CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-866

SUMMARY REVIEW

Summary Basis of Regulatory Action

Date	May 5, 2009
From	Mary H. Parks, M.D.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	20-866
Applicant Name	VeroScience, LLC
Date of Submission	April 13, 2008
PDUFA Goal Date	October 15, 2008
Proprietary Name / **Established (USAN) Name**	Cycloset® (bromocriptine mesylate)
Dosage Forms / Strength	0.8 mg tablets
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Robert Misbin, M.D.
Statistical Review	Lee Ping Pian, Ph.D.
Pharmacology Toxicology Review	Gemma Kuijpers, Ph.D.
CMC Review/OBP Review	Xavier Ysern, Ph.D.
Microbiology Review	Not applicable
Clinical Pharmacology Review	Jayabharathi Vaidyanathan, Ph.D.
DDMAC	Kendra Jones
DSI	Roy Blay
CDTL Review	Hylton Joffe, M.D., M.M.Sc.
OSE/DMEPA	Melina Griffis
OSE/DDRE	Parivash Nourjah
OSE/DSRCS	Nancy Carothers

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

Division Director's Summary Review

1. Introduction

This application represents a second resubmission to NDA 20-866 for bromocriptine mesylate in support of an indication for glycemic control in adults with type 2 diabetes mellitus.

2. Background

The original NDA for use of bromocriptine mesylate (hereafter referred to as the [redacted] bromocriptine) as an anti-diabetic therapy was submitted to the Agency on August 18, 1997 by Ergo Science Corporation (hereafter referred to as Ergo Science). The proposed tradename for bromocriptine in that application was Ergoset®. The original NDA was comprised of 3 pivotal studies of 24-weeks duration (Studies K, L, and M). The NDA was discussed before the Endocrine and Metabolic Drugs Advisory Committee (EMDAC) on May 14, 1998, wherein the committee unanimously voted against approval of Ergoset® for the treatment of T2DM. The Agency issued a Not-Approvable (NA) letter on November 20, 1998, listing a small treatment effect for which an accompanying small imbalance in cardiac adverse events did not yield a favorable risk-benefit profile. Overall, the average treatment difference in mean HbA1c change from Baseline was 0.5%. The cardiac safety signal was based on only a few events in the original NDA but the voluntary withdrawal of the indication for postpartum lactation due to postmarketing reports of myocardial infarctions, strokes, and seizures around the same time also contributed to the final decision. After issuance of the NA letter a complex regulatory history ensued, including Ergo Science's appeal to the Director of the Office of Review Management (presently Office of New Drugs) wherein a decision was made that the company had provided a complete response to the NA letter on April 15, 1999. A second review cycle of the NDA ultimately resulted in an Approvable (AE) letter issued on October 15, 1999. The following deficiencies were summarized in that letter:

b(4)

> *Based on the data submitted to the NDA, we remain concerned that treatment of patients with Type 2 diabetes with Ergoset may be associated with an increased risk of serious cardiac adverse events. The new data submitted in the April 15, 1999, response to the November 20, 1998, Not-Approvable letter (e.g., the Testa UK GPRD study), do not adequately address this concern. While you have demonstrated the efficacy of Ergoset in patients with Type 2 diabetes (see letter from Dr. Lumpkin dated June 10, 1999), the magnitude of the treatment effect seen in the phase 3 clinical trials was small. Given the small treatment benefit and the outstanding safety concerns, the overall risk versus benefit analysis for Ergoset for the treatment of patients with Type 2 diabetes does not support approval at this time. To address the outstanding safety concerns, we recommend that you conduct a new, placebo-controlled study of the safety of Ergoset in patients with Type 2 diabetes. The new study should be adequately designed and powered to evaluate the potential for a significant increase in the risk of*

serious cardiac adverse events with Ergoset treatment. We suggest that you consider using a large, "simple" trial design to achieve this objective.

Drs. Misbin and Joffe have summarized this regulatory history in their separate reviews. In addition, then Office Director, Dr. John Jenkins, who was the signatory authority for the October 15, 1999 action letter, has provided a thorough administrative memo on that same date that is archived in the Division Files System (DFS).

Since then the ownership of NDA 20-866 has been transferred twice resulting in 3 different formulations, which must be considered in any labeling of safety and effectiveness for this product. The following table summarizes the NDA ownership and formulations contributing to pivotal safety and efficacy data.

Table 1. Summary of NDA Holders and Formulation Changes of Bromocriptine Mesylate

NDA sponsor	Manufacturer of Bromocriptine	Role in Marketing Application	Comments
Ergo Science (filed NDA 8/97)	Geneva Pharmaceuticals, Broomfield, CO	This formulation was used in the pivotal efficacy and safety studies submitted with the original NDA on August 1997	NDA was NA'd initially then AE'd on 2nd review cycle. This formulation is no longer available for purposes of bridging to recent formulations.
Pliva (acquired NDA 11/03)	Pliva Croatia	This formulation was used in the cardiac safety trial conducted in response to the AE letter issued on 10/15/99	NDA acquired by VeroScience who plans to market a different formulation
VeroScience (acquired 5/06)	Patheon Inc Cincinnati, OH	This is the formulation proposed for marketing (to-be-marketed formulation). No clinical efficacy and safety studies conducted with this formulation	PK bridging study to Pliva formulation allows bridging to CV safety trial PK bridging to original efficacy data not feasible since Ergo Science formulation no longer available. A subset of patients from the CV safety trial was included in an efficacy analysis to allow bridging to the to-be-marketed formulation

Table 1 outlines that the required CV safety trial necessary to address the AE deficiency of the October 15, 1999 action letter was conducted by Pliva. The design of this trial was discussed with the Agency prior to its initiation and deemed acceptable. With the more recent acquisition of the NDA by VeroScience, a different formulation is proposed for marketing that had not been evaluated in any of the clinical efficacy or safety trials. As a result, several

bridging studies were necessary to allow a conclusion that the findings of safety and efficacy observed with prior formulations would also be observed with the to-be-marketed formulation. For the remainder of this memo, the to-be-marketed formulation will be referred to as Cycloset®, the proposed tradename for bromocriptine under NDA 20-866 owned by VeroScience.

This Division Director's Summary Review will focus only on the following issues:

- Adequacy of this NDA with regarding to addressing the deficiencies outlined in the October 15, 1999 AE letter
- Adequacy of the efficacy bridging study
- Adequacy of the findings from the CV safety trial with respect to the December 2008 Final Guidance to Industry entitled "Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes"

For the most part, these issues are covered under Sections 5, 7, 8, and 13 of my memo.

Please see the separate discipline reviews compiled in the complete action package supporting the final decision on this application. Unless I have a differing opinion to the conclusions of any of those reviews, my memo will only refer the reader to the discipline review for details of their findings.

3. CMC/ /Device

Please see Dr. Xavier Ysern's review. No pending issues precluding approval of this NDA.

4. Nonclinical Pharmacology/Toxicology

Please see Dr. Gemma Kuijper's reviewer. No pending issues precluding approval of this NDA.

5. Clinical Pharmacology/Biopharmaceutics

VeroScience submitted the results of a single center, randomized, single-dose, 2-period, 2-sequence crossover study conducted in healthy subjects under fed conditions to establish bioequivalency between the Pliva (formulation used in the CV safety trial) and Pantheon (Cycloset®) products. Please see Dr. Jayabharathi Vaidyanathan's review for a detailed description of the study and its results. Bioequivalence between these two products was established for all parameters assessed (Cmax, AUC_{0-t}, and $AUC_{0-\infty}$) by the applicant, as summarized in the following table obtained from Dr. Vaidyanathan's review. Similar results were obtained in the reviewer's analysis (see Table 6 in OCP review)

Table 2. Results of Bioequivalence Study Comparing Pliva vs Cycloset Formulations. Adapted from Dr. Vaidyanathan's Review.

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-t} pg-hr/mL	299.49	302.24	99.09	92.74	105.88
$AUC_{0-\infty}$ pg-hr/mL	323.71	334.10	96.89	90.23	104.04

Not only were the 90% confidence intervals for the ratios of the geometric LS means of the PK parameters within the pre-specified limits of 80-125% for establishing bioequivalence, but the actual ratios were close to 1.0 for each of these parameters. It should also be pointed out that [redacted] b(4)
[redacted] lending further support to the conclusion that these products are bioequivalent (Table 3).

Table 3. Composition of Three Formulations of Bromocriptine Mesylate. Adapted from Dr. Vaidyanathan's review.

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

b(4)

(*equivalent to 0.8 mg bromocriptine)

I concur with the OCP reviewers that Cycloset® is bioequivalent to Pliva's bromocriptine formulation evaluated in the safety study. Consequently, the labeling for safety of Cycloset® may rely on the findings from the submitted safety study. However, in order to include any efficacy information on bromocriptine from the original NDA in labeling, the applicant had to provide bridging of efficacy in a subset of patients in the safety study to the original efficacy trials. This analysis, discussed further in Section 7 of this memo, allows for FDA to conclude that since Cycloset® = Pliva and Pliva = Ergoset®, one can also conclude that Cycloset® = Ergoset® with respect to efficacy results.

6. Clinical Microbiology (where relevant)

Not applicable

7. Clinical/Statistical-Efficacy

The primary efficacy parameter for this application is glycemic control, measured as a change from Baseline in HbA1c relative to control. Although prior FDA decisional memos and the approvable letter dated October 15, 1999, have concluded bromocriptine to be effective at reducing HbA1c, this applicant was still obligated to provide evidence of effectiveness Cycloset®. As discussed extensively in the medical, clinical pharmacology and statistical reviews and summarized in Section 5 of this memo, the basis for this requirement is the unavailability of the formulation for which efficacy was demonstrated in the original NDA precluding a pharmacokinetic bridging to the to-be-marketed formulation manufactured by Patheon. As such, VeroScience had to provide evidence of efficacy via an analysis of a subset of patients in a safety study using a bioequivalent formulation to Cycloset®. The details of this "bridging efficacy" have been extensively discussed in Dr. Pian's statistical review.

In brief, the efficacy analyses in the CV safety study were confined to the ITT population with Baseline HbA1c $\geq$ 7.5% in patients on one or two oral agents, excluding insulin, who completed 24 weeks of the trial. The CV safety study was designed with the primary objective of identifying a safety signal with bromocriptine therapy, not glycemic efficacy. The patient population studied included those who had reasonable glycemic control at Baseline (mean 7.0%) for which additional anti-diabetic therapies could be added after 12 weeks to maintain a goal of HbA1c < 7%. At Week 52 (end of study) the mean HbA1c was 7.0% whereas placebo was 7.2%. Therefore, limiting efficacy analyses to the subset of patients with Baseline HbA1c $\geq$ 7.5% was to ensure the selection of a diabetic population who did not have adequate glycemic control for which any efficacy of bromocriptine could then be measured. Determining efficacy at 24 weeks was deemed appropriate as this timepoint has been established in prior trials with bromocriptine to be a sufficient duration to assess efficacy.

The CV safety study was comprised of 2054 Cycloset-treated patients and 1016 placebo-treated patients. Of these, 559 (18.2%) were included in the efficacy subset: 376 on Cycloset and 183 on placebo. Efficacy was further analyzed by the subset of patients who were taking metformin + SU, taking only metformin, taking only SU, and taking neither metformin nor a SU. It should be noted that the pivotal studies from the original NDA were conducted prior to the widespread use of metformin. Some key demographic characteristics of the CV safety population and Studies K, L, and M are summarized in the following table.

Table 4. Comparison of Selected Characteristics of Safety Study and Studies K, L, and M

Characteristics	CV Safety Study	Study K (add-on to SU)	Study L (add-on to SU)	Study M (monotherapy)
Mean Baseline HbA1c	7.0%	9.3%	9.3%	8.9%

Baseline BMI	32.4 kg/m2	32.5 kg/m2	32 kg/m2	---
Duration of Diabetes	7.9 years	7.0 years	7.0 years	4.5 years

Any comparison between the "bridging" efficacy subset from the CV safety study to Studies K, L, and M would need to consider that the more recently studied group of patients had better glycemic control than observed in the original study populations and the different background anti-diabetic therapies used. As such, the efficacy results from the subgroup in the CV safety study were only compared descriptively with the efficacy results in the 3 pivotal studies K, L, and M in the original NDA. No statistical comparisons were made between the different trials.

From Table 17 of Dr. Pian's review, the placebo-subtracted difference in HbA1c reduction in a LOCF analysis was 0.4 to 0.5% in the CV safety subgroup of patients. A completers analysis reveals a slightly greater range of efficacy (0.6-0.7% reduction). These results are similar to efficacy observed in studies K, L and M, which demonstrated mean reductions in HbA1c in the ITT/LOCF analysis of 0.4-0.6% relative to placebo. As pointed out by Dr. Misbin, the SU-only subset in the CV safety study had a mean 0.41% reduction in HbA1c relative to placebo and in Studies K and L, which would have also studied only SU and bromocriptine, had a mean reduction of 0.49-0.59%. The slightly higher response in the older studies might have been a result of a less adequately controlled diabetic population.

In conclusion, I agree that there has been provided sufficient bridging data (both pK and efficacy) to allow labeling of data derived from the Ergoset and Pliva formulations. The label describing glycemic efficacy will present these trial data separately. I also note that the applicant has proposed studying Cycloset in combination with a TZD and in combination with insulin. The results from these trials will provide future efficacy data with the to-be-marketed formulation.

8. Safety

The pivotal study (Study 165-AD-04-03-US-1) provided in this resubmission was designed to address safety of bromocriptine in patients with T2DM. This was a 52-week, double-blind, placebo-controlled, randomized, multicenter trial in patients with T2DM with HbA1c $\leq$ 10%. Patients were randomized in a 2:1 fashion to bromocriptine or placebo with the bromocriptine dosing carefully titrated over the course of several weeks to minimize intolerance to some known side-effects of the drug. The primary efficacy analysis was time to first serious adverse event. The secondary efficacy assessment included an analysis of a composite of serious cardiovascular adverse events of MI, stroke, hospitalization for heart failure or angina, and revascularization procedures and an analysis of these individual serious CV AEs. All serious AEs were blindly adjudicated by an independent events adjudication committee comprised of one endocrinologist and two cardiologists.

Reviews by Drs. Pian and Joffe have provided a very thorough description of the study design, conduct and results. The primary objective of this trial was to demonstrate non-inferiority of bromocriptine to placebo on the hazard ratio for serious AEs with a pre-specified NI margin of 1.5. For the CV AEs, it was determined that the sample size of 3000 would have 0.60 power to meet a non-inferiority margin of 1.5, assuming a placebo event rate of 3.43%.

Approximately 10% of the cohort had a prior history of MI at Baseline. Hypertension and hypercholesterolemia were reported in approximately 75% of the cohort.

The study met its primary objective based on the results in the ITT population. 8.6% of the Cycloset-treated patients versus 9.6% of the placebo-treated patients experience a serious AE (HR 1.02; 95% CI 0.82-1.27). Of particular relevance were the findings for the composite cardiovascular AEs. I have copied below a table from Dr. Pian's review which summarizes these findings:

Table 5. Secondary endpoint (adapted from Dr. Pian's review)

	Cycloset n (%)	Placebo n (%)	Hazard Ratio (95% confidence interval)
Cardiovascular composite	31 (1.5)	30 (3.0)	0.58 (0.35-0.96)
Individual components of the composite			
Myocardial infarction	6 (0.3)	8 (0.8)	0.44 (0.15-1.26)
Stroke	4 (0.2)	6 (0.6)	0.37 (0.10-1.32)
Inpatient hospitalization for angina	9 (0.4)	9 (0.9)	0.55 (0.22-1.38)
Inpatient hospitalization for heart failure	7 (0.3)	5 (0.5)	0.81 (0.26-2.57)
Revascularization surgery	9 (0.4)	6 (0.6)	0.85 (0.30-2.40)

These results are relevant in light of the recently published final Guidance to Industry titled "Diabetes Mellitus – evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes". In this guidance, the new regulatory requirements for an antidiabetic therapy include demonstrating that the upper bound of the two-sided 95% CI for the estimated risk ratio is < 1.8 in order to gain approval, assuming there are no other offsetting safety concerns and there is established efficacy. Subsequent to approval, the applicant would need to provide more definitive evidence that the anti-diabetic therapy does not increase cardiovascular risk to an unacceptable level by demonstrating that the upper bound of the two-sided 95% CI for the estimated risk ratio is < 1.3.

For these specific criteria, Cycloset met not only the first goal post of < 1.8, but it was also able to rule-out an upper-bound of the 95% CI of 1.3 for the cardiovascular composite endpoints of MI, stroke, hospitalization for angina, hospitalization for heart failure, and revascularization procedures. While the primary composite endpoint is not comprised of the traditional MACE endpoints of nonfatal MI, stroke and CV death, it is important to note in the above table that for MI and stroke the HR was well below 1.0 and the upper-bound of the 95% CI was < 1.3 for MI and just slightly above it for stroke.

Dr. Joffe has discussed the deaths during this safety trial. There were 4 deaths in the Cycloset group and 2 in the placebo group, which would be considered balanced given the 2:1 randomization. Of the 4 deaths in the Cycloset group, only 2 were CV-related whereas both

deaths in the placebo group were CV-related. All told, the rate of MI, stroke, and CV death was lower in the bromocriptine compared to placebo.

Also significant in the interpretation of these results in light of the Final Guidance is the methodology in which the CV events were assessed in this trial. Although the composite CV AEs were considered part of a secondary endpoint, they were adjudicated in a blinded fashion by an independent CV endpoints committee. This was an important recommendation made in the Final Guidance with the goal of assuring greater assurance of identifying and coding CV events completely and accurately.

Overall the favorable findings from the CV analysis support a conclusion that this NDA has not only addressed the deficiencies of the October 15, 1999 approvable letter but it has also met the requirements set forth in the December 2008 Guidance to Industry. No post-marketing study is required to further assess cardiovascular risk associated with bromocriptine use in diabetes mellitus. However, despite the favorable HRs and a marginally significant result on the primary composite CV endpoint, I agree with the reviewers that the high-drop rate in the bromocriptine group, the secondary nature of the analysis, and the still overall low event rates do not support a claim of [redacted]. Labeling can, however, include a statement that bromocriptine does not increase CV risk.

Other safety issues have been described in the reviews of Drs. Misbin and Joffe. I would note that many of these adverse events are known side-effects of bromocriptine which has been marketed since 1978. However, more recently valvulopathy has been described with two other dopamine agonists, Pergolide® and Cabergoline®. A case-control study was published in 2007 which described a greater rate of valvulopathy associated with these two drugs than Parlodel (brandname of bromocriptine) which was attributed to the two former drugs being potent 5-HT_{2B} receptor agonists. A review of postmarketing adverse events report by the Office of Surveillance and Epidemiology has revealed only a few reports of valvular disease associated with bromocriptine. Nonetheless, labeling will include a discussion of this finding in this class of drugs and routine postmarketing surveillance will include this adverse event as one of special interest.

9. Advisory Committee Meeting

It was determined that this application did not need to be discussed before an advisory committee for several reasons:

- This was not a new molecular entity (NME)
- The applicant fully addressed the deficiency of the AE letter issued on October 15, 1999 based on data of reasonable and reliable quality and for which statistical assessment could conclude that the findings were robust

10. Pediatrics

Please see Dr. Joffe's CDTL memo where he has provided an excellent summary of the deferred pediatric program.

11. Other Relevant Regulatory Issues

Please see Dr. Joffe's CDTL memo where he has thoroughly discussed remaining relevant regulatory issues, none of which precludes the approval of this application.

12. Labeling

Labeling has incorporated recommendations from all review disciplines and consulting divisions. Please see agreed-upon labeling attached with action letter.

13. Recommendations/Risk Benefit Assessment

- Regulatory Action

I recommend approval of this application.

- Risk Benefit Assessment

The applicant has adequately addressed all the deficiencies outlined in the October 15, 1999 action letter that are still considered relevant. Of note, the Safety Trial has not only addressed the 1999 deficiencies but also the requirements laid out in the December 2008 Guidance to Industry titled, "Diabetes Mellitus – evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes"

- Recommendation for Postmarketing Risk Management Activities

In conjunction with the Division's Deputy Director of Safety, Dr. Amy Egan, and the Office of Surveillance and Epidemiology, it has been concluded that no postmarketing risk management activities are necessary beyond routine surveillance.

- Recommendation for other Postmarketing Activities/Phase IV commitments

None required. The applicant has proposed to conduct additional studies in combination with TZDs and insulin. The Division confirmed its interest in having these studies performed and sent an information request letter on May 1, 2009.

- Comments to be Conveyed to the Applicant

See action letter.

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

/s/

Mary Parks
5/5/2009 09:26:08 AM
MEDICAL OFFICER