that we will have a recommendation before November 22. We can probably advise you of the firm's status on Nov 23 or 24.

Bill Sherer, Denver District Pre-Approval Manager

FERGUSONS@cdcr.fda.gov Wrote:

What is the status of the above referenced application?  
This application has  
a Nov. 22, 1998 user fee date. Will the district make a  
recommendation before  
the user fee date? Please respond....Thanks.

Shirnette



2 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

FDA CDER ERS  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

Application: NDA 20866/000 Action Goal:  
 Stamp: 22-AUG-1997 District Goal: 22-APR-1998  
 Regulatory Due: 22-NOV-1998 Brand Name: ERGOSET (BROMOCRIPTINE  
 MESYLATE) TABS 0.8  
 Applicant: ERGO Etab. Name:  
 100 1ST AVE 4TH FL Generic Name: BROMOCRIPTINE MESYLATE  
 CHARLESTOWN, MA 021292051  
 Priority: 3S Dosage Form: (TABLET)  
 Org Code: 510 Strength: 0.8, \_\_\_\_\_ MG b(4)

Application Comment: FIRM STATED THAT THEY WILL NOT BE READY FOR INSPECTION UNTIL  
 OCTOBER 1998 (on 13-AUG-1998 by W. SHERER (HFR-SW250) 303-236-  
 3050)

FDA Contacts: X. YSERN (HFD-510) 301-827-6430, Review Chemist

Overall Recommendation: WITHHOLD on 28-OCT-1998 by J. D AMBROGIO (HFD-324) 301-827-0062  
 WITHHOLD on 24-AUG-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: \_\_\_\_\_

DMF No. \_\_\_\_\_ AADA: b(4)  
 Responsibilities: DRUG SUBSTANCE MANUFACTURER  
 Profile: \_\_\_\_\_ OAI Status: NONE b(4)  
 Etab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-DEC-1997				YSERNX
SUBMITTED TO DO	23-DEC-1997	GMP			EGASM
ASSIGNED INSPECTION	23-DEC-1997	GMP			EGASM
INSPECTION PERFORMED	06-FEB-1998		05-FEB-1998		EGASM
DO RECOMMENDATION	28-APR-1998			ACCEPTABLE INSPECTION	EGASM
OC RECOMMENDATION	28-APR-1998			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

Establishment: 1717759

GENEVA PHARMACEUTICALS INC  
 2555 WEST MIDWAY BLVD  
 BROOMFIELD, CO 80038

DMF No: \_\_\_\_\_ AADA:  
 Responsibilities: FINISHED DOSAGE MANUFACTURER  
 Profile: TCM OAI Status: NONE  
 Etab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-DEC-1997				YSERNX
SUBMITTED TO DO	23-DEC-1997	10D			DAMBROGIOJ
ASSIGNED INSPECTION	20-FEB-1998	PS			WSHERER
INSPECTION SCHEDULED	20-FEB-1998		04-MAY-1998		WSHERER
DO RECOMMENDATION	19-AUG-1998			WITHHOLD FIRM NOT READY	DAMBROGIOJ
OC RECOMMENDATION	19-AUG-1998			WITHHOLD FIRM NOT READY	DAMBROGIOJ

FIRM SAYS THEY WILL BE READY 10/98.

FIRM STATED THAT THEY WOULD BE READY 10/98.

Establishment: 9611868

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

DMF No: \_\_\_\_\_ AADA: \_\_\_\_\_  
Responsibilities: DRUG SUBSTANCE MANUFACTURER  
Profile: \_\_\_\_\_ OAI Status: NONE  
Estab. Comment:

b(4)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-DEC-1997				YSERNK
SUBMITTED TO DO	23-DEC-1997	GMP			EGASM
ASSIGNED INSPECTION	23-DEC-1997	GMP			EGASM
ASSIGNED INSPECTION	04-FEB-1998	GMP			IRIVERA
INSPECTION SCHEDULED	05-JUN-1998		19-JUN-1998		EGASM
INSPECTION PERFORMED	30-JUN-1998		24-JUN-1998		EGASM
RECOMMENDING WITHHOLD DO RECOMMENDATION	24-AUG-1998			WITHHOLD COMPUTER VALIDATION INADEQUATE LAB CONTROLS PRODUCTION/PROCESS CONTROLS RECORDS/REPORTS	DAMBROGIOJ
WARNING LETTER TO BE ISSUED. OC RECOMMENDATION	24-AUG-1998			WITHHOLD WARNING LETTER ISSUED	DAMBROGIOJ
DO RECOMMENDATION	28-OCT-1998			ACCEPTABLE	DAMBROGIOJ
OC RECOMMENDATION	28-OCT-1998			ADEQUATE FIRM RESPONSE ACCEPTABLE FIRM RESPONSE TO DEFIC. ADEQUA	DAMBROGIOJ

Establishment: \_\_\_\_\_

b(4)

DMF No: \_\_\_\_\_ AADA: \_\_\_\_\_  
Responsibilities: FINISHED DOSAGE PACKAGER  
Profile: TCM OAI Status: NONE  
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-DEC-1997				YSERNK
OC RECOMMENDATION	23-DEC-1997			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

**DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510**  
**Review of Chemistry, Manufacturing and Controls**

**NDA 20-866**

**Chemistry Review # 3**

**Date Reviewed: 03-OCT-1998**

<b>Submission Type</b>	<b>Document Date</b>	<b>CDER Date</b>	<b>Assigned Date</b>
Original	22-AUG-1997	22-AUG-1997	26-AUG-1997
	19-DEC-1997	20-DEC-1997	20-DEC-1997
	14-AUG-1998	17-AUG-1998	

**Applicant:** Ergo Research Corporation (ErgoScience)  
100 First Avenue Phone: (617) 241-6800  
Charlestown, MA 02129-2051 Fax: (617) 241-8822

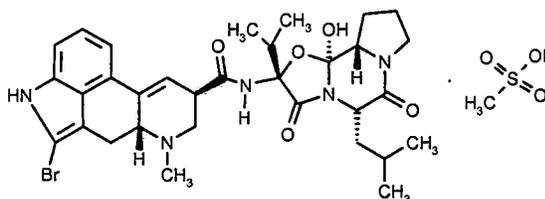
<b>Drug Product Name</b>	Proprietary:	Ergoset
	Nonproprietary/Established/USAN:	Bromocriptine Mesylate
	Chem. Type/ Ther. Class:	5 S

**Pharmacological Category/indication:** Hypoglycemic Agent. Adjunct to diet to improve glycemic control in patients with NIDDM whose hyperglycemia cannot be managed by diet alone.

<b>Dosage Form:</b> Tablets	<b>Strength(s):</b> 0.8, _____ mg	<b>b(4)</b>
<b>Route of Administration:</b> Oral	<b>Dispensed:</b> Rx	

**Chemical Name, Structural Formula, Molecular Formula, Molecular Weight:**

Bromocriptine Mesylate  
 $C_{32}H_{40}BrN_5O_5 \cdot CH_4SO_3$   
MW = 654.60 + 96.12 = 750.72  
CAS 22260-51-1  
CAS 25614-03-3 (Bromocriptine)



2-Bromoergocryptine monomethanesulfonate (salt) or Ergotaman-3',6',18'-trione,2-bromo-12'-hydroxy-2'-(1-methylethyl)-5'-(2-methylpropyl)-, monomethane sulfonate (salt)

**Remarks:** The originally proposed tradename "Ergoset" was found unacceptable by the CDER Labeling and Nomenclature Committee (NLC). The applicant proposed two new tradenames \_\_\_\_\_ and "Cycloset" to be considered by the NLC. The NLC found the proposed tradename \_\_\_\_\_ unacceptable, but found **CYCLOSET acceptable** (consult attached, on pages 2 and 3). The recommendation of the **Office of Compliance recommendation** still remains to **withhold approval** (copy of the Evaluation Report on pages 4 and 5) one of the facilities is not ready for inspection, and another facility has received a warning letter.

**Conclusions & Recommendations:** Trademark "**Cycloset**" acceptable as tradename for **Bromocriptine Mesylate tablets**. Although satisfactory CMC information has been provided for both, drug substance, Bromocriptine Mesylate, and drug product, Bromocriptine Mesylate Tablets (see CMC Review # 1), because the "**withhold approval**" recommendation from the **Office of Compliance** has not been changed, from the Chemistry viewpoint the application cannot be approved.

Orig. NDA 20-866  
cc: HFD-510/Division File  
HFD-510/RMisbin/SMoore/RSteigerwalt/JWeber/XYsern Xavier Ysern, PhD  
HFD-820/Jgibbs

R/D Init by: **NA** filename: /nda/20866\_3.doc

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT # 10825 HFD# 510 PROPOSED PROPRIETARY NAME: \_\_\_\_\_ PROPOSED ESTABLISHED NAME: bromocriptine mesylate  
ATTENTION: Dr. Xavier Yarn \_\_\_\_\_

b(4)

A. Look-alike/Sound-alike

Potential for confusion:

[Empty box for look-alike/sound-alike comparison]

\_\_\_\_ Low \_\_\_\_ Medium \_\_\_\_ High  
\_\_\_\_ Low \_\_\_\_ Medium \_\_\_\_ High

B. Misleading Aspects:

C. Other Concerns:

[Empty box for misleading aspects]

While proprietary names don't necessarily have a connection with the properties of a drug, the LNC could not understand the significance of either \_\_\_\_\_ or \_\_\_\_\_ in this brand name.

b(4)

D. Established Name

xxx Satisfactory  
\_\_\_\_ Unsatisfactory/Reason

[Empty box for unsatisfactory reason]

Recommended Established Name

[Empty box for recommended established name]

E. Proprietary Name Recommendations:

\_\_\_\_ ACCEPTABLE      xxx UNACCEPTABLE

F. Signature of Chair/Date

D. Berina 9/24/98

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT # 10625 HFD# 510 PROPOSED PROPRIETARY NAME: CYCLOSEY PROPOSED ESTABLISHED NAME: bromocriptine mesylate  
ATTENTION: Dr. Xavier Ysem

A. Look-alike/Sound-alike

CYTOTEC  
SYLLACT  
CYCLOGORT  
CYCLOPAR

Potential for confusion:

\_\_\_ Low XXX Medium \_\_\_ High  
XXX Low \_\_\_ Medium \_\_\_ High  
XXX Low \_\_\_ Medium \_\_\_ High  
\_\_\_ Low XXX Medium \_\_\_ High  
\_\_\_ Low \_\_\_ Medium \_\_\_ High

B. Misleading Aspects:

C. Other Concerns:

--	--

D. Established Name

XXX Satisfactory  
\_\_\_ Unsatisfactory/Reason

[Empty box for Unsatisfactory/Reason]

Recommended Established Name

[Empty box for Recommended Established Name]

E. Proprietary Name Recommendations:

XXX ACCEPTABLE \_\_\_ UNACCEPTABLE

F. Signature of Chair/Date:

D. Borja 4/22/07

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

Application: NDA 20866/000  
Stamp: 22-AUG-1997  
Regulatory Due: 22-AUG-1998  
Applicant: ERGO  
100 1ST AVE 4TH FL  
CHARLESTOWN, MA 021292051  
Priority: 3S  
Org Code: 510

Action Goal:  
District Goal: 22-APR-1998  
Brand Name: ERGOSET (BROMOCRIPTINE  
MESYLATE) TABS 0.8  
Estab. Name:  
Generic Name: BROMOCRIPTINE MESYLATE  
Dosage Form: (TABLET)  
Strength: 0.8, \_\_\_\_\_ MG b(4)

Application Comment: FIRM STATED THAT THEY WILL NOT BE READY FOR INSPECTION UNTIL  
OCTOBER 1998 (on 13-AUG-1998 by W. SHERER (MFR-SW250) 303-236-  
3050)

FDA Contacts: X. YSERN (HFD-510) 301-827-6430 , Review Chemist

Overall Recommendation: WITHHOLD on 24-AUG-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: \_\_\_\_\_

b(4)

DMF No: \_\_\_\_\_ AADA:  
Responsibilities: DRUG SUBSTANCE MANUFACTURER  
Profile: \_\_\_\_\_ OAI Status: NONE  
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-DEC-1997				YSERNX
SUBMITTED TO DO	23-DEC-1997	GMP			EGASM
ASSIGNED INSPECTION	23-DEC-1997	GMP			EGASM
INSPECTION PERFORMED	06-FEB-1998		05-FEB-1998		EGASM
DO RECOMMENDATION	28-APR-1998			ACCEPTABLE	EGASM
OC RECOMMENDATION	28-APR-1998			INSPECTION ACCEPTABLE	EGASM
				DISTRICT RECOMMENDATION	

Establishment: 1717759

GENEVA PHARMACEUTICALS INC  
2555 WEST MIDWAY BLVD  
BROOMFIELD, CO 80038

DMF No: \_\_\_\_\_ AADA:  
Responsibilities: FINISHED DOSAGE MANUFACTURER  
Profile: TCM OAI Status: NONE  
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-DEC-1997				YSERNX
SUBMITTED TO DO	23-DEC-1997	10D			DAMBROGIOJ
ASSIGNED INSPECTION	20-FEB-1998	PS			WSHERER
INSPECTION SCHEDULED	20-FEB-1998		04-MAY-1998		WSHERER
DO RECOMMENDATION	19-AUG-1998			WITHHOLD	DAMBROGIOJ
				FIRM NOT READY	
FIRM SAYS THEY WILL BE READY 10/98.					
OC RECOMMENDATION	19-AUG-1998			WITHHOLD	DAMBROGIOJ
				FIRM NOT READY	

FIRM STATED THAT THEY WOULD BE READY 10/98.

Establishment: \_\_\_\_\_

b(4)

DMF No: \_\_\_\_\_ AADA:  
 Responsibilities: DRUG SUBSTANCE MANUFACTURER  
 Profile: \_\_\_\_\_ OAI Status: NONE  
 Estab. Comment:

b(4)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-DEC-1997				YSERNX
SUBMITTED TO DO	23-DEC-1997	GMP			EGASM
ASSIGNED INSPECTION	23-DEC-1997	GMP			EGASM
ASSIGNED INSPECTION	04-FEB-1998	GMP			IRIVERA
INSPECTION SCHEDULED	05-JUN-1998		19-JUN-1998		EGASM
INSPECTION PERFORMED	30-JUN-1998		24-JUN-1998		EGASM
RECOMMENDING WITHHOLD DO RECOMMENDATION	24-AUG-1998			WITHHOLD COMPUTER VALIDATION INADEQUATE LAB CONTROLS PRODUCTION/PROCESS CONTROLS RECORDS/REPORTS	DAMBROGIOJ
WARNING LETTER TO BE ISSUED. OC RECOMMENDATION	24-AUG-1998			WITHHOLD WARNING LETTER ISSUED	DAMBROGIOJ

Establishment: \_\_\_\_\_

DMF No: \_\_\_\_\_ AADA: \_\_\_\_\_  
 Responsibilities: FINISHED DOSAGE PACKAGER  
 Profile: TCM OAI Status: NONE  
 Estab. Comment:

b(4)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-DEC-1997				YSERNX
OC RECOMMENDATION	23-DEC-1997			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

**DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510**  
**Review of Chemistry, Manufacturing and Controls**

**NDA 20-866**

**Chemistry Review # 2**

**Date Reviewed: 20-AUG-1998**

Submission Type	Document Date	CDER Date	Assigned Date
Original	22-AUG-1997	22-AUG-1997	26-AUG-1997
	19-DEC-1997	20-DEC-1997	20-DEC-1997

**Applicant:** Ergo Research Corporation (ErgoScience)  
100 First Avenue Phone: (617) 241-6800  
Charlestown, MA 02129-2051 Fax: (617) 241-8822

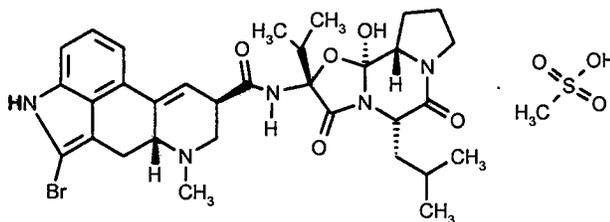
<b>Drug Product Name</b>	Proprietary:	Ergoset
	Nonproprietary/Established/USAN:	Bromocriptine Mesylate
	Chem. Type/ Ther. Class:	5 S

**Pharmacological Category/indication:** Hypoglycemic Agent. Adjunct to diet to improve glycemic control in patients with NIDDM whose hyperglycemia cannot be managed by diet alone.

**Dosage Form:** Tablets **Strength(s):** 0.8 \_\_\_\_\_ mg **b(4)**  
**Route of Administration:** Oral **Dispensed:** Rx

**Chemical Name, Structural Formula, Molecular Formula, Molecular Weight:**

Bromocriptine Mesylate  
 $C_{32}H_{40}BrN_5O_5 \cdot CH_4SO_3$   
MW = 654.60 + 96.12 = 750.72  
CAS 22260-51-1  
CAS 25614-03-3 (Bromocriptine)



2-Bromoergocryptine monomethanesulfonate (salt) or Ergotaman-3',6',18'-trione,2-bromo-12'-hydroxy-2'-(1-methylethyl)-5'-(2-methylpropyl)-, monomethane sulfonate (salt)

**Remarks:** : Satisfactory CMC information has been provided for drug substance, Bromocriptine Mesylate, and drug product, Bromocriptine Mesylate Tablets. Both drug substance and drug product meet compendial requirements (see CMC Review # 1). The pending result from the inspection (requested on December 23, 1997) of the Geneva Pharmaceutical Broomfield's facility has been issued and the **Office of Compliance recommendation** is to **withhold approval** (withhold decision August 19, 1998) because the firm was not ready for the inspection (page 2). A copy of the Evaluation Report is shown on pages 3 and 4.

**Conclusions & Recommendations:** Although satisfactory CMC information has been provided for both, drug substance, Bromocriptine Mesylate, and drug product, Bromocriptine Mesylate Tablets (see CMC Review # 1). From the Chemistry viewpoint the application cannot be approved because the drug product manufacturing facility is not ready.

Orig. NDA 20-866  
cc: HFD-510/Division File  
HFD-510/AFleming/SMoore/RSteigerwalt/JWeber/XYsern  
HFD-820/JGibbs

Xavier Ysern, PhD

R/D Init by:

filename: /nda/20866\_2.doc

**NA**

1   Page(s) Withheld

       Trade Secret / Confidential (b4)

       Draft Labeling (b4)

       Draft Labeling (b5)

  ✓   Deliberative Process (b5)

CDER Establishment Evaluation Report  
for August 20, 1998

Page 1 of 2

Application: NDA 20866/000  
Stamp: 22-AUG-1997 Regulatory Due: 22-AUG-1998  
Applicant: ERGO  
100 1ST AVE 4TH FL  
CHARLESTOWN, MA 021292051

Priority: 3S Org Code: 510  
Action Goal: District Goal: 22-APR-1998  
Brand Name: ERGOSET(BROMOCRIPTINE  
MESYLATE) TABS 0.8  
Established Name:  
Generic Name: BROMOCRIPTINE MESYLATE  
Dosage Form: TAB (TABLET)  
Strength: 0.8 MG b(4)

FDA Contacts: X. YSERN (HFD-510) 301-827-6430 , Review Chemist

Overall Recommendation:

Establishment: \_\_\_\_\_ DMF No: \_\_\_\_\_  
AADA No: b(4)

Profile: \_\_\_\_\_ OAI Status: NONE Responsibilities: DRUG SUBSTANCE  
Last Milestone: OC RECOMMENDATION MANUFACTURER  
Milestone Date 28-APR-1998  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION

Establishment: 1717759 DMF No:  
GENEVA PHARMACEUTICALS INC AADA No:  
2555 WEST MIDWAY BLVD  
BROOMFIELD, CO 80038

Profile: TCM OAI Status: NONE Responsibilities: FINISHED DOSAGE  
Last Milestone: OC RECOMMENDATION MANUFACTURER  
Milestone Date 19-AUG-1998  
Decision: WITHHOLD  
Reason: FIRM NOT READY

Establishment: \_\_\_\_\_ DMF No: \_\_\_\_\_  
AADA No: b(4)

Profile: \_\_\_\_\_ OAI Status: NONE Responsibilities: DRUG SUBSTANCE  
Last Milestone: INSPECTION PERFORMED MANUFACTURER  
Milestone Date 30-JUN-1998

Establishment: \_\_\_\_\_ DMF No: b(4)

CDER Establishment Evaluation Report  
for August 20, 1998

Page 2 of 2

AADA No:

b(4)

Profile: TCM            OAI Status: NONE            Responsibilities: FINISHED DOSAGE PACKAGER  
Last Milestone: OC RECOMMENDATION  
Milestone Date 23-DEC-1997  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION

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**DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510**  
**Review of Chemistry, Manufacturing and Controls**

**NDA 20-866**                      **Chemistry Review # 1**                      **Date Reviewed: 19-MAY-1998**

<b>Submission Type</b>	<b>Document Date</b>	<b>CDER Date</b>	<b>Assigned Date</b>
Original	22-AUG-1997	22-AUG-1997	26-AUG-1997
Amendment # 1	19-DEC-1997	20-DEC-1997	20-DEC-1997

**Applicant:** Ergo Research Corporation (ErgoScience)  
100 First Avenue                      Phone: (617) 241-6800  
Charlestown, MA 02129-2051                      Fax: (617) 241-8822

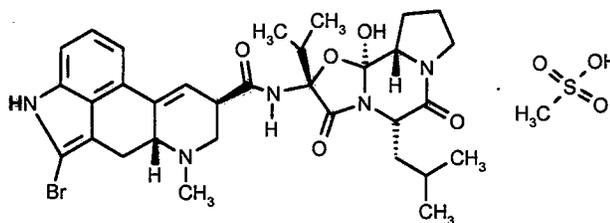
**Drug Product Name** Proprietary: Ergoset  
Nonproprietary/Established/USAN: Bromocriptine Mesylate  
Chem.Type/ Ther.Class: 5 S

**Pharmacological Category/indication:** Hypoglycemic Agent. Adjunct to diet to improve glycemic control in patients with NIDDM whose hyperglycemia cannot be managed by diet alone.

**Dosage Form:** Tablets                      **Strength(s):** 0.8 \_\_\_\_\_ .mg                      **b(4)**  
**Route of Administration:** Oral                      **Dispensed:** 

**Chemical Name, Structural Formula, Molecular Formula, Molecular Weight:**

Bromocriptine Mesylate  
 $C_{32}H_{40}BrN_5O_5 \cdot CH_4SO_3$   
MW = 654.60 + 96.12 = 750.72  
CAS 22260-51-1  
CAS 25614-03-3 (Bromocryptine)



2-Bromoergocryptine monomethanesulfonate (salt) or Ergotaman-3',6',18'-trione,2-bromo-12'-hydroxy-2'-(1-methylethyl)-5'-(2-methylpropyl)-, monomethane sulfonate (salt)

**Conclusions & Recommendations:** Satisfactory CMC information has been provided for drug substance, Bromocriptine Mesylate, and drug product, Bromocriptine Mesylate Tablets. Both drug substance and drug product meet compendial requirements. From the Chemistry viewpoint the application is approvable pending satisfactory results of the inspection of the manufacturing facilities and an acceptable trade name. See Draft Deficiencies and Comments.

Orig. NDA 20-866  
cc: HFD-510/Division File  
HFD-510/AFleming/SMoore/RSteigerwalt/JWeber/XYsern  
HFD-820/JGibbs

Xavier Ysern, PhD

R/D Init by:

AE

filename: /nda/20866\_1.doc

25 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

CDER Establishment Evaluation Report  
for May 19, 1998

Page 1 of 2

Application: **NDA 20866/000**  
Stamp: **22-AUG-1997** Regulatory Due: **22-AUG-1998**  
Applicant: **ERGO**  
**100 1ST AVE 4TH FL**  
**CHARLESTOWN, MA 021292051**

Priority: **3S** Org Code: **510**  
Action Goal: District Goal: **22-APR-1998**  
Brand Name: **ERGOSET(BROMOCRIPTINE**  
**MESYLATE)TABS 0.8**

Established Name:  
Generic Name: **BROMOCRIPTINE MESYLATE**  
Dosage Form: **TAB (TABLET)**  
Strength: **0.8, \_\_\_\_\_ MG** **b(4)**

FDA Contacts: **X. YSERN** (HFD-510) **301-827-6430**, Review Chemist

Overall Recommendation:

Establishment: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

DMF No: \_\_\_\_\_ **b(4)**  
AADA No:

Profile: \_\_\_\_\_ OAI Status: **NONE**  
Last Milestone: **OC RECOMMENDATION**  
Milestone Date: **28-APR-1998**  
Decision: **ACCEPTABLE**  
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE**  
**MANUFACTURER**

Establishment: **1717759**  
**GENEVA PHARMACEUTICALS INC**  
**2555 WEST MIDWAY BLVD**  
**BROOMFIELD, CO 80038**

DMF No:  
AADA No:

Profile: **TCM** OAI Status: **NONE**  
Last Milestone: **INSPECTION SCHEDULED**  
Milestone Date: **20-FEB-1998**

Responsibilities: **FINISHED DOSAGE**  
**MANUFACTURER**

Establishment: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

DMF No: \_\_\_\_\_ **b(4)**  
AADA No:

Profile: \_\_\_\_\_ OAI Status: **NONE**  
Last Milestone: **ASSIGNED INSPECTION TO IB**  
Milestone Date: **04-FEB-1998**

Responsibilities: **DRUG SUBSTANCE**  
**MANUFACTURER**

Establishment: \_\_\_\_\_ **b(4)**

DMF No:

CDER Establishment Evaluation Report  
for May 19, 1998

Page 2 of 2

AADA No:

b(4)

Profile: TCM                      OAI Status: NONE                      Responsibilities: FINISHED DOSAGE PACKAGER  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 23-DEC-1997  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION