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**

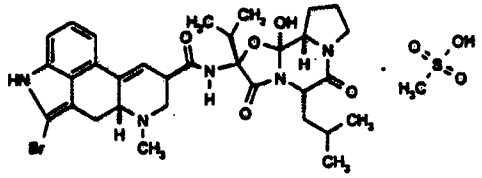
Consult:		
	EA:	Acceptable (categorical exclusion provided in the NDA)
	Pharm/Tox:	Acceptable
	Biopharm:	Acceptable
	Methods Validation:	Acceptable
	Microbiology:	N/A

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 *5R, 8R, 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. b(4)

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

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 (Bromocryptine)
(5')-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)-, monomethansulfonate (salt) [IUPAC]

Chemistry, Manufacture and Controls information for the drug substance is referred to [redacted] b(4)
proprietary Type II Drug Master File (DMF) [redacted] DMF [redacted] 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 b(4)
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 [redacted]

b(4)

The drug substance is packaged in a [redacted] and stored between [redacted]
The retest period of [redacted] at reduced temperature conditions (5 °C ± 3 °C) is fully supported b(4)
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 [redacted] b(4)

The in process control for the [redacted] for th [redacted] tep, [redacted] in process controls include tablet thickness, weight, hardness and friability.
The drug product is available as 0.8 mg strength tablets. Each table contain [redacted] of bromocriptine mesylate (equivalent to 0.8 mg bromocriptine [redacted]. Excipients include [redacted] b(4)
mg of corn starch [redacted] of citric acid [redacted] of lactose [redacted] of colloidal silicon dioxide [redacted] of magnesium stearate [redacted] The total weight of the tablet is [redacted] All excipients meet compendial requirements.
Specifications include appearance (visual), identification (UV and HPLC), Assay by HPLC (bromocriptine [redacted] Purity (bromocriptinine NMT [redacted] any other individual b(4)
impurity NMT [redacted] and the total impurity content NMT [redacted] dosage uniformity (USP <905>), and dissolution ([redacted] % 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 [redacted] HDPE bottles respectively.

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

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

CHEMISTRY REVIEW

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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C. CC Block 7

Chemistry Assessment

See CMC Review # 7

III. List of Deficiencies To Be Communicated (There are no defficiencies to be comunicatted.)

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:**

Previous Documents	Document Date
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:**

Submission(s) Reviewed	Document Date
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 Data Sheet

12. STRENGTH/POTENCY: 0.8 mg

13. ROUTE OF ADMINISTRATION: Oral

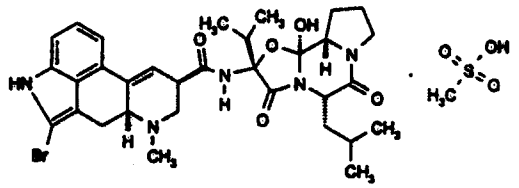
14. Rx/OTC DISPENSED: Rx

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

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

Bromocriptine Mesylate

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



(5')-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)-, monomethansulfonate (salt) [IUPAC]

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	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

b(4)

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

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
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18. STATUS:

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer
Biometrics	N.A.		
ETS	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)	Labelling issues still under review (multi disciplinary approach)		
EA	Acceptable		Part of this review
Microbiology	--		

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

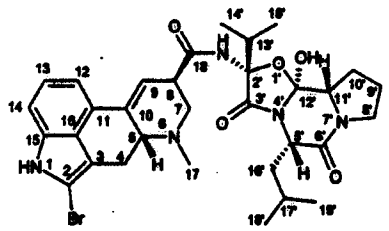
The drug substance is the mesylate salt of the active component bromocriptine. The applicant, VeroScience, LLC, obtains the drug substance from [redacted]. Chemistry, Manufacture and Controls' (CMC) information is referred to [redacted] proprietary Type II Drug Master File (DMF) [redacted] DMF [redacted] 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 [redacted]

b(4)

Bromocriptine free base (structure shown below) has six sterogenic 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.



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 °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, 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 ——— 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. b(4)

Drug product specifications comply with USP monograph for Bromocriptine Mesylate Tables with the exception of the allowed content for bromocriptinine. Bromocriptinine, the epimer 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 (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 b(4)

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 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 monoterappy 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

Jena Weber Project Manager/ OND/ DME

ATTACHED: **Page**
EER Summary Report (2 pages) 8

CHEMISTRY REVIEW

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application	: NDA 20866/000	Sponsor:	VEROSCIENCE
Org Code	: 510		1334 MAIN RD
Priority	: 3S		TIVERTON, RI 02878
Stamp Date	: 22-AUG-1997	Brand Name :	ERGOSET(BROMOCRIPTINE MESYLATE)TABS 0.8
PDUFA Date	: 15-OCT-2008		
Action Goal	:	Estab. Name:	
District Goal	: 22-APR-1998	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-2008by S. FERGUSON (HFD-322) 301-796-3247
WITHOLD 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 : [redacted] FEI : [redacted] b(4)

DMF No: 6737 AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : [redacted] 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 : [redacted] FEI : [redacted] b(4)

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

[redacted] b(4)

DMF No: 6955 AADA:

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

Establishment : CFN [redacted] FEI : [redacted] b(4)

DMF No: [redacted] 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 : [redacted] FEI : [redacted] b(4)

DMF No: [redacted] 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

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
10/15/2008 01:14:29 PM
CHEMIST

Blair Fraser
10/15/2008 01:15:20 PM
CHEMIST

CHEMISTRY REVIEW

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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C. CC Block 7

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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:**

Previous Documents	Document Date
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:**

Submission(s) Reviewed	Document Date
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

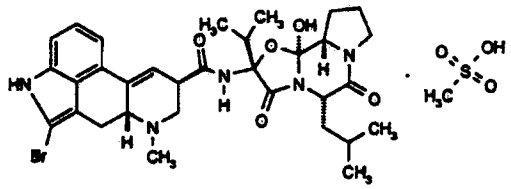
14. Rx/OTC DISPENSED: Rx

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 (Bromocryptine)



(5')-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)-, monomethansulfonate (salt) [IUPAC]

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	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

b(4)

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

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
--	--	--

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	--		

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 [redacted] 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 [redacted] Chemistry, Manufacture and Controls' (CMC) information is referred to [redacted] proprietary Type II Drug Master File (DMF) [redacted] DMF [redacted] has been reviewed and its current CMC status is adequate. b(4)

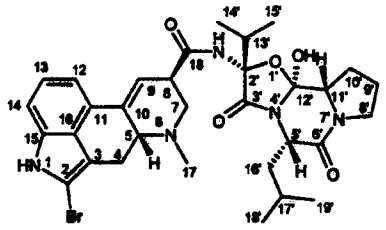
Bromocriptine mesylate is a white to off white powder (no polymorphs) very sensitive to light with a melting point range between 192 – 196 °C. Its pKa value, measured in water at 25 °C, is 4.9. [redacted] b(4)

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 [redacted]

b(4)

Bromocriptine [redacted] structure shown below) has [redacted] b(4)



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 °C ± 3 °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, Pathoen 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 corn starch ——— 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 Tables with the exception of the allowed content for bromocriptinine. Bromocriptinine, the epimer 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)

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 monoterappy 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

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 :
District Goal: 22-APR-1998

Sponsor: VEROSCIENCE
1334 MAIN RD
TIVERTON, RI 02878

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 [redacted] FEI [redacted]

b(4)

DMF No: 6737 AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : [redacted] 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 : [redacted] FEI [redacted]

b(4)

18-SEP-2008 FDA CDER EES Page 2 of 2
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT
DMF No: 6955 AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile : [redacted] OAI Status: NONE b(4)
Last Milestone: SUBMITTED TO DO
Milestone Date: 01-MAY-08
:
:

Establishment : CFN : [redacted] FEI [redacted] 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 : [redacted] FEI [redacted] 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

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

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
Amendment	20-NOV-1998	23-NOV-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:	Ergoset
	Nonproprietary/Established/USAN:	Bromocriptine Mesylate
	Chem. Type/ Ther. Class:	**5 S**

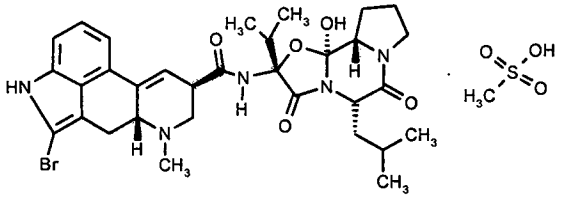
Pharmacological Category/indication: Hypoglycemic Agent. Adjunct to diet to improve glycemic control in patients with NIDDM whose hyperglycemia cannot be managed by diet alone.

b(4)

Dosage Form: Tablets **Strength(s):** 0.8 [redacted]
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 (Bromocryptine)



2-Bromoergocryptine 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 [redacted] 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. b(4)

Conclusions & Recommendations: Satisfactory CMC information has been provided for both, drug substance, Bromocritine 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
HFD-820/JGibbs

Xavier Ysern, PhD

R/D Init by:

filename: /nda/20866_6.doc

AP

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 20866/000
Stamp: 22-AUG-1997 Regulatory Due: 22-NOV-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, [redacted] MG b(4)

FDA Contacts: X. YSERN (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: [redacted]
DMF No: [redacted]
AADA No: b(4)

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

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

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

Establishment: [redacted]
DMF No: [redacted] b(4)
AADA No:
b(4)

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

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Decision: ACCEPTABLE
Reason: FIRM RESPONSE TO DEFIC. ADEQ

Establishment: [redacted]

DMF No:
AADA No: b(4)

Profile: TCM **OAI Status:** NONE
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
	09-NOV-1998	10-NOV-1998

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

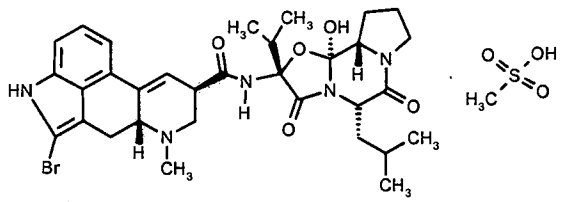
Drug Product Name	Proprietary:	Ergoset
	Nonproprietary/Established/USAN:	Bromocriptine Mesylate
	Chem. Type/ Ther. Class:	**5 S**

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, [redacted] 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 (Bromocryptine)



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

Related: DMF [redacted] b(4)

Remarks: The 02-OCT-1998 amendment provided adequate information regarding content uniformity of [redacted] halves. b(4) 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, Bromocritine 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/RSteigerwalt/JWeber/XYsern
HFD-820/JGibbs

Xavier Ysern, PhD

R/D Init by:
NA

filename: /nda/20866_5.doc

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
100 1ST AVE 4TH FL
CHARLESTOWN, MA 021292051
Brand Name: ERGOSET(BROMOCRIPTINE MESYLATE)TABS 0.8
Established Name:
Generic Name: BROMOCRIPTINE MESYLATE
Dosage Form: TAB (TABLET)
Strength: 0.8 [redacted] 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: [redacted]
DMF No: [redacted]
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: [redacted]
DMF No: [redacted]
AADA No: b(4)

Profile: [redacted]
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 28-OCT-1998
Decision: ACCEPTABLE
Responsibilities: DRUG SUBSTANCE MANUFACTURER b(4)

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Reason: FIRM RESPONSE TO DEFIC. ADEQ

Establishment: [redacted]

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@cder.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

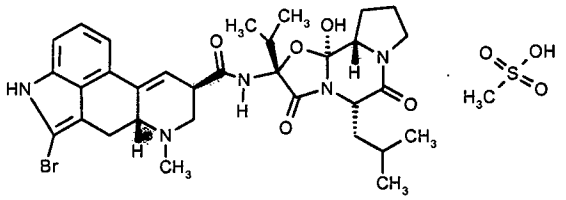
Drug Product Name	Proprietary:	Ergoset
	Nonproprietary/Established/USAN:	Bromocriptine Mesylate
	Chem. Type/ Ther. Class:	**5 S**

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, [redacted] ng 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 (Bromocryptine)



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

Related: DMF [redacted] b(4)

Remarks: This amendment provides for: (1) a revised GC method for the analysis of solvent content in the drug substance; (2) an scored [redacted] ablet (no changes in composition and specifications); (3) the use of a new [redacted], 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. b(4)

Conclusions & Recommendations: Although satisfactory CMC information has been provided for both, drug substance, Bromocritine 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 [redacted] scored tablets and halves is deferred to Biopharm. **The comment stated in the Draft Letter should be communicated to the Sponsor.** b(4)

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

Xavier Ysern, PhD

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)

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 20866/000
Stamp: 22-AUG-1997
Regulatory Due: 22-NOV-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, [redacted] 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: [redacted]

[redacted] b(4)

DMF No: [redacted] AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: [redacted] OAI Status: NONE b(4)
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 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
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 FIRM NOT READY	DAMBROGIOJ
FIRM SAYS THEY WILL BE READY 10/98.					
OC RECOMMENDATION	19-AUG-1998			WITHHOLD FIRM NOT READY	DAMBROGIOJ
FIRM STATED THAT THEY WOULD BE READY 10/98.					

Establishment: 9611868

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

DMF No: [redacted] AADA: b(4)
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: [redacted] 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
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	DAMBROGIOJ
				COMPUTER VALIDATION	
				INADEQUATE LAB CONTROLS	
				PRODUCTION/PROCESS CONTROLS	
				RECORDS/REPORTS	
WARNING LETTER TO BE ISSUED.					
OC RECOMMENDATION	24-AUG-1998			WITHHOLD	DAMBROGIOJ
				WARNING LETTER ISSUED	
DO RECOMMENDATION	28-OCT-1998			ACCEPTABLE	DAMBROGIOJ
				ADEQUATE FIRM RESPONSE	
OC RECOMMENDATION	28-OCT-1998			ACCEPTABLE	DAMBROGIOJ
				FIRM RESPONSE TO DEFIC.	
				ADEQUA	

Establishment: [redacted]

[redacted] 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				YSERNX
OC RECOMMENDATION	23-DEC-1997			ACCEPTABLE	DAMBROGIOJ
				DISTRICT RECOMMENDATION	

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**
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

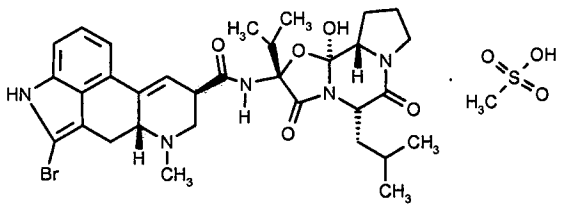
Drug Product Name Proprietary: Ergoset
Nonproprietary/Established/USAN: Bromocriptine Mesylate
Chem. Type/ Ther. Class: **5 S**

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, [redacted] 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 (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 [redacted] and "Cycloset" to be considered by the NLC. The NLC found the proposed **tradename** [redacted] 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. b(4)

Conclusions & Recommendations: Trademark **"Cycloset" acceptable as tradename for Bromocryptine Mesylate tablets.** Although satisfactory CMC information has been provided for both, drug substance, Bromocritine 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: **filename:** /nda/20866_3.doc
NA

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT # 1062a	HFD# 510	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION: Dr. Xavier Ysern		[redacted]	bromocriptine mesylate

b(4)

A. Look-alike/Sound-alike

	Potential for confusion:
	___ Low ___ Medium ___ High
	___ Low ___ Medium ___ High
	___ Low ___ Medium ___ High
	___ Low ___ Medium ___ High
	___ Low ___ Medium ___ High

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 [redacted] or [redacted] in this brand name.

b(4)

D. Established Name

XXX Satisfactory

___ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

___ ACCEPTABLE XXX UNACCEPTABLE

F. Signature of Chair/Date D'Boring 9/2.1/98

CDER LABELING AND NOMENCLATURE COMMITTEE

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

A. Look-alike/Sound-alike

	Potential for confusion:
CYTOTEC	___ Low XXX Medium ___ High
SYLLACT	XXX Low ___ Medium ___ High
CYCLOCORT	XXX Low ___ Medium ___ High
CYCLOPAR	___ Low XXX Medium ___ High
	___ Low ___ Medium ___ High

B. Misleading Aspects:

C. Other Concerns:

D. Established Name

XXX Satisfactory

___ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

XXX ACCEPTABLE ___ UNACCEPTABLE

F. Signature of Chair/Date: D. Boring 4/22/04

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, [redacted] 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 24-AUG-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted]

b(4)

DMF No: [redacted] AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: [redacted] 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 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
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 FIRM NOT READY	DAMBROGIOJ
FIRM SAYS THEY WILL BE READY 10/98.					
OC RECOMMENDATION	19-AUG-1998			WITHHOLD FIRM NOT READY	DAMBROGIOJ
FIRM STATED THAT THEY WOULD BE READY 10/98.					

Establishment: [redacted]

b(4)

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

DMF No: [redacted] AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER b(4)
Profile: [redacted] 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
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	DAMBROGIOJ
				COMPUTER VALIDATION	
				INADEQUATE LAB CONTROLS	
				PRODUCTION/PROCESS CONTROLS	
				RECORDS/REPORTS	
WARNING LETTER TO BE ISSUED.					
OC RECOMMENDATION	24-AUG-1998			WITHHOLD	DAMBROGIOJ
				WARNING LETTER ISSUED	

Establishment: [redacted]

DMF No: [redacted] b(4) 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				YSERNX
OC RECOMMENDATION	23-DEC-1997			ACCEPTABLE	DAMBROGIOJ
				DISTRICT RECOMMENDATION	

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

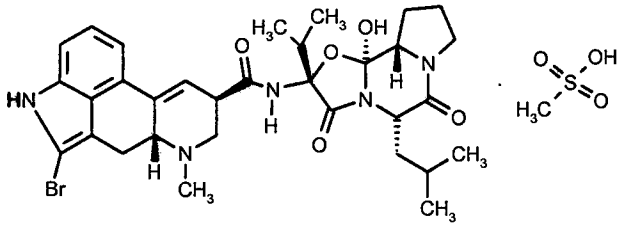
Drug Product Name Proprietary: Ergoset
Nonproprietary/Established/USAN: Bromocriptine Mesylate
Chem. Type/ Ther. Class: **5 S**

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:** 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 (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: : Satisfactory CMC information has been provided for drug substance, Bromocritine 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, Bromocritine 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 Xavier Ysern, PhD
HFD-820/JGibbs

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filename: /nda/20866_2.doc

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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

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 [redacted] MG b(4)

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

Overall Recommendation:

Establishment: [redacted]
DMF No: [redacted]
AADA No: b(4)

Profile: [redacted] 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: OC RECOMMENDATION
Milestone Date 19-AUG-1998
Decision: WITHHOLD
Reason: FIRM NOT READY
Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment: [redacted]
DMF No: [redacted]
AADA No: b(4)

Profile: [redacted] OAI Status: NONE
Last Milestone: INSPECTION PERFORMED
Milestone Date 30-JUN-1998
Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment: [redacted]
DMF No: b(4)

AADA No:

[redacted] 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

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**
Original	22-AUG-1997	22-AUG-1997	26-AUG-1997
Amendment # 1	19-DEC-1997	20-DEC-1997	20-DEC-1997

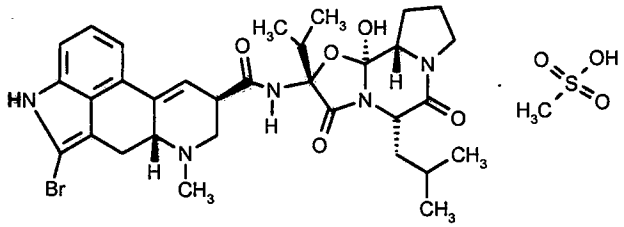
Applicant:	Ergo Research Corporation (ErgoScience) 100 First Avenue Charlestown, MA 02129-2051	 Phone: (617) 241-6800 Fax: (617) 241-8822
Drug Product Name	Proprietary: Nonproprietary/Established/USAN: Chem.Type/ Ther.Class:	Ergoset Bromocriptine Mesylate **5 S**

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 [redacted] mg b(4)
Route of Administration: Oral **Dispensed:** [redacted]

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, Bromocritine 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

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:

AADA No:

[redacted] 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