CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-100

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-100 APPLICANT: Lek Pharmaceutical

DRUG PRODUCT: Bromocriptine mesylate, U.S.P., 5 mg capsules

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in U.S.P. 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

for Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Bromocriptine Mesylate
5 mg Capsules
ANDA # 75-100
Reviewer: Man M. Kochhar
75100SD.397

Lek Pharmaceutical
Englewood Cliffs, NJ
Submission Date:
March 25, 1997

AMENDMENT TO BIOEQUIVALENCE STUDY AND DISSOLUTION DATA

NON-FASTING

INTRODUCTION:

Bromocriptine mesylate is an ergot derivative with potent dopamine receptor agonist activity. Bromocriptine mesylate is a nonhormonal nonestrogenic agent that inhibits the secretion of prolactin in humans,with little or no effect on other pituitary hormones.

The pharmacokinetics and metabolism of bromocriptine in human subjects were studied with the help of radioactivity labeled drug.Twenty-eight percent of an oral dose was absorbed from the GI tract. The plasma levels with a 2.5 mg dose were in the range of 4-6 ng/mL.

It is recommended that bromocriptine should be taken with food. The initial dose is half of 2.5 mg daily. An additional 2.5 mg tablet may be added to the treatment regimen as tolerated every 3-7 days until an optimal therapeutic response is achieved. It is available as 2.5 mg tablets or 5 mg capsules.

OBJECTIVE:

The objective of this study is to compare the relative bioavailability of two different formulations of bromocriptine mesylate using a single dose two-way crossover study in healthy volunteers under non-fasting conditions.

IN-VIVO STUDY:

The clinical part of bioequivalence study was conducted at Department for Medicine, Medical School, under the supervision of of and . The analysis of plasma samples was done at LEK Pharmaceutical and Chemical Company, Ljubljana, Slovenia under the supervision of Lucka Povsic, Milojka Mohar and Janja Urbancic.

STUDY DESIGN:

The study was designed as a randomized, single dose (2 x 5 mg), two-way crossover bioequivalence study in 28 healthy volunteers under non-fasting conditions.

Subjects:

The study employed twenty-eight (28) healthy male volunteers between the ages of 18--40, whose weight did not deviate by more than ±10% of the ideal for their height and age (Metropolitan Life Insurance Company Bulletin,1983). Volunteers without history of serious gastrointestinal, hepatic, cardiovascular, hematological or renal disease were employed. In addition, subjects were required to be without history of alcohol or drug use and prior sensitivity to drug product being tested.

Good health was ascertained from medical history, physical examination and routine laboratory tests (blood chemistry, hematology, urinalysis). The subjects were required not to take any prescription medications for atleast 14 days and OTC preparations for at least 72 hours prior to the start and until the end of the study. The volunteers were not allowed to drink alcoholic beverages or caffeine-containing products for 48 hours prior to dosing until after completion of the study. Each subject signed a written informed consent.

The subjects remained in the clinic from 10 hours before the drug administration till the completion of the study.

Methods:

The product and dosage employed in this study were as follows:

A. Test: 2 x 5 mg Bromocriptine Mesylate (test drug), lot # PD068 01 with 240 mL of water.
Batch size: Date of Manuf: May 1996
Content Uniformity: 100.7%

B. Reference: 2 x 5 mg Parlodel (Sandoz)), lot # 196 X9136 with 240 mL of water. Expiry Date: 10-98
Content Uniformity: 100.78%

The subjects fasted from 10 P.M. the evening before the trial. On the testing day an i.v. cannula was inserted and the pre-dose sample was taken. The volunteers were then given 0.3 mg/kg body weight of metoclopramide in 200 mL of 0.9% NaCl infusion. The infusion started 30 minutes before drug administration and lasted on average 25 minutes. In the meantime, the volunteers were served breakfast which was consumed 5 minutes before the drug intake. Standard lunch and dinner were served at noon and 6.0 p.m. respectively.

Ten (10) mL of venous blood were drawn in Vacutainers with heparin at 0, 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 24, and 48 hours. The plasma was separated and frozen immediately and stored at -70°C until assayed.

WASHOUT PERIOD: 14 days

ANALYTICAL METHODOLOGY:

Bromocriptine in plasma was measured by a specific developed by the company.

-o-

ASSAY VALIDATION:

1. **Limit of Quantitation:** It is defined as the calculated value of the first standard point concentration (20 pg/mL) of the calibration curve and is calculated for 13 curves and expressed with standard deviation.

Calculated Value 1st point (pg/mL)	Mean	20.6463
	RSD%	10.4
	Range	

2. **Limit of Detection:** It is defined as the concentration at 85% binding (ED 85%) and is calculated for 13 calibration curves and expressed as the mean values of 13 calibration curves.

Concentration at 85% binding (ED 85%)	Mean	12.1793
	Range	

3. **Specificity:** It is determined by cross-reactivity between the standard bromocriptine methanesulfonate and tested substances using the antiserum KT-2

Cross-reactivities are expressed with the concentration of the standard or test substance (pg/mL) at 50% binding.

4. **Precision and Accuracy:** It is evaluated with within-day and day-to-day variability of the results of the quality control samples.

Within-day (N=21) variability-calibration curve with 21 replicates of quality control samples is prepared at three concentrations:

Actual (pg/mL)	50	200	800
Observed (pg/mL)	49.20	208.91	894.76
Accuracy %	98.4	104.45	111.84
RSD%	8.6	6.8	10.3

Day-to-Day (N=12) variability during 12 consecutive days. 12 calibration curves are prepared with quality control samples.

Actual (pg/mL)	50	200	800
Observed (pg/mL)	50.91	195.50	904.88
Accuracy %	101.82	0.98	113.11
RSD %	14.10	5.70	7.80

5. The assay was validated by analyzing three standard curve sets per day for a total of 12 days. The assay was documented to be reproducible. For standards, the within-day precision showed mean RSDs less than 12% and Day-to-Day accuracy mean RSD were less than 12%.

6. The stability of bromocriptine in plasma samples at -70°C was determined with bromocriptine concentrations of 0.25 ng, 0.50, 0.75 ng, 1.0 ng and 1.5 ng per mL. Individual plasma samples were prepared in quantities enough to carry out seven determinations with one month intervals.

Conc. ng/mL	Initial Determ.	after 1 mo.	after 2 mo.	after 3 mo.	after 4 mo.	after 5 mo.	after 7 mo.
0.25	0.27	0.19	0.22	0.17	0.24	0.16	0.21
0.50	0.43	0.46	0.41	0.45	0.55	0.47	0.48
0.75	0.70	0.74	0.76	0.69	0.95	0.69	0.80
1.00	1.02	1.04	1.07	1.04	1.19	0.97	1.13
1.50	1.97	1.56	1.85	1.59	1.83	1.63	1.90
Recovery in percentage (%)							
0.25	108	76	88	66	96	64	84
0.50	86	92	82	90	110	94	96
0.75	93	99	101	92	127	92	107
1.00	102	104	107	104	119	129	113
1.50	131	104	123	106	122	108	127
Mean	104	95	102.2	92	114.8	97.4	105.4
RSD(%)	16.6	12.3	16.1	16.5	10.6	24.4	15.5

Significance determined by T-test showed no significant difference between the mean value of the initial determination and the mean value of the determination after 1, 2, 3, 4, 5, and

7 months.

Tritiated dihydro-alpha-ergocriptine was used for determining 6-month stability of bromocriptine in plasma. It was stable for 6 months.

DATA ANALYSIS:

Analysis of variance (ANOVA with factors including drug, phase, and sequence) was carried out to compare plasma levels at each sampling time, AUCo-t, AUCinf, Cmax, Tmax, t1/2, Kel with SAS General Linear Models Procedures (GLM). 90% confidence intervals (two one-sided t-test) were calculated for bromocriptine pharmacokinetic parameters.

IN VIVO BIOEQUIVALENCE STUDY RESULTS:

All of the twenty-eight (28) subjects completed the crossover study. Plasma samples from 28 subjects were assayed for bromocriptine as per the protocol. The results of the study comparing the bioavailability of bromocriptine test and reference products are given in Table 1 and 2. The mean plasma bromocriptine concentrations for test and reference treatments are given in Figure 1. The individual pharmacokinetic parameters are attached as an appendix

TABLE 1

Mean Plasma Concentration of Bromocriptine (N= 28)
(Non-fasting)

Time (hours)	Lek's Bromocriptine Mesylate Lot # PD068 01 pg/mL (RSD%)	Sandoz's Parlodel Lot # 196X9136 pg/mL (RSD%)	T/R
0.00	0.0	0.0	
0.25	2.58 (368)	3.27 (296)	0.79
0.50	46.03 (145)	40.12 (112)	1.14
0.75	117.31 (86)	143.49 (74)	0.82
1.00	176.71 (67)	213.00 (51)	0.83
1.50	176.55 (41)	200.40 (36)	0.88
2.00	157.20 (32)	175.00 (39)	0.89
3.00	118.87 (33)	118.10 (35)	1.00
4.00	100.42 (47)	98.19 (36)	1.02
6.00	60.40 (42)	58.95 (30)	1.02
8.00	45.14 (39)	45.51 (34)	0.99
10.00	32.30 (52)	33.01 (55)	0.98
12.00	15.99 (100)	21.80 (77)	0.73

14.00	5.25	(197)	8.42	(153)	0.62
16.00	0.84	(529)	0.69	(529)	1.21
24.00	0.00	(---)	0.00	(---)	0.00
48.00	0.00	(---)	0.00	(---)	0.00

TABLE 2

A Summary of Pharmacokinetic Parameters for 28 Subjects (RSD%)
(Non-fasting)

Parameters	Lek's Bromocriptine	Sandoz's Parlodel	T/R	90% Confidence Interval
AUC_{0-48} pg.hr/mL	876.84 (34)	931.18 (31)	0.94	
AUC_{inf} pg.hr/mL	1032.88 (30)	1115.44 (29)	0.92	
C_{max} pg/mL	242.30 (34)	269.09 (32)	0.90	
T_{max} hours	1.48 (49)	1.32 (42)	1.12	
K_{el} 1/hr	0.186 (32)	0.168 (31)	1.10	
$t_{1/2}$ hours	4.07 (32)	4.47 (28)	0.91	
Ln AUC_{0-48} pg.hr/mL	6.72 (7)	6.79 (5)		85; 103
Ln AUC_{inf} Pg.hr/mL	6.90 (4)	6.98 (4)		84; 101
Ln Cmax pg/mL	5.44 (6)	5.55 (6)		82; 98

The bromocriptine AUC_{0-48} and AUC_{inf} produced by Lek formulation are 5.8% lower and 7.4% lower than the respective values for the reference drug. The C_{max} is 9.9% lower for test. The T_{max}, K_{el} and $t_{1/2}$ values differ by 12.1%, 10.7% and 8.9% respectively. The firm did calculate Ln AUC0-t, Ln AUCinf, and Ln Cmax and the 90%

confidence intervals for log-transformed parameters were 85 to 103 for Ln AUC0-t, 84 to 101 for Ln AUCinf and 82 to 98 for Ln Cmax.

The bromocriptine concentration/time profiles of the two products were same with less than 20% difference between the products being observed at each of the timed collection points except 12 and 14 hours.

No serious adverse effects were experienced by any subject during the study.

On the basis of non-fasting in vivo bioavailability data it is determined that Lek's bromocriptine mesylate 5 mg capsules and Sandoz's Parlodel 5 mg capsules are bioequivalent.

DISSOLUTION TEST RESULTS:

In vitro dissolution testing was conducted in 500 mL of 0.1 N HCl at 37°C using USP XXIII apparatus 2 (paddle) at 50 rpm. Results for 5 mg capsules are presented in Table 3. Both the test and reference products meet the dissolution specifications of not less than 75% of the labeled amount of the drug dissolved from the capsule in 60 minutes.

The batch size was capsules.

The lots of test and reference products employed in the in vitro dissolution test were identical to those employed in the in vivo bioequivalence study.

COMMENTS:

1. All the 28 subjects completed the study. The data from 28 were assayed as per the protocol, comparing the plasma concentrations from Lek's bromocriptine mesylate, 5 mg capsules to that of Parlodel (reference) , 5 mg capsules manufactured by Sandoz.

2. Each subject was given metoclopramide (0.3 mg/kg of body weight) in 200 mL of 0.9 % NaCl infusion. The infusion was started 30 minutes before bromocriptine administration and lasted for 25 minutes. The metoclopramide was used to avoid the vomiting and nausea caused by the drug.

3. The bromocriptine AUC_{0-48}, AUC_{inf}, and C_{max} of Lek's formulation were 5.8% lower, 7.4% lower and 9.9% lower respectively than the corresponding Sandoz's reference values. The differences were not statistically significant. These results indicate that the test drug is bioequivalent to the reference product under non-fasting conditions. Both treatments yielded similar mean plasma bromocriptine concentration-time profiles except at 12 and 14 hours.

4. Reanalysis by ANOVA, SAS, GLM for the pharmacokinetic parameters gave the following CI values for Ln AUC0-t 85 to 103, Ln AUCinf 84 to 101 and Ln Cmax 82 to 98.

5. Our statistical analysis is same as provided by the firm.

6. No serious side effects were observed.

7. The in vitro dissolution testing conducted on both the test and reference products show greater than 75% of the labeled amount of bromocriptine dissolved in 60 minutes.

8. The lots of test and reference products employed in the in vitro dissolution test were identical to those employed in the in vivo bioequivalence study.

9. Both in vivo non-fasting bioequivalence study and in vitro dissolution testing are acceptable.

DEFICIENCY: None

RECOMMENDATIONS:

1. The non-fasting bioequivalence study conducted by Lek Ljubljana on its Bromocriptine Mesylate 5 mg capsuls, lot # PD068-01, comparing it to Parlodel 5 mg capsuless, lot # 196X9136 manufactured by Sandoz have been found acceptable by the Division of Bioequivalence. The study demonstrates that under non-fasting condition the Lek's Bromocriptine Mesylate capsules, 5 mg are bioequivalent to the reference product, Parlodel 5 mg manufactured by Sandoz.

2. The in vitro dissolution testing conducted for 5 mg capsules of the test and reference products is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 500 mL of 0.1 N hydrochloric acid at 37° C using USP XXIII apparatus 2 (paddle) at 50 rpm. The test should meet the following specifications:

> Not less than 75% of the labeled amount of the drug in the tablet is dissolved in 60 minutes.

3. Fromm the bioequivalence point of view, the firm has met the requirements for in vivo bioequivalence and in vitro dissolution testing and the study is acceptable.

/S/

Man M. Kochhar, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

/S/ 2/3/97

Ramakant M. Mhatre, Ph.D.
Branch Chief, Review Branch III

/S/

Concur: _____ Date: 12/4/97

Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

(Please select Typeover for Input.)

Table 3 . In Vitro Dissolution Testing

Drug (Generic Name): Bromocriptine Mesylate
Dose Strength: 5 mg
ANDA No.: 75-100
Firm: Lek Ljubljana
Submission Date: March 25, 1997
File Name: USP METHOD

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: Volume: 500 0.1N HCl
Specifications: 75% in 60 minutes
Reference Drug: Parlodel
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # PD068-01 Strength(5 mg)			Reference Product Lot # 196X9136 Strength(5 mg)		
	Mean %	Range	%RSD	Mean %	Range	%RSD
15	86.5		5.8	85.3		13.4
30	90.9		4.2	91.9		5.9
45	93.2		2.9	93.5		4.4
60	94.0		2.8	94.4		4.2
90	95.2		2.8	95.4		4.1

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-100 APPLICANT: Lek Pharmaceutical

DRUG PRODUCT: Bromocriptine mesylate, U.S.P., 5 mg capsules

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in U.S.P. 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for

Rabindra N. Patnaik, Ph.D.
~~Acting~~ Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Office of Generic Drugs

DIVISION OF BIOEQUIVALENCE

ANDA 75-100 Sponsor: Lek Pharmaceutical
Drug and Dosage form: Bromocriptine Mesylate Capsules
Strength: 5 mg
Type of Study: SD: SDF: X MULT: OTHER:

Study Summary Non-fasting BE Study (5 mg) Acceptable
Dissolution Data Acceptable

Primary Reviewer: Man M. Kochar Branch: III

Initial: /S/ Date: 11/30/98

Team Leader: Ramakant M. Mhatre Branch: III

for

Initial: /S/ Date: 11/30/98

Director, Division of Bioequivalence

Initial: /S/ Date: 12/1/98

Director, Office of Generic Drugs

Initial: _____ Date: _____

The BE review by Dr. Kochhar describes the review of "Amendment to Bioequivalence Study and dissolution data". As per Nasser's thorough review of the application, the BE study and the related data are the original submission, not an amendment.

/S/ 11/30/98

No fasting study - see attached communication - Rm 12/1/98

Food and Drug Administr
Rockville MD 20857

Bromocriptine Mesylate Capsules USP
Bromocriptine Mesylate Tablets USP

MAY 10 1996

cc: Gabrijelcic

Dear

Reference is made to the proposed fasting bioequivalence study protocols submitted to the Office of Generic Drugs (OGD) for review, dated for Bromocriptine Mesylate Capsules, 5 mg, and Bromocriptine Mesylate Tablets USP, 2.5 mg (eq. base),

This correspondence is to advise you that OGD has revised the in vivo bioequivalence requirements for this drug product. The following comments are provided for your consideration:

As a condition of approval you may either:

1. Conduct the traditional fasting and non-fasting studies which must satisfy the current bioequivalence criteria for the critical pharmacokinetic parameters (Cmax, Auct and AUCinf),

2. As an alternative you may conduct one pivotal single dose 2-way cross-over study under non-fasting conditions. The pivotal single dose food study would be required to satisfy current bioequivalence requirements as specified in the Guidance "Statistical Procedures for Bioequivalence Studies Using a Standard Two-treatment Crossover Design" for fasting single dose studies, for the pharmacokinetic parameters, AUCt, AUCinf, and Cmax.

If you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours.

/S/

Keith K. Chan, ~~Ph.~~D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Bromocriptine Mesylate Capsules USP
5 mg
ANDA 75-100
Reviewer: Barbara M. Davit, Ph.D.
v:\firmsam\lek\ltrs&rev\75100a.399.doc

LEK Pharmaceutical & Chemical Co. d.d.
1526 Ljubljana
Verovškova 57, PO Box 81, Slovenia
Submission Date: 3/10/99

Addendum to the Review
Review of Dissolution Testing by CDER Div. of Testing & Applied Analytical Dev.
LEK's Bromocriptine Mesylate Capsules USP 5 mg vs Parlodel® Capsules 5 mg

Background: In response to a request by the Division of Bioequivalence, the Division of Testing and Applied Analytical Development, St. Louis, MO, (DTAAD) conducted dissolution testing on LEK's bromocriptine mesylate capsules 5 mg USP (test product) and Parlodel® capsules 5 mg (Reference Listed Drug, RLD). Following the method of USP 23, the St. Louis lab determined the percent of labeled amount dissolved at 60 minutes. At the time the study was conducted, the St. Louis lab did not have access to the Whatman GF/F glass fiber filters specified by USP 23, and substituted Millipore HVLP cellulose acetate filters.

Although both products passed USP Level 2 specifications, the percent of labeled amount of bromocriptine dissolved at 60 min was low, ranging from 67.4-86.3% for test, 68.6-88.1% for RLD. By contrast, dissolution data submitted by LEK to ANDA 75-100 showed that the percent of bromocriptine dissolved at 60 min ranged from 85-100% for test, 90-98% for RLD. It was speculated that perhaps the dissolution values obtained by DTAAD were low because a cellulose acetate filter was substituted for the glass fiber filter. For details see DBE review of dissolution data, ANDA 75-100, finalized 2/28/99.

DBE asked the DTAAD to repeat the dissolution studies of bromocriptine mesylate as specified in USP 23 with the Whatman GF/F glass fiber filter, and to characterize full dissolution profiles. Studies were conducted on 2/24/99 and 3/1/99, and data were sent to DBE on 3/10/99. A review of these data follows.

Methods: USP 23 Apparatus II (paddles), 50 rpm
500 mL 0.1 N HCl, 37°C
Sampling times: 15, 30, 45, 60 min.
Specifications: NLT 80% (Q) dissolved in 60 minutes
Test (LEK) Lot No: TS20901
Reference (Sandoz) Lot No: 230 Z 5093

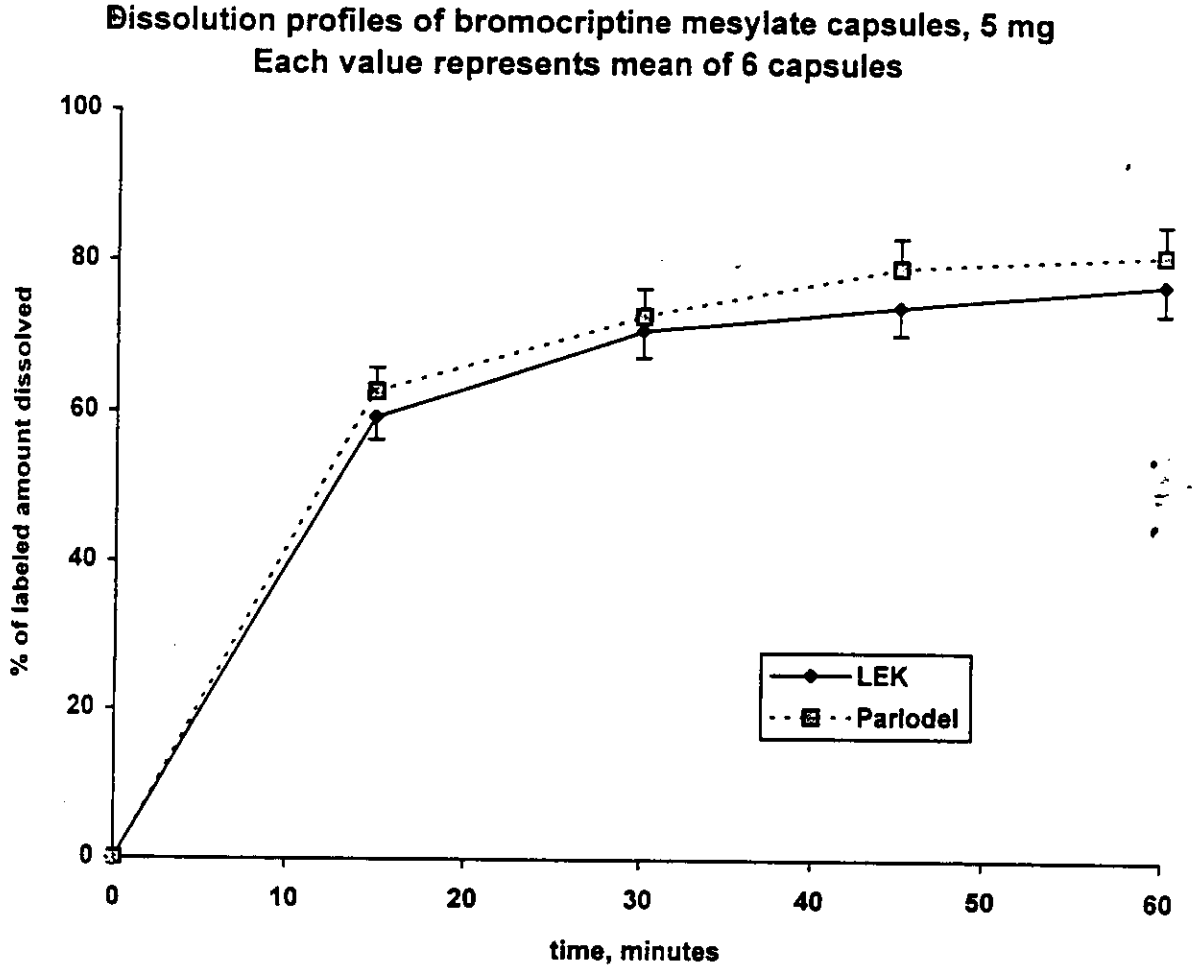
Results: Two sets of six test capsules and six RLD capsules were tested. For the first set of 6 (tested 2/24/99), only the percent dissolved at 60 min was assayed. For the second set of 6 (tested 3/1/99), full dissolution profiles were obtained. The percent dissolved at 60 min is shown below:

% of labeled amount of bromocriptine dissolved at 60 minutes, % per capsule and mean ± S.D. from 6 capsules									
Product, date	#1	#2	#3	#4	#5	#6	Mean	Std. Dev.	Range
Test, 2/24/99	87.7	81.1	79.2	75.6	68.5	75.8	78.0	6.4	68.5-87.7
Test, 3/1/99	80.7	77.3	80.6	79.4	73.9	70.6	77.1	4.1	70.6-80.7
Ref, 2/24/99	86.5	76.3	86.3	77.7	74.9	76.8	79.9	5.4	74.9-86.5
Ref, 3/1/99	85.4	78.6	82.3	82.2	74.1	83.9	81.1	4.1	74.1-85.4

The test and RLD capsules tested on 2/24/99 did not pass USP 23 Level 1 specifications, as the % of labeled amount of bromocriptine dissolved < Q+5% (80%) for

4/6 LEK capsules and 4/6 Parlodel® capsules. Six additional capsules of test and RLD each were tested on 3/1/99. Combining the dissolution data from 2/24 and 3/1, both test and RLD passed USP 23 Level 2 specifications (mean of 12 capsules > 75%). At 60 minutes, the mean±S.D. percent of labeled amount was 77.5±5.1% for the LEK capsules, and 80.5±4.6% for Parlodel®.

Dissolution profiles of the test product and RLD are compared below:



A profile similarity factor (F2) of 68 was calculated for the test product and RLD, using the equation recommended by the CDER Guidance for Industry BP1, August, 1997. Since F2 > 50, it is concluded that the two dissolution profiles are similar.

Conclusions:

1. Both test and reference products passed USP 23 dissolution specifications.
2. Dissolution profiles of test and reference product were comparable.
3. Use of the glass fiber filter did not improve dissolution at 60 minutes, compared with data obtained using cellulose acetate filters. It is not known why DTAAD could not duplicate the results obtained by LEK Pharmaceutical and Chemical Company.

Recommendation:

In vitro dissolution profiles obtained using the method of USP 23 were comparable between bromocriptine mesylate capsules, 5 mg, USP, manufactured by LEK Pharmaceutical and Chemical Company, and Parlodel® capsules, 5 mg, manufactured by Sandoz.

5/19/99

Barbara M. Davit, Ph.D.
Team Leader, Review Branch III
Division of Bioequivalence

/S/ 5/19/99

Rabinandra Patnaik, Ph.D.
Deputy Division Director
Division of Bioequivalence

Concur /S/ Date: 6/14/99

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Please enter as US document

OTHR 5mg
AC

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Adnimistration
Center for Drug Evaluation and Research
Division of Testing and Applied Analytical Development
1114 Market Street, Room 1002
St. Louis, MO 63101
Tel. (314) 539-2136
FAX Tel (314) 539-2113

DATE : March 10, 1999

From : Terry W. Moore, Team Leader

Subject: Bromocriptine Mesylate, Study 99C, additional testing /S/

TO : Dr. Dale Conner, OGD, DBE

THRU : Moheb M. Nasr, Ph.D.
Deputy Director Lab I, DTAAD, HFD-920 /S/

The additicnal testing of Bromocriptine Mesylate, Study 99C, has been completed. The USP monograph specified filtering the dissoluted sample solutions with glass fiber filters. Whatman GF/F glass fiber filters were used. Two sets of 6 capsules were tested. A profile was obtained for each of the second set of 6 capsules. The results are as follows.

Sample # 40121, (Bromocriptine Mesylate Capsules, 5.0 mg, Rosemont, Lot TS20901)

1st set of 6 capsules, % bromocriptine:

	Capsule #							
Time	1	2	3	4	5	6	Avg.	SD
60 min							78.0	6.4

2nd set of 6 capsules, % bromocriptine:

	Capsule #							
Time	1	2	3	4	5	6	Avg.	SD
15 min							59.2	7.4
30 min							70.8	5.0
45 min							74.0	4.4
60 min							77.1	4.1

Sample # 99-BRO-230, (Parlodel Capsules, 5.0 mg. Sandoz, Lot 230 Z 5093)

1st set of 6 capsules, % bromocriptine:

	Caplule #							
Time	1	2	3	4	5	6	Avg.	SD
60 min							79.9	5.4

2nd set of 6 capsules, % bromocriptine:

	Capsule #							
Time	1	2	3	4	5	6	Avg.	SD
15 min							62.7	5.9
30 min							72.8	5.5
45 min							79.3	3.1
60 min							81.1	4.1

Company:	**LEK Pharmaceutical and Chemical Company d.d.** **1526 Ljubljana** **Verovškova 57, P.O. Box 81** **Slovenia**
Subject:	**Bromocriptine Mesylate Tablets USP, 2.5 mg** **Bromocriptine Mesylate Capsules USP, 5 mg**
ANDA No:	**74-631** **75-100**
Submission Date:	**2/10/99**
Reviewer:	**Barbara M. Davit, Ph.D.**

Review of Dissolution Testing of LEK's Bromocriptine Mesylate Products and Parlodel® by FDA Division of Testing and Applied Analytical Development, St. Louis

Background: The Division of Testing and Applied Analytical Development was asked by OGD on 1/7/99 to investigate dissolution of bromocriptine from 2.5 mg tablets and 5 mg capsules. The dissolution of LEK's bromocriptine mesylate tablets, USP, 2.5 mg, and bromocriptine mesylate capsules, USP, 5 mg, was compared to that of Parlodel® 2.5 mg tablets and 5 mg capsules, respectively. The official dissolution media (USP 23) is 0.1 N HCl, but the laboratory was also asked to dissolute the products in water, acetate buffer and phosphate buffer.

Method: Dissolution testing was conducted in two different media, 0.1 N HCl (compendial method) and water. Dissolution conditions were:

For the 2.5 mg tablet

USP 23 Apparatus I (basket), 120 rpm
500 mL 0.1 N HCl or water
Specifications: NLT 80% (Q) of the labeled amount of bromocriptine dissolved in 60 minutes

For the 5 mg capsule

USP 23 Apparatus II (paddles), 50 rpm
500 mL 0.1 N HCl or water
Specifications: NLT 75% (Q) of the labeled amount of bromocriptine dissolved in 60 minutes

Results:

1. 2.5 mg tablets

Assay results for the 2.5 mg tablets were as follows:

Assay of bromocriptine in 2.5 mg bromocriptine mesylate tablets; USP Limits = 90-110%						
	Parlodel Lot # 987 A 5510	LEK Lot # V189 01	LEK Lot # V140 01	LEK BE Study Lot # TS131 02	Parlodel BE Study Lot # 937 X 8890	Mylan Lot # 99-BRO-MYO MY013 01
Potency (%)	99.4	97.6	101.1	98.1	96.6	97.2

Results of dissolution testing of LEK's 5 mg bromocriptine mesylate capsules USP and Parlodel® 5 mg capsules is shown below. Dissolution of Parlodel® 5 mg capsules, but not LEK's 5 mg capsules, was greater in water than in 0.1 N HCl.

Dissolution testing of 5 mg bromocriptine mesylate capsules, media = water, 6 units per test		
	Parlodel Lot # 230 Z 509	LEK Lot # TS209 01
Mean % dissolved	86.7	77.0
% CV	5.3	5.8
Range (%)		

Comments:

1. Due to the lack of solubility of bromocriptine mesylate in acetate and phosphate buffers, the dissolution evaluation in these media was not performed.
2. Prior to starting the dissolution analysis, it was found that a glass fiber filter (GF/A) retained a high percent of the drug when a standard solution containing about 1% alcohol in water was filtered, although USP 23 specifies use of a glass fiber filter.
3. Millipore HVLP(cellulose acetate filters) were used by the St. Louis Lab.
4. According to the reviewing chemist for Parlodel® 5 mg capsules (Dr. Swapan De, HFD-580), a Whatman GF/F glass fiber filter is specified in the dissolution procedure. Terry Moore from St. Louis indicated that rather than wait for a shipment of GF/F filters, it was decided to use HVLP filters to expedite the study.
5. It is not known if a higher percentage of bromocriptine would have dissolved from the 5 mg bromocriptine mesylate capsules in 0.1 N HCl media had GF/F filters been used.
6. Dissolution testing was performed on the first set of 5 mg bromocriptine mesylate capsules (LEK's capsules vs Parlodel®) on 1/29/99. Since both test and reference products did not pass Level 1 specifications (each of the 6 units must not be less than Q + 5%), the Division of Testing and Applied Analytical Development performed a second set of dissolution tests (n=6) on 2/1/99. Both LEK's capsules and Parlodel® passed Level 2 criteria in that the average of all 12 units was equal to or greater than Q (75%) and no unit was less than Q-15% (60% in this case). Mean ± SD % (range) dissolved at 60 minutes (n=12) was 77±6.3% (range 67.4 to 86.3%) for Parlodel®, and 78.8±5.9% (range 68.8 to 87.8%) for LEK's product.

Conclusions:

1. From the dissolution data using the USP compendial method, no conclusions can be made about the dissolution performance of LEK's bromocriptine capsules, USP, 5 mg, vs Parlodel® capsules 5 mg. Neither LEK's nor the innovator's product passed USP 23 Level 1 specifications, but both passed Level 2 specifications. LEK's 5 mg capsule performed similarly to Parlodel® 5 mg capsule.
2. The 5 mg capsules used in the pivotal BE study passed dissolution specifications. Thus, the 5 mg capsules tested by the St. Louis lab performed differently in dissolution testing than the 5 mg capsules from the pivotal BE study and tested by LEK. Mean values at 60 minutes (n=12) were 94% dissolved for LEK's capsules USP and 94.4% dissolved for Parlodel®.
3. Using water as the media, dissolution of bromocriptine from Parlodel® 5 mg capsules at 60 minutes (mean of 86.7%) exceeded that of LEK's 5 mg capsules (mean of 77%).

4. It is not known if the different filters used by LEK vs the St. Louis lab in performing the dissolution procedures for the 5 mg bromocriptine mesylate capsule contributed to the differences in percentage of bromocriptine dissolved at 60 minutes observed at the two different sites.
5. Both LEK's 2.5 mg bromocriptine mesylate tablets USP and Parlodel® 2.5 mg tablets passed dissolution specifications in 0.1 N HCl.
6. Using water as the media, the percentage of bromocriptine mesylate dissolved at 60 minute from Parlodel® 2.5 mg tablets exceeded 100% (range , despite assay values of about 100%. It is not clear if the assay results or the dissolution results are in error.

Recommendation:

1. It is concluded that LEK's bromocriptine mesylate tablets, USP, 2.5 mg, performed similar to Parlodel® 2.5 mg tablets with respect to bromocriptine dissolution when tested according to the USP 23 compendial method.
2. The Division of Testing and Applied Analytical Development in St. Louis will be asked to repeat the dissolution procedure for the LEK's bromocriptine mesylate capsules, USP, 5 mg and Parlodel® 5 mg capsules using the following procedures:

   USP 23 compendial method (using 0.1 N HCl as media)
   Filtration accomplished using a Whatman GF/F glass fiber filter

/S/ 2/28/99

Barbara M. Davit, Ph.D.
Team Leader, Review Branch III
Division of Bioequivalence

/S/

Rabinandra Patnaik, Ph.D.
Deputy Division Director
Division of Bioequivalence

Concur: /S/ Date: 2/28/99

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 24, 1999

FROM: G.T. Viswanathan, Ph.D. G.T. Viswanathan 2/24/99
Associate Director
Division of Scientific Investigations (HFD-345)

SUBJECT: Review of bioequivalence studies sponsored by LEK Pharmaceutical and Chemical Company

TO: Douglas L. Sporn
Director
Office of Generic Drugs (HFD-600)

In June 1998, the Division of Scientific Investigations conducted an audit of a bioequivalence study in ANDA 74-631 based on a request from HFD-650. This study (#9709 BCT1) was sponsored by LEK Pharmaceuticals and entitled "Comparative Bioavailability of Two Formulations with Bromocriptine: Bromocriptine Mesylate 2.5 mg Tablets and Parlodel 2.5 mg Tablet." Following the inspection, DSI recommended that the study data be not accepted for Agency review based on the significant deficiencies found in the clinical data documentation. Due to these inspectional findings, HFD-650 further requested that additional bioequivalence studies sponsored by LEK be audited. The bio studies from the following applications were recently audited at the sites in Slovenia and Croatia.

ANDA 75-100 bromocriptine mesylate 5 mg capsules
ANDA
ANDA
ANDA

The follow-up inspections, conducted by DSI in February 1999, revealed similar deficiencies as before in that the clinical sites failed to (1) record the drug treatment administered to each study subject and (2) adequately document dosing and blood sampling times. Since there were no source documents for the above, the accuracy of the study data could not be verified.

In light of similar deficiencies found in both the June 1998 and February 1999 inspections of multiple studies from various applications submitted by Lek Pharmaceuticals, it is recommended that in vivo bioequivalence studies, conducted at the subject sites in Slovenia and Croatia during that specific period be not reviewed by OGD as the probability of encountering similar problems remains quite high.

Any future bio studies conducted by LEK following their change in study procedures, data collection and documentation should be referred to DSI for an audit to ensure compliance.