

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-866

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 20-866	Submission Date: 4/13/08
Brand Name	Cycloset™
Generic Name	Bromocriptine mesylate
Reviewer	Jaya bharathi Vaidyanathan, Ph.D.
Team Leader	Sally Choe, Ph.D.
OCP Division	DCP-2
OND Division	Metabolic and Endocrine Products
Sponsor	VeroScience LLC
Submission Type; Code	505 (b) (1); Complete response to AE letter
Formulation; Strength(s)	0.8 mg tablets
Indication	Treatment of Type 2 Diabetes

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I. Executive Summary

CyclosetTM (bromocriptine mesylate tablets) is an immediate release formulation of bromocriptine mesylate that is intended for the treatment of type 2 diabetes. The NDA 20-866 was originally filed by ErgoScience Corp in 1997. The Agency issued an approvable letter (dated Oct 15, 1999) with the major requirement for approval being conducting a safety study of CyclosetTM in patients with type 2 diabetes. The Agency required that the safety study adequately evaluate the potential for a significant increase in the risk of serious cardiac adverse events with CyclosetTM treatment.

ErgoScience transferred the NDA to Pliva in 2003. Pliva then transferred the ownership of the NDA to VeroScience in May 2006. VeroScience collaborated with Pliva on the study design and execution of the safety study (# 165-AD-04-03-US-1) which started in July 2004. With this application, the current sponsor, VeroScience LLC is filing a complete response to the Agency's approvable letter for this NDA.

Three different formulations were used in this NDA and are described in Table 1 below:

Table 1: Formulations used in development of CyclosetTM

<i>Sponsor</i>	<i>Manufacturer of CyclosetTM Tablets</i>	<i>Formulation used in Clinical Trials</i>
ErgoScience	Geneva Pharmaceuticals, Broomfield, CO	Studies submitted with the originally filed NDA in 1999
Transferred to Pliva	Pliva, Croatia	Subsequent clinical studies, including safety trial (# 165-AD- 04-03-US-1)
VeroScience	Patheon Inc, Cincinnati, Ohio	To-be-marketed formulation

VeroScience had a Type B meeting with FDA on Feb 21, 2007 to discuss the approvable letter. One of the issues discussed was the need of bridging the data obtained from the NDA with the to-be-marketed product from Patheon Inc. Since the Geneva product used in original NDA is no longer available, the sponsor was required to provide an efficacy bridge between the Geneva product and Pliva product using efficacy data from pre-specified efficacy subgroups in the safety trial ((# 165-AD-04-03-US-1) to the efficacy data from Phase 3 studies in the original NDA. Please refer to medical and statistical

reviews of this NDA for details on the efficacy bridging. Additionally, the sponsor performed a bioequivalence (BE) study to bridge the Patheon product and the Pliva product used in the large Cycloset™ safety trial. This BE study (# BON-P6-262) is included in this submission. This review will focus on this BE study.

A Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology-2 (OCP/DCP-2) has reviewed the bioequivalence study submitted on 4/13/08 under NDA 20-866 as part of Complete Response to the Approvable Letter and finds it acceptable pending the DSI inspection of the bioequivalence study (BON-P6-262). Recommendation and labeling comments should be conveyed to the sponsor as appropriate.

B Phase IV Commitments

Not applicable.

C Summary of CPB Findings

BE study: The bioequivalence of the bromocriptine mesylate tablets manufactured at Patheon was compared to Cycloset™ manufactured by Pliva in a single center, randomized, single dose, 2-period, 2-sequence crossover study which was conducted in healthy subjects under fed conditions. The sponsor concluded that the test product was bioequivalent to the reference product based on the 90% CI for the ratio of log transformed AUC and Cmax (Table 2). The reviewer reanalyzed the data and concurs with the sponsor's results and conclusions.

Table 2: Summary of the statistical comparisons of the PK parameters for the test vs. reference products

PARAMETER	GEOMETRIC LSMEANS		RATIO (%)	90% CONFIDENCE LIMITS (%)	
	Patheon 3057485R	Pliva 4845106		LOWER	UPPER
C _{max} pg/mL	88.12	92.21	95.57	86.63	105.43
AUC ₀₋₄ pg-hr/mL	299.49	302.24	99.09	92.74	105.88
AUC _{0-∞} pg-hr/mL	323.71	334.10	96.89	90.23	104.04

II QBR

A General Attributes

What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of the drug?

The application of the current NDA for bromocriptine mesylate tablets was originally submitted by the first sponsor, Ergo Science Corporation in August 1997. An approvable letter was issued by the Agency on October 15, 1999. The major requirement of the approvable letter was to perform a large scale safety study. The initiation of the safety study was delayed due to the change in ownership of the application to Pliva.

Pliva manufactured the product for the safety study at their facility in Croatia and initiated the safety trial in July 2004. In May 2006, the ownership of the IND 34,661 and NDA 20-866 for Cycloset tablets was transferred from Pliva to VeroScience LLC. Veroscience managed the completion of the safety study. Consequently, the manufacturing of the drug product was transferred from Pliva to a new manufacturer, Patheon Pharmaceuticals. Patheon manufactured the registration batches in the current application and will also manufacture the commercial drug product upon NDA approval.

The sponsor discussed with the Agency regarding the process to show the bioequivalence between the Ergo product used in the Phase 3 studies, the Pliva product used in the safety trial and the to-be-marketed product produced by Patheon. Since the initial product is not available, the Agency agreed that comparison of efficacy of the Cycloset product (Geneva) used in the phase 3 trials of the NDA to the Cycloset product (Pliva) used in the safety trial would serve as an acceptable link. In addition, the sponsor performed a bioequivalence study comparing the Pliva product used in the safety study and the to-be-marketed product manufactured by Patheon.

The formulations used in the Phase 3 clinical studies, safety study as well as the BE study were identical in terms of composition (Table 3).

Table 3: Summary of bromocriptine mesylate 0.8 mg tablet formulations:

Ingredient	Geneva (Clinical Studies)	Pliva (Safety study)	Patheon (BE study)
Bromocriptine mesylate			
Starch, corn			
Citric acid, _____			
Lactose, _____			
Silicon dioxide, colloidal			
Magnesium stearate			
Theoretical tablet weight (mg)			

(*equivalent to 0.8 mg bromocriptine)

b(4)

What is the mechanism of action and therapeutic indication?

Bromocriptine mesylate is indicated for the treatment of type 2 diabetes.

Bromocriptine mesylate, an ergot derivative, is a sympatholytic dopamine D2 receptor agonist. It has been proposed that appropriately timed daily administration of bromocriptine can reverse many of the metabolic alterations associated with insulin resistance and obesity in part by resetting central circadian organization of monoamine neuronal activities.

Morning administration of bromocriptine is proposed to improve glycemic control in patients with type 2 diabetes by improving insulin sensitivity in peripheral tissues, particularly after a meal and without acting as an insulin secretagogue.

Once daily, morning administration of bromocriptine is also proposed to increase dopaminergic tone in insulin resistant patients. This in turn can facilitate neuroendocrine activities, including resetting of the daily plasma prolactin rhythm, that potentiate peripheral insulin sensitivity.

Are the active moieties in the plasma appropriately identified and measured?

Yes.

B Clinical Study Description

Are the to-be-marketed CyclosetTM tablets manufactured by Patheon bioequivalent to the Cycloset tablets manufactured by Pliva?

In order to evaluate the bioequivalence of the two formulations (Pliva vs. Patheon), a single center, randomized, single dose, 2-period, 2-sequence crossover study was conducted in healthy subjects under fed conditions. The two treatment arms were:

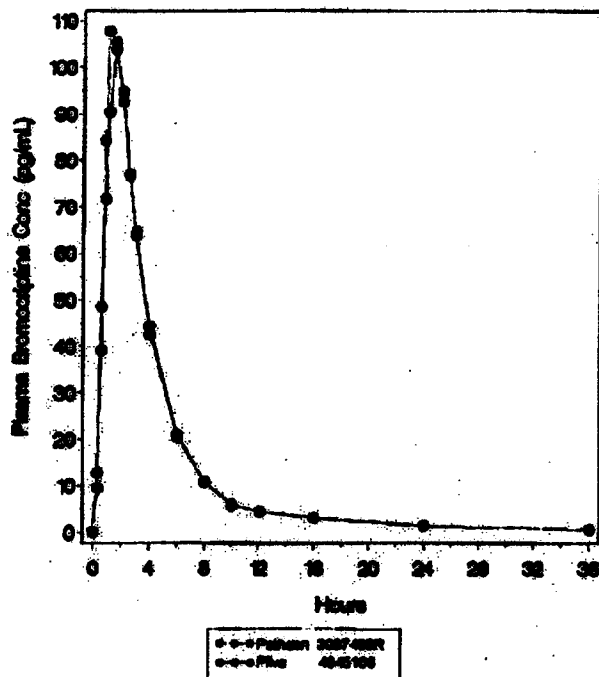
Test: Six (6) Bromocriptine Mesylate 0.8 mg tablets, USP (Manufactured by Patheon)

Reference: Six (6) Cycloset (bromocriptine Mesylate) 0.8 mg tablets (Manufactured by Pliva)

63 healthy subjects were randomized and 58 subjects completed the study. In each period, after an overnight fast, a single dose of 10 mg of metoclopramide was administered intramuscularly approximately 45 minutes before bromocriptine mesylate tablets administration to alleviate the nausea and avoid vomiting caused by bromocriptine. Subsequently, subjects received a high-fat meal within 30 minutes before bromocriptine mesylate tablet administration. A washout period of at least 7 days separated the two treatments. Blood samples were collected for 36 hours after each drug administration.

The plasma concentration time profiles from the two formulations following the administration of 0.8 mg bromocriptine mesylate tablets were superimposable (Figure 1).

Figure 1: Mean plasma concentrations following administration of bromocriptine mesylate 0.8 mg tablets formulations manufactured at Pliva and Patheon.



The mean C_{max} were 126.5 and 128.9 pg/mL for the test and reference respectively. The median T_{max} was 1.5 hours for both formulations. The mean AUC_{inf} were 456.2 and 472.4 pg.h/mL for the test and reference, respectively (Table 4).

Table 4: Mean PK parameters of bromocriptine mesylate tablets (6 x 0.8 mg)

Study ID	Cyclotest Lot No.	Route/ Dosage Form	Dose	Pharmacokinetic Parameters Arithmetic Means $\pm$ SD				
				C _{max} pg/mL	AUC ₀₋₄ pg-hr/mL	AUC _{0-∞} pg-hr/mL	T _{max} ^a hours	T _{1/2} hours
BON-P6-262 (VS-CYCLO-BE-06-2)	3057485R Patheon	Oral/ 0.8 mg tablets	6 x 0.8 mg (4.8 mg)	126.49 $\pm$ 98.41	435.30 $\pm$ 358.02	456.27 $\pm$ 402.75	1.50 (0.5 - 4.0)	5.95 $\pm$ 4.95
	4845106 Pliva	Oral/ 0.8 mg tablets	6 x 0.8 mg (4.8 mg)	128.95 $\pm$ 99.72	440.57 $\pm$ 375.47	472.45 $\pm$ 421.24	1.5 (0.75 - 4.0)	6.02 $\pm$ 5.12

^a median with range

The 90% confidence intervals for the ratios of the geometric LS means of the PK parameters (AUC and C_{max}) were within the pre-specified limits of 80-125% for establishing bioequivalence (Table 5).

Table 5: Comparison of results for bioequivalence assessment between the Pliva and Patheon formulations

PARAMETER	GEOMETRIC LSMEANS		RATIO (%)	90% CONFIDENCE LIMITS (%)	
	Patheon 3057485R	Pliva 4845106		LOWER	UPPER
C _{max} pg/mL	88.12	92.21	95.57	86.63	103.43
AUC _{0-t} pg-h/mL	299.49	302.24	99.09	92.74	105.88
AUC _{0-∞} pg-h/mL	323.71	334.10	96.89	90.23	104.04

The reviewer also reanalyzed the BE study data sets and the results are summarized in the following table. The PK parameters were obtained using WinNonlin and the BE analysis was done using SAS. As shown the results were very similar to that obtained by the sponsor (Table 6).

Table 6: Statistical summary of PK parameters (Reviewer's analysis)

PK Parameter	Geometric LS Means		Ratio (%)	90% Confidence Limit	
	Patheon	Pliva		Lower	Upper
C _{max} (pg/mL)	88.63	92.63	95.68	86.71	105.58
AUC _{0-t} (pg.h/mL)	301.28	303.61	99.23	92.83	106.07
AUC _{0-inf} (pg.h/mL)	326.25	332.14	98.22	91.88	105.00

Based on the above results, it can be concluded that the test formulation (Bromocriptine mesylate 0.8 mg tablets, Patheon) is bioequivalent to the reference formulation [Cycloset (bromocriptine mesylate) 0.8 mg tablets, Pliva] under fed conditions.

[Note: It is not clear why the sponsor chose the dose for this BE study to be 6 x 0.8 mg bromocriptine tablets as compared to a single 0.8 mg tablet. Also the fed BE approach in this case is acceptable since bromocriptine mesylate tablets will be indicated to be taken with food.]

C Analytical

How was the analytical assay performed and validated?

Bromocriptine and internal standard _____ were separated from plasma by liquid-liquid extraction, followed by solid phase extraction. The samples were analyzed by LC-MS/MS using Atmospheric Pressure Chemical Ionization. The standard curves were linear in the measured range between _____ the overall precision (expressed as CV) and accuracy (expressed as bias) of quality controls and standards were within the acceptable criteria. The lower limit of quantification for the determination of bromocriptine in human plasma was _____

b(4)

b(4)

Table 7: Summary of standard curve and QC data for bioequivalence sample analyses

Concentration (pg/mL)	2.00	5.00	10.0	20.0	50.0	100	200	500
Inter day Precision (%CV)								
Inter day Accuracy (%Actual)								
Linearity	Range of R ² values							
Linearity Range (ng/mL)								
Sensitivity/LOQ (pg/mL)	2.00							

b(4)

b(4)

Concentration (pg/mL)	6.00	60.0	400
Inter day Precision (%CV)			
Inter day Accuracy (%Actual)			

b(4)

III Labeling Comments

There is no Clinical Pharmacology labeling comments based on this particular review. A separate labeling review will be done to address the PLR conversion.

38 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

B BE study synopsis

Clinical Study Report N° BON-P6-262
Sponsor Project N° VS-CYCLO-BE-06-2



2. SYNOPSIS

Title of Study:

Single Dose Crossover Comparative Bioavailability Study of Bromocriptine Mesylate 0.8 mg Tablets Following Administration of a 4.8 mg Dose in Healthy Male and Female Volunteers / Fed State

Protocol N°: BON-P6-262 (Sponsor Project N° VS-CYCLO-BE-06-2)

Qualified Investigator:

Eric Sicard, M.D., Clinical Investigator.

Study Center:

Algorithmes Pharma Inc., Algorithmes Pharma Inc., 1200 Bonaventure Ave., Mount-Royal, Quebec, Canada, H3P 3P1.

Publication (reference):

None

Time of Clinical Part:
2007/08/13 to 2007/09/12

Phase of Development:
Phase I

Objectives:

To evaluate and compare the relative bioavailability and therefore the bioequivalence of two formulations of bromocriptine mesylate after a single oral dose administration under fed conditions.

Methodology:

Single center, randomized, single dose, laboratory-blinded, 2-period, 2-sequence, crossover study.

Number of Subjects (Planned and Analyzed):

Planned for inclusion: 66

Included: 63

Drop-outs: 6

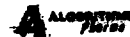
Analyzed: 63

Considered in the statistical analysis: 57

Diagnosis and Main Criteria of Inclusion:

Male and female volunteers, non- or ex-smokers, of at least 18 years of age but not older than 45 years with a body mass index (BMI) greater than or equal to 19 and below 30 kg/m². Subjects were in good health as determined by a medical history, physical examination (including vital signs), electrocardiogram (12-lead ECG) and the usual clinical laboratory tests (hematology, biochemistry, urinalysis) including prolactin measurements, negative HIV, Hepatitis B and

Clinical Study Report N° BON-P6-262
Sponsor Project N° YS-CYCLO-BE-06-2



Hepatitis C tests as well as negative screening of ethyl alcohol and drugs of abuse in urine and negative pregnancy test (for female subjects).

Test Product, Dose and Mode of Administration, Batch Number:

Name: Bromocriptine Mesylate
Dosage form/Route of administration: tablet, USP/oral
Regimen: single dose of 4.8 mg (6 x 0.8 mg)
Batch no.: 3057485R

Reference Product, Dose and Mode of Administration, Batch Number:

Name: CyclosetTM (bromocriptine mesylate)
Dosage form/Route of administration: tablet/oral
Regimen: single dose of 4.8 mg (6 x 0.8 mg)
Batch no.: 4845106

Concomitant Medication, Dose and Mode of Administration, Batch Number:

Name: Metoclopramide Hydrochloride
Dosage form/Route of administration: injection Sandoz Standard/intramuscular
Regimen: single dose of 10 mg (2 mL of x 5 mg/mL)
Lot no: 136767

Treatment Periods:

Group A:
Period 1: 2007/08/14
Period 2: 2007/08/21

Group B:
Period 1: 2007/08/23
Period 2: 2007/08/30

Duration of Treatment:

A single oral dose was administered under fed conditions in each study period. Each period was separated by a wash-out of 7 days.

Blood Sampling Points:

Blood samples were collected prior to metoclopramide administration and 0.25, 0.50, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, and 36 hours post bromocriptine mesylate administration.

Criteria for Evaluation

Analytical Method:

Analyte: Bromocriptine in human plasma
Method: LC-MS/MS
Assay range: 2.00 pg/mL to 500.00 pg/mL

Safety:

Safety was evaluated through the assessment of adverse events, standard laboratory evaluations and vital signs.

Mathematical Model and Statistical Methods of Pharmacokinetic Parameters

Main absorption and disposition parameters were estimated using a non-compartmental approach with a log-linear terminal phase assumption. The trapezoidal rule to estimate area under the curve, with the terminal phase estimation based on maximizing the coefficient of determination. The pharmacokinetic parameters of this trial were C_{max} , T_{max} , AUC_T , AUC_{∞} , $AUC_{T/\infty}$, K_d and $T_{1/2}$.

Statistical analysis was based on a parametric ANOVA model of the pharmacokinetic parameters; two-sided 90% confidence interval of the ratio of geometric means for the C_{max} , AUC_T and AUC_{∞} based on ln-transformed data; T_{max} rank-transformed. The level of significance was assessed at the two-sided 5% level.

ANOVA model:

- fixed factors: study group, treatment received, period in which it is given (nested within study group), sequence in which each treatment is received, study group-by-sequence interaction and study group-by-treatment interaction (whenever statistically significant at the two-sided 5% level).
- random factor: subject effect (nested within the study group-by-sequence interaction).

Criteria for Bioequivalence

- The 90% confidence interval for the exponential of the difference between the Test and the Reference product for the ln-transformed parameters C_{max} , AUC_T and AUC_{∞} were to be between 80.00 and 125.00%.

Safety:

Descriptive statistics.

SUMMARY - CONCLUSIONS

Pharmacokinetic Results:

A single center, randomized, single dose, laboratory-blinded, two-way, crossover comparative bioequivalence study was conducted under fed conditions on sixty-three (63) healthy male and female subjects. The rate and extent of absorption of bromocriptine were measured and compared following a single dose (6 x 0.8 mg) of bromocriptine mesylate tablets and CyclosetTM (Bromocriptine mesylate) tablets. The bioavailability of the two formulations of bromocriptine mesylate was equivalent under fed conditions. The results from measured data based on fifty-seven (57) subjects are summarized in the following summary tables (see page 6).

Safety Results:

Forty-four (44) of the sixty-three (63) subjects experienced a total of eighty-seven (87) adverse events during the study. Fifty-seven (57) adverse events (18 different types) were reported after the single dose administration of the Test product and thirty-three (33) adverse events (16 different types) were reported after the single dose administration of the Reference product. Three (3) adverse events associated with post-study laboratory test results were imputed to both formulations. Three (3) possibly related events (neutrophil count increased (reported twice), vaginal discharge and hiccups) were unexpected. No serious adverse events (SAEs) were recorded in this study.

Conclusion:

The study can be considered to have been conducted with a good tolerance of the subjects to the study drugs.

The results presented herein show that the criteria used to assess bioequivalence between the Test and Reference formulations were all fulfilled. The Test to Reference ratio of geometric LSmeans and corresponding 90% confidence interval for the C_{max} , AUC_7 and AUC_{∞} were all within the acceptance range of 80.00 to 125.00%.

Therefore, the Test formulation (Bromocriptine mesylate 0.8 mg tablets, Patheon Pharmaceuticals Inc. for VeroScience LLC) is judged to be bioequivalent to the Reference formulation [CyclosetTM (bromocriptine mesylate) 0.8 mg tablets, Pitva Croatia, Ltd, Croatia] under fed conditions.

C Filing Memo

1.1.1 Office of Clinical Pharmacology				
2 New Drug Application Filing and Review Form				
2.1.1.1 General Information About the Submission				
NDA Number	Information	Brand Name	Information	
OCP Division	2	Generic Name	Cycloset	
Medical Division	DMEP	Drug Class		
OCP Reviewer	Jayabharathi Valayathan, Ph.D.	Indication(s)	Treatment of type 2 diabetes	
OCP Team Leader	Sally Choo, Ph.D.	Dosage Form	0.8 mg tablets	
		Dosing Regimen	1.6 to 4.8 mg QD to be taken within 2 hours after waking in the morning	
Date of Submission	4/13/08	Route of Administration	Oral	
Estimated Due Date of OCPB Review		Sponsor	VereScience LLC	
FOUFA Due Date	10/16/08	Priority Classification	Priority	
2.1.1.2 Division Due Date		Submission Type	805 (b) (1) Complete response to approvable letter	
2.1.1.2.1.1.1 Cln. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
PK Summary	X			
Labeling	X			
Reference Bionalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Dose balance:				
Isotonic characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I):				
2.2 Healthy Volunteers-				
single dose:				
multiple dose:				
2.2.1 Patients-				
single dose:				
multiple dose:				
Dose proportionality:				
Fasting / non-fasting single dose:				
Fasting / non-fasting multiple dose:				
Drug-drug interaction studies:				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies:				

ethnically:							
gender:							
pediatrics:							
geriatrics:							
renal impairment:							
hepatic impairment:							
PD:							
Phase 2:							
Phase 3:							
PK/PD:							
Phase 1 and/or 2, proof of concept:							
Phase 3 clinical trial:							
Population Analyses -							
Data rich:							
Data sparse:							
B. Biopharmaceutics							
Absolute bioavailability:							
Relative bioavailability -							
solution as reference:							
alternate formulation as reference:							
Bioequivalence studies -							
traditional design: single / multi dose:	x	1					
replicate design: single / multi dose:							
Food-drug interaction studies:							
Discoloration:							
(IVC):							
No-waiver request based on BCS							
BCS class							
C. Other CBE Studies							
Genotype/phenotype studies:							
Chromopharmacokinetics							
Post-drug development plan							
Literature References							
Total Number of Studies		1					
2.2.1.1.1							
2.2.1.1.2	Feasibility and QBR comments						
2.2.1.2	X if yes	2.2.1.2.1.1.1.1.1.1 Comments					
2.2.1.3	X	Yes, it is feasible.					
2.2.1.4	Application feasible ?	Please submit the SAS transport files (or if submitted, indicate where the files are located) for the BE study data.					
2.2.1.5	Comments sent to firm ?						
QBR questions (key issues to be considered)	Are the to-be marketed tablets bioequivalent to the tablets used in the large safety trial (PLIVA product)?						
Other comments or information not included above	DSI inspection is requested for the BE study BON-P6-262.						
Primary reviewer Signature and Date	Jaya Bharathi Vaidyanathan, Ph.D.						
Secondary reviewer Signature and Date	Sally Choo, Ph.D.						

Summary:

With this application, the current sponsor, VeroScience LLC is filing a complete response to Agency's approvable letter for this NDA, dated Oct 15, 1999. The NDA was originally filed by ErgoScience Corp. The Agency issued an approvable letter with the major requirement for approval being to conduct a large, safety study (# 165-AD-04-03-US-1) of Cycloset in patients with type 2 diabetes. ErgoScience transferred the NDA to PLIVA in 2003. VeroScience collaborated with PLIVA on the study design and execution of the safety study which was started in July 2004. PLIVA then transferred the ownership of the NDA to VeroScience in May, 2006.

The different formulations used in this NDA are described in the Table below:

<i>Sponsor</i>	<i>Manufacturer of Cycloset tablets</i>	<i>Formulation used in Clinical Trials</i>
ErgoScience	Geneva Pharmaceuticals, Broomfield, CO	Studies submitted with the originally filed NDA
Transferred to PLIVA	PLIVA, Croatia	Subsequent clinical studies, including safety trial (# 165-AD-04-03-US-1)
VeroScience	Patheon Inc, Cincinnati, Ohio	To-be-marketed formulation

VeroScience had a Type B meeting with FDA on Feb 21, 2007 to discuss the approvable letter. One of the issues discussed was the need of bridging the data obtained from the NDA with the to-be-marketed product from Patheon Inc. Since the Geneva product used in original NDA is no longer available, the sponsor was required to provide an efficacy bridge between the Geneva product and PLIVA product using efficacy data from pre-specified efficacy subgroups in the safety trial ((# 165-AD-04-03-US-1) to the efficacy data from Phase 3 studies in the original NDA. Also, the sponsor performed a BE study to bridge the Patheon product and the PLIVA product used in the large Cycloset safety trial. This BE study (# BON-P6-262) is included in this submission.

The sponsor's question and discussion regarding this issue is attached from the meeting minutes as follows:

5. The previous sponsor (Pliva d.d.) was also the manufacturer of the Cycloset product utilized in the ongoing safety trial. However, Pliva d.d. is no longer manufacturing Cycloset. Consequently, VeroScience has contracted with a new U.S. manufacturer for the manufacture of registration batches and commercialization of Cycloset product. As a result of moving the manufacture of Cycloset to a new facility, the amended NDA will compare three different versions of drug product:

- The product used for the original clinical trials in the originally filed NDA
- The product used in the current safety study, and
- The product proposed for marketing.

VeroScience has provided a plan for bridging of bioequivalence among these three versions. These protocols and the overall bridging approach were submitted recently for review under the Cycloset IND (Serial No. 0321). Does the FDA agree with these plans?

FDA Response: We have never granted a pivotal BE assessment based on cross-study comparison. Therefore, the proposed bioequivalence study to demonstrate BE between the products used in original NDA submission and the products used in the ongoing safety trial is not acceptable. Pivotal bioequivalence needs to be established in a single study. If the products used in the pivotal clinical trials in the original NDA are no longer available, a clinical efficacy bridge study is recommended.

From 2/21/07 meeting: the company stated that a non-traditional approach was taken to assess BE of this product due to the 3 different sponsors and 3 different manufacturing sites. The current manufacturing contractor is Patheon Inc. (Cincinnati, OH), and provides for the same ingredients, formulations, chemical features, etc. The company provided a dissolution profile of tablets from three manufacturing sites. A BE trial of the PLIVA product versus the Patheon product will be conducted.

FDA emphasized that the dissolution profile for Geneva site was from historic data. Such dissolution analysis for f_2 calculation across studies is not valid. The site change is considered a Level 3, which requires an in-vivo BE study. The originally proposed BE study only can be used as supportive.

This method of bridging between formulations is not acceptable. While the Division recognizes that there is no other alternative since the initial drug product is no longer available, the company must provide sufficient evidence supporting efficacy of the to-be-marketed formulation. There was extensive discussion surrounding efficacy analyses from the cardiac safety study. The medical and statistical reviewers expressed concern that confounding effects of background therapy or study design will not permit a reliable estimate of efficacy. We can not commit that this proposal is adequate for establishing efficacy and it will therefore be a review issue. Alternatively, the company can conduct an efficacy study evaluating the effect of Cycloset in combination with metformin. As there is a high likelihood that these two drugs would be used together in practice, a well-designed study to evaluate efficacy (and safety) may overcome the problems of bridging efficacy through indirect bioequivalence studies and analysis of your safety study.

The Biopharmaceutics section contains the bioequivalence study BON-P6-262 comparing the PLIVA product used in the long term safety trial and the to-be-marketed product manufactured by Patheon. This was a single dose, randomized, two-way crossover study under fed conditions in 63 healthy male and female subjects. The two treatments were:

- Bromocriptine mesylate tablets (Test, Patheon) (6 x 0.8 mg)
- Cycloset (Bromocriptine mesylate) tablets (Reference, PLIVA) (6 x 0.8 mg)

The sponsor's results are summarized in the following Tables.

Bromocriptine mesylate PK parameters:

PARAMETER	TEST		REFERENCE		F (treatment)	p *
	MEAN	C.V. (%)	MEAN	C.V. (%)		
C_{max} (pg/mL)	126.49	77.8	128.95	77.3	0.09	N.S.
$\ln(C_{max})$	4.4829	20.9	4.5257	20.0	0.60	N.S.
T_{max} (hours) §	1.50	60.0	1.50	47.0	0.59	N.S.
AUC_T (pg·h/mL)	435.30	82.2	440.57	85.2	0.03	N.S.
$\ln(AUC_T)$	5.7054	16.7	5.7161	16.9	0.05	N.S.
AUC_{∞} (pg·h/mL)	456.27	88.3	472.45	89.2	0.42	N.S.
$\ln(AUC_{\infty})$	5.7563	15.8	5.7884	16.1	0.56	N.S.
$AUC_{T/\infty}$ (%)	93.16	6.5	92.88	7.1	0.13	N.S.
K_{el} (hour ⁻¹)	0.2158	66.8	0.2178	69.8	0.00	N.S.
$T_{1/2}$ (hours)	5.95	83.2	6.02	85.0	0.00	N.S.

* N.S.= Not Significant. Significant whenever p-value < 0.05.

§ For T_{max} , the median is presented and the statistical analysis is based on a rank-transformation.

Statistical analysis:

H3P 3P1

Analytical site:

b(4)

- Application is filable from a Clinical Pharmacology perspective.

Comments to Sponsor:

- Please submit the SAS transport files (or if submitted, indicate where the files are located) for the BE study BON-P6-262 data.

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

/s/

Jayabharathi Vaidyanathan
10/8/2008 10:22:10 AM
BIOPHARMACEUTICS

Sally Choe
10/8/2008 10:26:46 AM
BIOPHARMACEUTICS

NDA 20-866
Clinical Pharmacology Filing
Review
Cycloset
Bromocriptine mesylate tablets
(0.8 mg)

Formulations Used

<i>Sponsor</i>	<i>Manufacturer of Cycloset tablets</i>	<i>Formulation used in Clinical Trials</i>
ErgoScience	Geneva Pharmaceuticals, Broomfield, CO	Studies submitted with the originally filed NDA
Transferred to PLIVA	PLIVA, Croatia	Subsequent clinical studies, including safety trial (# 145-AD-04-03-US-1)
VeriScience	Pfizer Inc, Cincinnati, Ohio	<u>To-be-marketed formulation</u> ✕

Clinical Pharmacology Study

- Compares the PLIVA product to the Patheon product.
- Single dose, randomized, 2-way crossover study design
- Under fed conditions
- 63 healthy male and female subjects

2 TO BE compared TO NEW #3
(TBM)

BE- 2+3
efficacy basis 1+2

Result: Sponsor's Analysis

PARAMETER	TEST		REFERENCE		F (treatment)	P [*]
	MEAN	C.V. (%)	MEAN	C.V. (%)		
C _{max} (pg/mL)	126.69	77.3	128.93	77.3	0.09	N.S.
ln (C _{max})	4.4829	28.9	4.9357	28.8	0.68	N.S.
T _{max} (hours) [†]	1.50	68.8	1.50	47.0	0.59	N.S.
AUC _T (pg·h/mL)	436.38	82.2	448.57	83.2	0.03	N.S.
ln (AUC _T)	5.7844	16.7	5.7161	16.9	0.05	N.S.
AUC _∞ (pg·h/mL)	496.27	88.3	472.45	89.2	0.42	N.S.
ln (AUC _∞)	5.7983	15.8	5.7884	16.1	0.56	N.S.
AUC _{0-∞} (%)	93.16	6.3	92.88	7.1	0.13	N.S.
K _{el} (hour ⁻¹)	0.2158	66.8	0.2178	69.8	0.00	N.S.
T _{1/2} (hours)	5.95	83.2	6.02	85.0	0.00	N.S.

* N.S. = Not Significant. Significant whenever p-value < 0.05.

[†] For T_{max}, the median is presented and the statistical analysis is based on a rank-transformation.

Result: Sponsor's Analysis

PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC MEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C _{max}	32.1	88.12	92.21	95.57	86.63	105.43
AUC _T	21.3	299.49	302.24	99.09	92.74	105.88
AUC _∞	20.5	323.71	334.10	96.89	90.23	104.04

* units are pg/mL for C_{max} and pg·h/mL for AUC_T and AUC_∞

Issues

- To-be-marketed formulation not identical to the formulation used in Phase 3 clinical trials.
 - * - Efficacy bridge: Efficacy data from original submission and Subset from Safety trial (165-AD-04-03-US-1)
 - Fed BE study (linking PLIVA safety trial formulation and to-be-marketed formulation)
- * • DSI inspection requested for the BE study
 = TO BE DONE (samples)

* BE study (Elscomunic) cannot be located

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20-866/ N-000

SUBMISSION DATE:

22-AUG-97

19-DEC-97

15-JAN-98

30-JAN-98

02-MAR-98

BRAND NAME:

Ergoset™

0.8 _____ ng oral tablets

b(4)

GENERIC NAME:

bromocriptine mesylate

REVIEWER:

Robert M. Shore, Pharm.D.

SPONSOR:

Erge Research Corp.,
Charlestown, MA

TYPE OF SUBMISSION:

Original NDA Application, 505(b)(2)
Code: 13

SYNOPSIS:

Ergoset (bromocriptine mesylate), a semisynthetic derivative of the ergotoxine group of ergot alkaloids, is a dopamine receptor agonist. Clinically, bromocriptine reduces plasma levels of prolactin in patients with elevated prolactin concentrations. The sponsor states that the effects of bromocriptine on prolactin secretion and lipogenesis have important implications in the management of patients with NIDDM.

Bromocriptine mesylate is currently marketed in the U.S. by Sandoz (Parlodel®) as 2.5 mg Snaptabs® and 5 mg capsules for hyperprolactinemia-associated dysfunction and the prevention of physiological lactation. It is also used concomitantly with other drugs to treat the signs and symptoms of Parkinson's disease, and as adjunct therapy for Acromegaly. It was approved in the late 1970s.

The sponsor claims that Ergoset is a faster-acting tablet (i.e., shorter T_{max} than Parlodel®). This claim is based on more complete dissolution at 30 minutes of the Ergoset tablets than Parlodel® 2.5 mg tablets. However, the sponsor has not submitted any comparative *in vivo* data to support this claim. In addition, Ergoset tablets, when dosed with food, demonstrated a T_{max} of about 2 hours which does not correlate in any way with a 30 minute dissolution.

Erge Research Corporation proposes to market _____ Ergoset tablet _____ 0.8 mg, _____ and _____
_____ *In vivo* data are available. _____ All pivotal clinical trials
were conducted with only the 0.8 mg tablet (multiple tablets were taken for higher doses). The sponsor
has demonstrated that there is dosage form equivalence between the 0.8 mg and _____ when
administered in a fasted or fed state; there was a failure to demonstrate it between the _____ and
either the 0.8 mg _____ tablet in the fasted state. Dosage form equivalence between the 0.8 mg,
_____ was demonstrated when administered with food (high fat FDA meal). Since
patients enrolled in the pivotal clinical efficacy and safety trials were instructed to take their Ergoset dose
with breakfast and dosage form equivalence was demonstrated under fed but not fasted conditions, the
labeling should indicate that Ergoset must be taken with food.

There have been no *in vivo* data generated with the _____ The sponsor has requested _____

However, at an FDA Biopharmaceutics Coordinating Committee meeting on 19-MAR-98, it was determined that

b(4)

Much of the human pharmacokinetic information about bromocriptine comes from the published literature and from the Parlodel® labeling. About 30% of a radioactively labeled oral dose is absorbed. Bromocriptine is highly extracted by the liver, undergoes first-pass metabolism, and only about 7% of the oral dose can be detected systemically. Bromocriptine is 90-96% protein bound with only 2-5% of the dose excreted in urine, probably as metabolites. Metabolism data, mostly from animals, indicate that there are many metabolites (literature indicates as many as 16-30) which appear not to be active. *In vitro* work by the sponsor with human liver microsomes indicate that two major metabolites are formed exclusively by CYP3A4, a P450 hepatic enzyme; however, the Agency is awaiting validation data for these studies (requested 07-APR-98). Pharmacokinetic parameters of bromocriptine have been generated with Ergoset using an assay system (mass spectroscopy) that appears to be more sensitive and specific than assays (radioimmunoassays) used in the published literature; some previous published data often indicated a half-life of bromocriptine of up to 50 hours, whereas the half-life of bromocriptine in the Ergoset NDA is 3-4 hours. Also, many published articles indicate maximum plasma bromocriptine concentrations, after doses of 5 mg, in the ng/mL range, whereas the Ergoset NDA demonstrates pg/mL concentrations after similar size doses of Ergoset. This brings into question the absolute certainty of the older published literature (based on older assays) in regard to the pharmacokinetics of bromocriptine.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed NDA 20-866 submitted 22-AUG-97, 19-DEC-97, 15-JAN-98, 30-JAN-98, and 02-MAR-98. The overall Human Pharmacokinetic Section is acceptable to OCPB.

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_____ This recommendation, comments (p. 17), and labeling comments (p. 17) should be sent to the sponsor as appropriate.