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APPLICATION NUMBER:

17-962/S-063

17-962/S-064

ADMINISTRATIVE DOCUMENTS

Division of Reproductive and Urologic Products

REGULATORY PROJECT MANAGER REVIEW

NDA Number: **17-962/S-063**
17-962/S-064

Name of Drug: **Parlodel (bromocriptine mesylate) Capsules and Tablets**

Applicant: **Novartis Pharmaceutical Corporation**

Material Reviewed:

S-053 Latest approved labeling (November 9, 1999)
S-063 Original submission dated: April 15, 2002 (received April 19, 2002)
S-063 Amendment dated: May 5, 2005 (received May 9, 2005)
S-064 Original submission dated: May 9, 2003 (received May 12, 2003)
S-064 Amendment dated: May 5, 2005 (received May 9, 2005)

Y-029 Annual report dated: December 4, 2002 (received December 6, 2002)
Y-030 Annual report dated: August 28, 2003 (received August 29, 2003)
Y-031 Annual report dated: March 1, 2004 (received March 1, 2004)
Y-032 Annual report dated: August 24, 2004 (received August 25, 2004)
Y-033 Annual report dated: August 12, 2005 (received August 15, 2005)

Background and Summary

(S-053) Latest approved labeling (November 9, 1999). The Sponsor's Final Printed Labeling (FPL) for the package insert (PI) has the revision date of May 2000 and print# 89009901, T2000-32.

(S-063) Labeling revisions were submitted as prior approval supplement on April 15, 2002 (received April 19, 2002) in conjunction to the Final Rule entitled, "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Additional of 'Geriatric Use' subsection in the labeling," which was published in the Federal Register on August 27, 1997. The Sponsor has proposed a "Geriatric Use" subsection to be added to the **PRECAUTIONS** section.

(S-064) Labeling revisions were submitted as "Supplement-Changes Being Effected" on May 9, 2003 (received May 12, 2003) to add paragraphs to reflect safety data reported in post-marketing experience that related to sudden onset of sleep and pleuropulmonary and pericardial changes during Parlodel treatment in patients with Parkinson's disease. Also, minor editorial changes to avoid unnecessary repetition.

(Y-029) Annual report submitted on December 4, 2002 (received December 6, 2002) contained the latest approved PI, revision date of May 2000 and print# 89009901, T2000-32.

(Y-030, Y-031, Y-032, and Y-033) Annual reports were submitted on August 28, 2003 (received August 29, 2003), March 1, 2004 (received March 1, 2004), August 24, 2004 (received August 25, 2004), and August 12, 2005 (received August 15, 2005), respectively. These annual reports contained an updated PI with the revision date of March 2003 and print# 89009903, T2003-25.

On January 15, 2004, an approvable letter was issued for both supplements, S-063 and S-064. This letter indicated that before these applications may be approved, the Sponsor must submit draft labeling revised to include an additional paragraph concerning neuroleptic malignant syndrome (NMS) in the 'Parkinson's Disease'section. In addition, provide supporting documentation for the rates of dizziness, drowsiness, fainting and syncopy for the 'Information for Patients' section.

On May 5, 2005 (received May 9, 2005), the Sponsor submitted a complete response to the Agency's January 15, 2004 approvable letter.

The labeling provided in the submissions listed above were compared to the last approved labeling (S-053). The following is a combined summary review of these submissions.

Review

15 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 1

Conclusion

In the May 5, 2005 submission, the Sponsor incorporated all of the requested changes in the approvable letter dated January 15, 2004. The Sponsor added a paragraph concerning neuroleptic malignant syndrome (NMS) under the **Parkinson's Disease** section. The Sponsor also removed the rates for dizziness, drowsiness, fainting, and syncope under the **Information for Patients** section. An approval letter should be sent to the Sponsor with the agreed upon labeling attached.

John Kim, R.Ph., J.D.
Regulatory Health Project Manager

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/s/

John C. Kim
11/9/2005 06:40:59 PM
CSO

Division of Reproductive and Urologic Drug Products

REGULATORY PROJECT MANAGER REVIEW

NDA Number: **17-962**

Name of Drug: **Parlodel (bromocriptine mesylate) Capsules and Tablets**

Applicant: **Novartis Pharmaceutical Corporation**

Material Reviewed: **S-063, S-064**

Submission Date: **April 15, 2002**
May 9, 2003

Receipt Date: **April 19, 2002**
May 12, 2003

Background and Summary

(S-053) Latest approved labeling.

(S-063) Labeling revisions were submitted on April 15, 2002 in conjunction to the Final Rule entitled, "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Additional of 'Geriatric Use' subsection in the labeling", which was published in the Federal Register on August 27, 1997. The applicant has proposed a "Geriatric Use" subsection to be added to the PRECAUTIONS section.

(S-064) Labeling revisions were submitted on May 9, 2003 to add paragraphs to reflect safety data reported in post-marketing experience that related to sudden onset of sleep and pleuropulmonary and pericardial changes during Parlodel treatment in patients with Parkinson's disease. Also, minor editorial changes to avoid unnecessary repetition.

Review

S-053 Sept. 8, 2002	S-063 April 15, 2002	S-064 May 9, 2003	Comments
	(proposed geriatric subsection)		
PRECAUTIONS	**PRECAUTIONS**		
Geriatric Use-no current information in labeling	**Geriatric Use** Clinical studies for Parlodel did not include sufficient numbers of subjects aged 65 and over to determine whether the elderly respond differently from younger subjects. However, other reported clinical experiences, including post-marketing reporting of adverse events, have not identified differences in response or tolerability between elderly and younger patients. Even though no variation in efficacy or adverse reaction profile in geriatric patients taking Parlodel has been observed, greater sensitivity of some elderly individuals cannot be categorically ruled out. In general, dose selection for an elderly patient should be cautious, starting at the lower end of the dose range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy in this population.		Acceptable.
		(proposed paragraph regarding visual impairment)	
PRECAUTIONS		**PRECAUTIONS**	
Hyperprolactinemic States *(No current paragraph.)*		**Hyperprolactinemic States** Visual field impairment is a known complication of macroprolactinoma. Effective treatment with Parlodel leads to a reduction in hyperprolactinaemia and often to a resolution of the	This is acceptable.

		visual impairment. In some patients, however, a secondary deterioration of visual fields may subsequently develop despite normalized prolactin levels and tumor shrinkage, which may result from traction on the optic chiasm which is pulled down into the now partially empty sella. In these cases the visual field defect may improve on reduction of bromocriptine dosage while there is some elevation of prolactin and some tumor re-expansion. Monitoring of visual fields in patients with macroprolactinoma is therefore recommended for an early recognition of secondary field loss due to chiasmal herniation and adaptation of drug dosage.	This is acceptable.
Information for Patients *(No current paragraph.)*		**Information for Patients** During clinical trials, dizziness, drowsiness, faintness, fainting, and syncopy have been reportede early in the course of Parlodel Therapy. In post-marketing reports, Parlodel has been associated with somnolence, and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Sudden onset of sleep during daily activities, in some cases without awarness or warning signs, has been reported very rarely.	**Not Acceptable.**
When initiating therapy, all patients receiving Parlodel, (bromocriptine mesylate) should be cautioned with regard to engaging in activities requiring rapid and precise responses, such as		All patients receiving Parlodel should be cautioned with regard to engaging in activities requiring rapid and precise responses, such as driving an automobile or operating machinery.	Acceptable

driving an automobile or operating machinery since dizziness (8%-16%), drowsiness (8%), faintness (8%), and syncope (less than 1%) have been reported early in the course of therapy.			
Patients receiving Parlodel, (bromocriptine mesylate) for hyperprolactinemic states associated with macroadenoma or those who have had previous transsphenoidal surgery, should be told to report any persistent watery nasal discharge to their physician. Patients receiving Parlodel, (bromocriptine mesylate) for treatment of a macroadenoma should be told that discontinuation of drug may be associated with rapid regrowth of the tumor and recurrence of their original symptoms.		Patients receiving Parlodel for hyperprolactinemic states associated with macroadenoma or those who have had pervious transsphenoidal surgery, should be told to report any persistent watery nasal discharge to their physician. Patients receiving Parlodel for treatment of a macroadenoma should be told that discontinuation of drug may be associated with rapid regrowth of the tumor and recurrence of their original symptoms.	Acceptable
		ADVERSE REACTIONS Parkinson's Disease Pleural and pericardial effusions, pleural, and pulmonary fibrosis or retroperitoneal fibrosis and constrictive pericarditis have been reported rarely in patients treated with Parlodel.	Acceptable
HOW SUPPLIED **Parlodel®(bromocriptin mesylate) SnapTabs®** *2½ mg* Round, white, scored SnapTabs®, each containing 2½ mg bromocriptine (as the mesylate). Engraved "PARLODEL 2½" on		**HOW SUPPLIED** **Parlodel® (bromocriptine mesylate) SnapTabs®** *2 ½ mg* Round, off-white, bevelled-edge SnapTab®, each containing 2 ½ mg bromocriptine (as the mesylate). Engraved	

one side and scored on reverse side. **Parlodel®(bromocriptine mesylate) Capsules** **5 mg** Caramel and white capsules, each containing 5 mg bromocriptine (as the mesylate). Imprinted "PARLODEL 5 mg" on one half and " Ⓢ " on other half Packages of 30..... Packages of 100... **Store and Dispense** Below 77°F (25°C); tight, light-resistant container. T200023-322501		"PARLODEL 2 ½" on one side and scroed on reverse side. Complies with USP dissolution test 1. **Parlodel® (bromocriptine mesylate) Capsules** **5 mg** Caramel and white capsules, each containing 5 mg bromocriptine (as the mesylate). Imprinted in red ink "PARLODEL 5 mg" on one half and " Ⓢ " on other half Packages of 30 NDC 0078-0102-15 Packages of 100 NDC 0078-0102-05 **Store and Dispense** Below 25°C (77°F); tight, light-resistant container. T2003-25	

Conclusions/Recommendations:

1. These labeling changes are not all acceptable.
2. The removal of the generic name and the maintaining of the trade name is acceptable in the labeling.
3. The updated serial number and copyright date is acceptable.
4. In the 'Information for Patients' section, the sponsor should provide supporting documentation for the rates of dizziness, drowsiness, fainting and syncopy.
5. An additional paragraph concerning neuroleptic malignant syndrome (NMS) should be added to the Parkinson's Disease section.
6. A copy of any revised or future proposed labeling should be sent to ODS for evaluation.

Actions:

1. An approvable letter should be sent advising the applicant that these supplemental NDA submissions are acceptable.
2. An additional paragraph concerning neuroleptic malignant syndrome (NMS) should be added to the Parkinson's Disease section by the sponsor.

Dale Cutright, Reviewer
Project Manager

Drafted:dc:6/17/03; 7/1/03; AGassman 12/18/03
Concurrence: KSherrod 7/1/03; AGassman 7/10/03, 12/5/03, SDe 7/17/03

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/s/

Dale Cutright
12/24/03 06:30:17 AM
CSO

Additional signers at TL request

Kassandra C. Sherrod
1/2/04 01:17:26 PM
CSO

Audrey Gassman
1/3/04 02:29:22 PM
MEDICAL OFFICER

Shelley Slaughter
1/8/04 11:49:40 AM
MEDICAL OFFICER
I concur.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 17-962/S-063
NDA 17-962/S-064

Novartis Pharmaceuticals Corporation
Attention: Gregory R. King
Senior TA Manager, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Mr. King:

We acknowledge receipt on May 9, 2005 of your May 5, 2005 resubmission to your supplemental new drug application for Parlodel® (bromocriptine mesylate).

This amendment constitutes a complete response to our January 15, 2004 action letter.

If you have any questions, call John C. Kim, R.Ph., J.D., Regulatory Health Project Manager, at (301) 827-3003.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
6/29/05 09:18:57 AM
Chief, Project Management Staff

MEMORANDUM

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

DATE: January 13, 2004

TO: NDA 17-962/S-063 & 064

FROM: Dale Cutright, Project Manager, HFD-580

SUBJECT: Correction to labeling review for Parlodel Capsules and Tablets
NDA 17-962/S-063 & 064

The labeling revisions of supplement 063 (April 15, 2002) and supplement 064 (April 19, 2002) were compared to the latest approved labeling of supplement 053 dated September 8, 2000 (not 2002, as stated in the review of January 8, 2004).

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/s/

Dale Cutright
1/13/04 04:06:27 PM
CSO

Margaret Kober
1/13/04 05:32:14 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 17-962/S-063

PRIOR APPROVAL SUPPLEMENT

Novartis Pharmacetuicals Corporation
Attention: Ayanna J. Abadie, Pharm.D., Drug Regulatory Affairs
One Health Plaza
East Hanover, New Jersey 07936

Dear Dr. Abadie:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Parlodel® (bromocriptine mesylate)Tablets and Capsules

NDA Number: 17-962

Supplement number: 063

Date of supplement: April 15, 2002

Date of receipt: April 19, 2002

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 22, 2002 in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room, 17B20
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Document Room 17B20

5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Leslie Stephens, M.S.N., R.N., Regulatory Project Manager, at (301) 827-4259.

Sincerely,

{See appended electronic signature page}

Leslie Stephens, MSN, RN
Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Leslie Stephens
5/15/02 02:42:49 PM