

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20-866

OTHER ACTION LETTER(s)

510 / Weber

OCT 15 1999

NDA 20-866

Ergo Research Corporation
Attention: David Burt
43 High Street
North Andover Mills
North Andover, MA 08145

Dear Mr. Burt:

Please refer to your new drug application (NDA) dated August 22, 1997, received August 22, 1997, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cycloset (bromocriptine mesylate) Tablets.

We acknowledge receipt of your submissions dated November 20, 23, and 30, 1998, March 18, April 15, August 5 (fax to Diane Wysowski), and September 27, 1999. Your submission of April 15, 1999, received April 16, 1999, constituted a complete response to our November 20, 1998, action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following deficiencies:

Clinical:

1. We remain concerned that treatment of patients with Type 2 diabetes with Cycloset may be associated with an increased risk of serious cardiac adverse events. The new data submitted in the April 15, 1999, response to our November 20, 1998, action letter (e.g., the Testa UK GPRD study) do not adequately address this issue. While you have demonstrated the efficacy of Cycloset 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 and demands a higher level of assurance that there are not serious adverse cardiac effects. Given the small treatment benefit and the significant unresolved safety concerns, the overall risk versus benefit analysis for Cycloset for the treatment of patients with Type 2 diabetes does not support approval. To address the outstanding safety concerns, we recommend that you conduct a new, placebo-controlled study of the safety of Cycloset 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 Cycloset treatment.

We suggest that you consider a large, "simple" trial design to achieve this objective. You are strongly encouraged to discuss the details of such a study with the Division of Metabolic and Endocrine Drug Products prior to the conduct of the study.

Biopharmaceutics:

2. ✓

b(4)

✓

✓

✓

b(4)

3. Physically halving tablets can affect dissolution. You should assess dissolution profiles between 12 halved tablets (the 2 halves of the same tablet placed in one dissolution vessel, preferably from the same 0.8 mg lot as the previously tested whole scored tablet) and 12 whole unscored tablets. The f_2 value should be calculated for comparative purposes. The methods should be the same as for the previous comparison of the whole scored and unscored tablets.

Pharmacology and Toxicology:

4. Qualification of the impurities _____ should be performed according to ICH recommendations.

b(4)

Any resubmission should include updated draft labeling. As communicated to Dr. Richard Paul, Ergo Science, via facsimile on August 6, 1998, we consider the tradename "Ergoset" unacceptable because of the possibility of confusion with the sound-alike names Ergostat and Percocet. The tradename "Cycloset" is considered acceptable. The statement "Pregnancy Category C" should be added to the Pregnancy subsection of the package insert along with information regarding the fetal and pup deaths that occurred when male rats treated with bromocriptine were mated with untreated female rats. We will provide additional comments on the draft labeling when the clinical and biopharmaceutic deficiencies listed above have been addressed.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

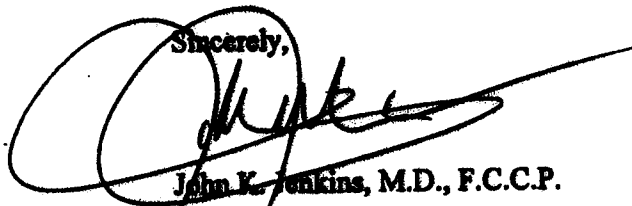
1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.
2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.
3. Details of any significant changes or findings.
4. Summary of worldwide experience on the safety of this drug.
5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.
6. English translations of any approved foreign labeling not previously submitted.
7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact Ms. Jena Weber, Regulatory Project Manager, at (301) 827-6422.

Sincerely,



John K. Jenkins, M.D., F.C.C.P.
Director

Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Archival NDA 20-866

HFD-510/Div. Files

HFD-510/JWeber

HFD510/SSobel/GTroendle/RMisbin/SMalozowski/BSchneider/BStadel/

XYsern/SMoore/GKuijpers/RSteigerewalt/RShore/HYAhn/LPian/

TSahlroot/EGalliers

HFD-002/ORM

HFD-102/ADRA

HFD-40/DDMAC (with labeling)

HFD-440/JStaffa/ERodriguez

HFD-820/DNDC Division Director

DISTRICT OFFICE

Drafted by: jmw/October 14, 1999

Initialed by: RSteigerewalt 10/15/RShore 10/15/HYAhn 10/15/LRipper 10/15/

JJenkins 10/15/99

final: JWeber 10/15/99

filename: c:/office/wpwin/wpdocs/ErgoAE2.doc

APPROVABLE (AE)

NOV 20 1998

Ergoscience
Attention: Ronald H. Abrahams, Ph.D.
100 First Avenue
Charlestown, MA 02129-2051

Dear Dr. Abrahams:

Please refer to your new drug application dated August 18, 1997, received August 22, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ergoset™ (bromocriptine mesylate).

We acknowledge receipt of your submissions dated August 18, November 25, December 19, and 23(3), 1997, January 13, 15, 26 and 30; February 23, March 2, 23, 24, and 31; April 8 and 10; May 7, 11(2), and 20; August 14 and 20, September 17, October 2, 5, 13, 20 (2), 22, and November 9, 1998. Your submission of August 20, 1998, extended the user fee goal date for this application to November 20, 1998.

We have completed our review and find the information is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). In our judgment, the modest degree of efficacy demonstrated in the clinical trials does not outweigh the potential safety risks.

A. Efficacy considerations

1. In studies K and L, the effect of Ergoset on HbA1c levels was evaluated over a 6-month period in patients who were also being treated with sulfonylurea hypoglycemic agents. Using a last-observation-carried-forward (LOCF) analysis of the intent-to-treat (ITT) population comparing the effect of Ergoset and placebo treatment on HbA1c, the least square mean difference was -0.49 percentage units for study K and -0.59 percentage units for study L, both statistically significant results. In study M, the effect of Ergoset on the same endpoint was also evaluated over a 6-month period in patients who were not being treated with sulfonylurea agents. Using the LOCF analysis of the ITT population, the least square mean difference was -0.38, which was borderline statistically significant ($p=0.052$).
2. The clinical benefit to patients of this degree of lowering of HbA1c by Ergoset, whether over a 6-month period as demonstrated in the clinical trials or whether the assumption is made that the effect would persist over longer time periods, is unknown.

The recently published results of the United Kingdom Prospective Diabetes Study (UKPDS) suggest that tighter control of blood glucose as reflected in decreased HbA1c levels with the use of certain sulfonylurea agents, metformin, and insulin in type 2 diabetes was associated with improvement in some cardiovascular complications of diabetes. However, the results of this complex study also present inconsistencies, and it remains unclear how the findings with the specific drugs studied over a period of years in the UKPDS apply to the modest effects on HbA1c observed with Ergoset.

3. An early response subgroup analysis was provided in which patients in the Ergoset treatment groups were identified who had a response equal to or greater than a 0.3% decrease in HbA1c by week 8. The HbA1c response in this subgroup was compared to the response in the entire placebo group, a biased comparison. In a subsequent analysis, a placebo comparison group was constructed as a weighted average of placebo responders and non-responders. Although the changes in HbA1c for the Ergoset early responders compared to the constructed placebo group were somewhat higher in each of the 3 studies with this analysis compared to the ITT analysis, the method of analysis remains flawed for estimating treatment effects because these subgroups were not randomized as such.

B. Safety considerations

1. We have concerns about the possible adverse cardiovascular effects of Ergoset. The manufacturer of Parlodel (bromocriptine) withdrew the drug for use in postpartum breast engorgement after reports of myocardial infarction and strokes when used for that indication. During the placebo-controlled phase of studies K, L, and M, 3 myocardial infarctions occurred in Ergoset-treated patients and 1 occurred in placebo-treated patients. The incidence rate was 2.4 (3/124) per 100 patient-years for Ergoset patients and 0.7 (1/137) per 100 patient-years for placebo patients. In the controlled and uncontrolled portions of all clinical trials in the NDA, the incidence rates of myocardial infarctions for Ergoset and placebo were 2.15 (8/372) and 0.59 (1/168.8) per 100 patient-years, respectively. Although these results do not reach statistical significance, the increased number of myocardial infarctions in the Ergoset group is of concern.
2. You cite the long-term use of bromocriptine in Parkinson's disease patients at higher doses than intended for Ergoset as providing assurance about its safety. While bromocriptine has been used in high doses in some Parkinsonian patients, the majority of patients appear to be treated with dosages in the range of 15 to 20 mg per day. Parkinson's disease patients in general are older than the population that used the drug for lactation suppression, and cardiovascular events would be expected to occur at a background rate more frequently in these patients than in lactation suppression patients.

The fact that no large increase in cardiovascular events has been detected by the spontaneous reporting system for Parkinson's disease patients treated with bromocriptine does not give a high degree of reassurance that the drug has no effect on cardiovascular events.

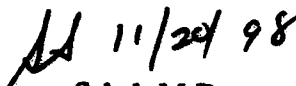
The Endocrinologic and Metabolic Drugs Advisory Committee met on May 14, 1998, to discuss the safety and effectiveness of Ergoset. In a unanimous vote, the Committee recommended that FDA not approve Ergoset for marketing. The Committee members expressed reservations about the drug's overall safety and benefit profile. We believe a review of the transcript of the meeting does not support the views expressed in your July 16, 1998, letter suggesting that FDA staff communicated new efficacy requirements to the Advisory Committee and made inappropriate comparisons to, or misstatements about, the efficacy of other drugs.

On October 5, 1998, the results of the insulin clamp study conducted by Dr. Ralph DeFronzo were submitted. After reviewing these and other requested data relating to the study, we conclude that a primary mechanism of action of Ergoset was not conclusively demonstrated. There was an imbalance of randomization for sulfonylurea users in the study and there was also a lack of correlation between changes in non-oxidative glucose disposal and key outcome variables among individual patients, e.g., HbA1c and fasting blood glucose.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, please contact Ms. Jena Weber, Project Manager, at (301) 827-6422.

Sincerely yours,

 11/24/98
Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug
Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: Original NDA 20-866

HFD-510/Div. files

HFD-002/Med Watch

HFI-20/Press Office

HFD-102/Office Director

HFD-102/JBilstad/Houn/LRipper

HFD-101/L. Carter

HFD-820/ONDC Division Director

DISTRICT OFFICE

HFD-735/DPE

HFD-92/DDM-DIAB

HFD-613/OGD

HFD-510/JWeber

HFD-510/GTroendle/SSobel/SMoore/XYsern/GKuijpers/RSteigerwalt

Rshore/HYAhn/LPian/TSahlroot/EGalliers

Drafted by: Jweber/11/12/98

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11/20/JBilstad 11/20/EGalliers 11/20/98

final: JWeber 11/20/98

NOT APPROVABLE (NA)