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

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 α-ergocryptine obtained by fermentation. Bromidation at the C-2 position of α-ergocryptine does not involve the stereogenic centers present in the molecule.

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

Bromocriptine Mesylate

C_{13}H_{26}BrN_{4}O_{7}CH_{2}SO_{3}
MW = 654.60 + 96.12 = 750.72
CAS 22260-51-1
CAS 25260-03-3 (Bromocryptine)
(5')-3-Bromo-12'-hydroxy-2'-(1-methylpropyl)-5'-(2-methylpropyl)-ergotamin-3',6',18-trione monomethanesulfonate (salt)
Ergotamin-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 propriety Type II Drug Master File (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.

Bromocriptine mesylate is manufactured by

The drug substance is packaged in and stored between

The retest period of at reduced temperature conditions (5 °C ± 3 °C) is fully supported by the stability data.

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

The in process control for the for the

in process controls include tablet thickness, weight, hardness and friability.

The drug product is available as 0.8 mg strength tablets. Each tablet 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.

Specifications include appearance (visual), identification (UV and HPLC), Assay by HPLC (bromocriptine), Purity (bromocriptine 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.
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/JONDQA
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
________________________
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
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   C. CC Block 7

Chemistry Assessment
   See CMC Review #7

III. List of Deficiencies To Be Communicated (There are no deficiencies to be communicated.)
CHEMISTRY REVIEW

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:

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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:

Bromocriptide Mesylate

C_{22}H_{24}BrN_{4}O_{7}·CH_{2}SO_{3}

MW = 654.60 + 96.12 = 750.72

CAS 22260-51-1

CAS 22260-03-3 (Bromocriptide)

\( \text{15}^{\circ\prime}-2\)-Bromo-12'-hydroxy-\text{2'}-(1-methyl-ethyl)-5'-(2-methyl-propyl)-ergotamine-3',6',18-trione mononemethanesulphonate (salt)

Ergotamine-17',27',30'-trione, 2-bromo-1'-hydroxy-19'-\text{1}(1-methyl-ethyl)-28'-(2-methyl-propyl), mononemethanesulphonate (salt) [IUPAC]

17. RELATED/SUPPORTING DOCUMENTS:

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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")

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

B. Other Documents:

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NDA 20-866 CMC Review # 8 Page 4 of 9
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--as 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 5R, 8R, 2'R, 5'S, 11'S, 12'S, is produced with a fix stereochemistry by the natural configuration α-ergocrystine obtained by fermentation. Bromidation at the C-2 position of α-ergocrystine does not involve the stereogenic centers present in the molecule.
Bromocriptine mesylate manufactured and supplied by —— complies with the USP bromocriptine mesylate monograph.

The drug substance is packaged in —— and stored between ———. The latest period of ——— at reduced temperature conditions (5 °C ± 3 °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 manufacture drug product and a new contract manufacturer, Pathoen Pharmaceuticals Inc. (Pathoen), manufactures the drug product.

The manufacturing process by Pathoen 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 tablet 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 bromocriptine. Bromocriptine, the amine of bromocriptine at C-8 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 (bromocriptine 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
are distributed as courtesy or professional samples. All bottles will have a tamper-evident seal and a HDPE

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 56 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. All pending issues: (1)
acceptability of the impurity content for the bromocriptine 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.

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

Jens Weber Project Manager/ OND/ DME

ATTACHED:
EER Summary Report (2 pages)
CHEMISTRY REVIEW

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

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

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

Sponsor: VEROSCIENCE
1334 MAIN RD
TIVERTON, RI 02878

Brand Name: ERGOSET (BROMOCRIPTINE MESYLYATE) TABS 0.8
Estab. Name: BROMOCRIPTINE MESYLYATE
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-1999 by DAMBROGOJ
WITHHOLD on 28-OCT-1998 by DAMBROGOJ
WITHHOLD on 24-AUG-1998 by DAMBROGOJ

Establishment: FEI: b(4)

DMF No: 6737
AADA:

Responsibilities:
DRUG SUBSTANCE MANUFACTURER

Profile: OC RECOMMENDATION
Last Milestone: 01-MAY-08
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: 1510437
FEI: 1510437
PATHION 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
Last Milestone: OC RECOMMENDATION
Milestone Date: 19-MAY-08
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: FEI: 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:  
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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/
------------------------
Xavier Ysern
10/15/2008 01:14:29 PM
CHEMIST

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 DMNP
# Table of Contents

## Chemistry Review Data Sheet

## The Executive Summary

### I. Recommendations

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

### II. Summary of Chemistry Assessments

- A. Description of the Drug Product(s) and Drug Substance(s)
- B. Description of How the Drug Product is Intended to be Used
- C. Basis for Approvability or Not-Approval Recommendation

### III. Administrative

- A. Reviewer’s Signature
- B. Endorsement Block
- C. CC Block

## Chemistry Assessment

### I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

- S DRUG SUBSTANCE Bromocriptine Mesylate USP
- P DRUG PRODUCT Cycloset™ (Bromocrytine Mesylate) Tablets

### II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

- A. Labeling & Package Insert
- B. Environmental Assessment Or Claim Of Categorical Exclusion
- C. Establishment Inspection

### III. List Of Deficiencies To Be Communicated

(There are no deficiencies to be communicated.)
1. NDA #: 20-866

2. REVIEW #: 7

3. REVIEW DATE: 25-Sep-2008

4. REVIEWER: Xavier Ysern, PhD

5. PREVIOUS DOCUMENTS:

   Previous Documents
   Original: Document Date
   Amendments: 22-Aug-1997
                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:

   Submission(s) Reviewed
   Amendment 29 Document Date 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: 0.3 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<sub>33</sub>H<sub>41</sub>BrN<sub>7</sub>O<sub>5</sub>S<sub>2</sub>·CH<sub>3</sub>S<sub>2</sub>O

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-methyl-propyl)-ergotamine-3',6',18-trione monomethanesulfonate (salt)
Ergotamin-17',27',30'-trione, 2-bromo-1'-hydroxy-19'-(1-methyl-ethyl)-28'-(2-methyl-propyl), monomethanesulfonate (salt) [IUPAC]

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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<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:

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18. STATUS:

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NDA 20-866  CMC Review # 7  Page 4 of 34
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 bromocriptine 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 (68-77 °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 proprietary Type II Drug Master File (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.

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

---

Bromocriptine structure shown below has

---

b(4)

---

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

The drug substance is packaged in and stored between the retest period of at reduced temperature conditions (5 °C ± 3 °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, Pathoem Pharmaceuticals Inc. (Pathoem), manufactures the drug product.

The manufacturing process by Pathoem does not differ appreciably from the manufacturing process carried out by Geneva Pharmaceuticals and by PLIVA. The manufacturing processes is conventional for a solid dosage form. It includes in-process controls for the in-process controls include tablet thickness, weight, hardness and friability.

The drug product is available as 0.8 mg strength tablets. Each tablet 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.

Drug product specifications comply with USP monograph for Bromocriptine Mesylate Tablets with the exception of the allowed content for bromocriptine. Bromocriptine, 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 (bromocriptine NMT any other individual impurity NMT and the total impurity content NMT dosage uniformity (USP <905>), and dissolution (Q 130 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 are distributed as courtesy or professional samples. All bottles will have a tamper-evident seal and a HDPE canister with
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

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

---

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

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- **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
- PATHRON PHARMACEUTICALS INC
- 2110 E GALKRAITH RD
- CINCINNATI, OH 452371625

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

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

NDA 20-866  Chemistry Review # 6  Date Reviewed: 04-DEC-1998

Submission Type  Document Date  CDER Date
Original  22-AUG-1997  22-AUG-1997

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

Drug Product Name  Proprietary:
Nonproprietary/Established/USAN:
Chem. Type/ Ther. Class:
Ergoset
Bromocriptine Mesylate
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
Route of Administration:  Oral
Strength(s):  0.8
Dispensed:  Rx

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

Bromocriptine Mesylate
C_{33}H_{40}BrN_{5}O_{7}CH_{2}SO_{3}
MW = 654.60 + 96.12 = 750.72
CAS 22260-51-1
CAS 25614-03-3 (Bromocriptine)

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

Related:  --

Remarks:  The 20-NOV-1998 [BC] amendment provides additional and satisfactory information regarding content uniformity of halves. The withhold recommendation, issued by the Office of Compliance has now been lifted (approval date 30-NOV-1998). All pending CMC related issues, including the cGMP status of the facilities, are now acceptable. An EER summary report, dated 04-DEC-1998, is attached.

Conclusions & Recommendations:  Satisfactory CMC information has been provided for both, drug substance, Bromocriptine Mesylate, and drug product, Bromocriptine Mesylate Tablets. From the Chemistry viewpoint this application can 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:

filename: /nda/20866_6.doc

AP
FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 20866/000
Applicant: ERGO
100 1ST AVE 4TH FL
CHARLESTOWN, MA 021292051

Priority: 38 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) 301-527-6430, 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: b(4)
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
GENEVA PHARMACEUTICALS INC
2955 WEST MIDWAY BLVD
BROOMFIELD, CO 80038
DMF No:
AADA No:

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
| Decision: | ACCEPTABLE |
| Reason: | FIRM RESPONSE TO DEFIC. ADEQ |

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| Last Milestone: |/OC RECOMMENDATION|
| Milestone Date: |23-DEC-1997|
| Decision:      | ACCEPTABLE   |
| Reason:        | DISTRICT RECOMMENDATION |

Responsibilities: FINISHED DOSAGE PACKAGER
DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA 20-866                  Chemistry Review # 5                  Date Reviewed: 20-NOV-1998

Submission Type            Document Date              CDER Date
Original                  22-AUG-1997                22-AUG-1997
Amendment                 02-OCT-1998                07-OCT-1998

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

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

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
Route of Administration: Oral
Strength(s):              0.8,
Dispensed:                Rx

Chemical Name, Structural Formula, Molecular Formula, Molecular Weight:
Bromocriptine Mesylate
C_{32}H_{40}BrN_{5}O_{3}CH_{2}SO_{3}
MW = 654.60 + 96.12 = 750.72
CAS 22260-51-1
CAS 25614-03-3 (Bromocryptine)

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

Related:                 DMF

Remarks: The 02-OCT-1998 amendment provided adequate information regarding content uniformity of halves. The 09-NOV-1998 amendment clarifies statements contained in the original NDA submission regarding the number of times the assay and related compounds analysis are performed during testing of drug substance and drug product. The "withhold approval" recommendation from the Office of Compliance has not been changed, EER summary report dated 16-NOV-1998 is attached (see pages 2 and 3). Copy of e-mail sent by Bill Sherer, Denver District Pre-Approval Manager is also attached (page 4).

Conclusions & Recommendations: Although satisfactory CMC information has been provided for both, drug substance, Bromocriptine Mesylate, and drug product, Bromocriptine Mesylate Tablets (see CMC Reviews # 1, 2, 3 and 4), from the Chemistry viewpoint the application cannot be approved because the "withhold approval" recommendation from the Office of Compliance remains unchanged.

Orig. NDA 20-866
cc: HFD-510/Division File
    HFD-510/RMisbin/SMoore/RSsteigerwalt/JWeber/Xysern
    Xavier Ysern, PhD
    HFD-820/JGibbs

R/D Init by: NA

filename: /nda/20866_5.doc

NDA 20-866 CMC Review # 5 Page 1 of 4
FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 20886/000
Applicant: ERGO
100 1ST AVE 4TH FL
CHARLESTOWN, MA 021292051

Priority: 3S
Action Goal: 
Brand Name: ERGOSET(BROMOCRIPTINE MESYLATE)TABLETS 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:
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 Responsibilities: DRUG SUBSTANCE MANUFACTURER
Last Milestone: OC RECOMMENDATION
Milestone Date: 20-APR-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: 1717799
GENEVA PHARMACEUTICALS INC
2555 WEST MIDWAY BLVD
BROOMFIELD, CO 80038

DMF No: 
AADA No: 

Profile: TCM OAI Status: NONE Responsibilities: FINISHED DOSAGE MANUFACTURER
Last Milestone: ASSIGNED INSPECTION TO 1B
Milestone Date: 13-NOV-1998

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

Profile: 
OAI Status: NONE Responsibilities: DRUG SUBSTANCE MANUFACTURER b(4)
Last Milestone: OC RECOMMENDATION
Milestone Date: 28-OCT-1998
Decision: ACCEPTABLE
**Reason:** FIRM RESPONSE TO DEFIC. ADEQ

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**Profile:** TCM  
**OAI Status:** NONE  
**Last Milestone:** OC RECOMMENDATION  
**Milestone Date:** 23-DEC-1997  
**Decision:** ACCEPTABLE  
**Reason:** DISTRICT RECOMMENDATION  

**Responsibilities:** FINISHED DOSAGE PACKAGER
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@cdr.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
DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA 20-866  Chemistry Review # 4  Date Reviewed: 05-NOV-1998

Submission Type  Document Date  CDER Date
Original  22-AUG-1997  22-AUG-1997
Amendment  02-OCT-1998  07-OCT-1998

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

Drug Product Name  Proprietary:
Nonproprietary/Established/USAN:
Chem. Type/ Ther. Class:

Ergoset
Bromocriptine Mesylate
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
Route of Administration: Oral
Strength(s): 0.8, ng
Dispensed: Rx

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

Bromocriptine Mesylate
C_{17}H_{40}BrN_{3}O_{5}CH_{4}SO_{3}
MW = 654.60 + 96.12 = 750.72
CAS 22260-51-1
CAS 25614-03-3 (Bromocriptine)

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

Related:
DMF

Remarks: This amendment provides for: (1) a revised GC method for the analysis of solvent content in the drug substance; (2) an scored tablet (no changes in composition and specifications); (3) the use of a new in the manufacture of the HDPE bottles; and (4) an update of the stability studies. The “withhold approval” recommendation from the Office of Compliance has not been changed, EER detail report dated 05-NOV-1998 is attached.

Conclusions & Recommendations: Although satisfactory CMC information has been provided for both, drug substance, Bromocriptine Mesylate, and drug product, Bromocriptine Mesylate Tablets (see CMC Reviews # 1, 2 and 3), because the “withhold approval” recommendation from the Office of Compliance has not been changed, from the Chemistry viewpoint the application cannot be approved. Review of dissolution data for the scored tablets and halves is deferred to Biopharm. The comment stated in the Draft Letter should be communicated to the Sponsor.

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

R/D Init by: NA

filename: /nda/20866_4.doc
2 Page(s) Withheld

✔ Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)
**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

100 1ST AVE 4TH FL
CHARLESTOWN, MA 021292051

**Establishment Name:**

**Generic Name:** BROMOCRIPTINE MESYLATE

**Priority:** 3S

**Org Code:** S10

**Dosage Form:** (TABLET)

**Strength:** 0.8, ——— MG

**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:**

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER

**Profile:** OAI Status: NONE

**Establishment Comment:**

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**Establishment:** 1717759

**GENEVA PHARMACEUTICALS INC**

2555 WEST MIDWAY BLVD
BROOMFIELD, CO 80038

**DMF No.:**

**AADA:**

**Responsibilities:** FINISHED DOSAGE MANUFACTURER

**Profile:** TCM

**OAI Status:** NONE

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FIRM SAYS THEY WILL BE READY 10/98.

FIRM STATED THAT THEY WOULD BE READY 10/98.
**Establishment Evaluation Request Detail Report**

**DMF No:**

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER

**Profile:**

**OAI Status:** NONE

### Milestone Table 1

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**Recommendation Withhold**

DO RECOMMENDATION 24-AUG-1998

**Withhold DAMBROGIOJ**

- COMPUTER VALIDATION
- INADEQUATE LAB CONTROLS
- PRODUCTION/PROCESS CONTROLS
- RECORDS/REPORTS

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**Warning Letter to Be Issued**

OC RECOMMENDATION 24-AUG-1998

**Withhold DAMBROGIOJ**

- WARNING LETTER ISSUED
- ACCEPTABLE DAMBROGIOJ

### Milestone Table 3

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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

Submission Type        Document Date    CDER Date        Assigned Date
14-AUG-1998

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

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

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
Route of Administration: Oral
Strength(s): 0.8, ___________ mg [4]
Dispensed: Rx

Chemical Name, Structural Formula, Molecular Formula, Molecular Weight:
Bromocriptine Mesylate
C_{32}H_{40}BrN_{2}O_{5}CH_{4}SO_{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)

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/Steigerwalt/JWeber/XYsern
    Xavier Ysern, PhD
    HFD-820/Jgibbs

R/D Init by: NA

filename: /nda/20866_3.doc

NDA 20-866  CMC Review # 3  Page 1 of 5
COER LABELING AND NOMENCLATURE COMMITTEE

CONSULT # 10528  HFD 510  PROPOSED PROPRIETARY NAME:  PROPOSED ESTABLISHED NAME:
ATTENTION:  Dr. Xavier Yasen  Bromodipine mesylate  b(4)

A. Look-alike/Sound-alike

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B. Misleading Aspects:

C. Other Concerns:

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.

D. Established Name

xxx Satisfactory
--- Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

ACCEPTABLE  XXX UNACCEPTABLE

F. Signature of Chair/Date  D. Buring  9/22/98
CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT # 10625  HFDS §10  PROPOSED PROPRIETARY NAME: CYCLOSET
ATTENTION: Dr. Xavier Ysem  PROPOSED ESTABLISHED NAME: bromocriptine mesylate

A. Look-alike/Sound-alike

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B. Misleading Aspects:

C. Other Concerns:

D. Established Name

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| Un satisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

XXX ACCEPTABLE  UNACCEPTABLE

F. Signature of Chair/Date

D. Berging
**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:** ERGOSBT (BROMOCRIPTINE MESYLATE) TABS 0.8  
**Estab. Name:**  
**Generic Name:** BROMOCRIPTINE MESYLATE  
**Dosage Form:** (TABLET)  
**Strength:** 0.8 mg  
**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 24-AUG-1998 by J. D AMBROGIO (HFD-324) 301-827-0062  
**Establishment:** b(4)  
**DMF No:**  
**Responsibilities:** DRUG SUBSTANCE MANUFACTURER  
**Profile:**  
**OAI Status:** NONE  
**Estab. Comment:**  

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**Establishment:** 1717759  
**GENEVA PHARMACEUTICALS INC**  
2555 WEST MIDWAY BLVD  
BROOMFIELD, CO 80038  
**DMF No:**  
**Responsibilities:** FINISHED DOSAGE MANUFACTURER  
**Profile:** TCM  
**OAI Status:** NONE  
**Estab. Comment:**  

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**RECOMMENDING WITHHOLD**

**DO RECOMMENDATION** 24-AUG-1998

**WITHHOLD DAMBROGIJOJ**

**WARNING LETTER TO BE ISSUED.**

**OC RECOMMENDATION** 24-AUG-1998

**WITHHOLD DAMBROGIJOJ**

**WARNING LETTER ISSUED**

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

Submission Type     Document Date     CDER Date     Assigned Date

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

Drug Product Name     Proprietary:
                      Nonproprietary/Established/USAN:
                      Chem. Type/ Ther. Class:

Ergoset     Bromocriptine Mesylate
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_{46}BrN_{5}O_{5}CH_{4}SO_{3}
MW = 654.60 + 96.12 = 750.72
CAS 22260-51-1
CAS 25614-03-3 (Bromocriptine)

2-Bromoergocriptine 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, Bromocriptide 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, Bromocriptide Mesylate, and drug product, Bromocriptide 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/XYscrn
    HFD-820/JGibbs
    Xavier Ysern, PhD

R/D Init by:

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CDER Establishment Evaluation Report
for August 20, 1998

Application: NDA 20866/000
Applicant: ERGO
100 1st Ave 4th FL
Charlestown, MA 021292051

Priority: 38 Org Code: 510
Brand Name: ERGOSET(BROMOCRIPTINE MESYLATE) TABS 0.8
Established Name: Generic Name: BROMOCRIPTINE MESYLATE
Dosage Form: TAB (TABLET)
Strength: 0.8 MG

FDA Contacts: X. YSERN (HFD-510) 301-227-6430, Review Chemist

Overall Recommendation:

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

Profile: OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 22-APR-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: 1717759 GENEVA PHARMACEUTICALS INC
2555 West Midway Blvd
BROOMFIELD, CO 80028

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

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

Profile: OAI Status: NONE
Last Milestone: INSPECTION PERFORMED
Milestone Date 30-JUN-1998

Establishment: DMF 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

b(4)
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

Submission Type  Document Date  CDER Date  Assigned Date

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

Drug Product Name  Proprietary:
Nonproprietary/Established/USAN:  Ergoset
Chem.Type/ Ther.Class:  Bromocriptine Mesylate  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  ng  b(4)
Route of Administration: Oral  Dispensed:  

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

Bromocriptine Mesylate
C_{32}H_{46}BrN_{5}O_{5}·CH_{4}SO_{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)

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

R/D Init by:

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☑️ Trade Secret / Confidential (b4)

☐ Draft Labeling (b4)

☐ Draft Labeling (b5)

☐ Deliberative Process (b5)
CDER Establishment Evaluation Report
for May 19, 1998

Application: NDA 20866/000
Applicant: ERGO
100 1ST AVE 4TH FL
CHARLESTOWN, MA 021292051

Priority: 3S
Org Code: 510
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. YSEN 
(HFD-510)
301-827-6430, Review Chemist

Overall Recommendation:
Establishment: ————
DMF No: ———— b(4)
AADA No: ————

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

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

DMF No: ————
AADA No: ————

Profile: TCM OAI Status: NONE
Responsibilities: FINISHED DOSAGE MANUFACTURER
Last Milestone: INSPECTION SCHEDULED
Milestone Date: 20-FEB-1998

Establishment: ————
DMF No: ———— b(4)
AADA No: ————

Profile: ———— OAI Status: NONE
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Last Milestone: ASSIGNED INSPECTION TO IR
Milestone Date: 04-FEB-1998

Establishment: ————
DMF No: ————
Profile: TCM  OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-DEC-1997
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION