CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 020664

Trade Name : DOSTINEX 0.5MG TABLETS

Generic Name: Cabergoline 0.5mg Tablets

Sponsor : Pharmacia and Upjohn Co.

Approval Date: **December 23, 1996**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020664

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-664

DEC 23 1996

Pharmacia & Upjohn Company
Attention: Susan M. Mondabaugh, Ph.D.
Director, Regulatory Affairs
Unit 0635-298-113
7000 Portage Road
Kalamazoo, MI 49001

Dear Dr. Mondabaugh:

Please refer to your December 26, 1995, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dostinex (cabergoline tablets), 0.5 mg.

We acknowledge receipt of your submissions dated January 26, March 4 and 18, April 16, May 2 and 15, June 26, July 31 (2), October 25 and 31, November 13 and 20(2), and December 4 and 23, 1996.

This new drug application provides for the use of Dostinex tablets in the treatment of hyperprolactinemic disorders, either idiopathic or due to pituitary adenomas.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft physician labeling submitted on December 23, 1996, and the draft carton and container labeling submitted on December 10, 1996. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-664. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Randy Hedin, R.Ph., Consumer Safety Officer, at (301) 443-3520.

Sincerely yours,

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

PATENT INFORMATION STATEMENT
FILED PURSUANT TO 21 U.S.C §355(b)(1)

The following United States patent(s) either claims the drug cabergoline which is the subject of this NDA No.20-664 filed December 20 1995 or claims a method of using cabergoline and which respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use or sale of cabergoline. A copy of the patent is enclosed for the convenience of the FDA.

PATENT NUMBER	EXPIRATION DATE	CLAIMS
4,526,892	02/JUL/2002	1. The compound cabergoline; 2. Pharmaceutical compositions containing cabergoline.

Respectfully submitted,

Patricia A. Coburn

Patricia A. Coburn
Director, Intellectual Property

CARBERGOLINE

United States Patent [19]

Salvati et al.

[11] Patent Number: 4,526,892

[45] Date of Patent: Jul. 2, 1985

[54] **DIMETHYLAMINOALKYL-3-(ERGOLINE-8'βCARBONYL)-UREAS**

[75] Inventors: **Patricia Salvati; Anna M. Caravaggi; Aldemio Temperilli; Germano Bosisio, all of Milan; Osvaldo Sapini, Gallarate; Enrico di Salle, Milan, all of Italy**

[73] Assignee: **Farmitalia Carlo Erba, S.p.A., Milan, Italy**

[21] Appl. No.: **448,364**

[22] Filed: **Dec. 9, 1982**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 249,995, Mar. 3, 1981.

[51] Int. Cl.³ C07D 457/06; A61K 31/48

[52] U.S. Cl. 514/288; 546/69

[58] Field of Search 546/67, 68, 69; 424/261

[56] **References Cited**

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Bernardi, et al., "Derivati Della D.6-metil-8-β-aminometil-10α-ergoline", *Gazz Chem. Ital.* 94, 936-978 (1964).

Primary Examiner—Donald G. Daus
Assistant Examiner—G. Hendricks
Attorney, Agent, or Firm—Brooks Haidt Haffner & Delahunty

[57] **ABSTRACT**

Novel ergoline derivatives formed by reaction of an 8-carboxy ergoline with a carbodiimide and having hypotensive and antiprolatinic activity.

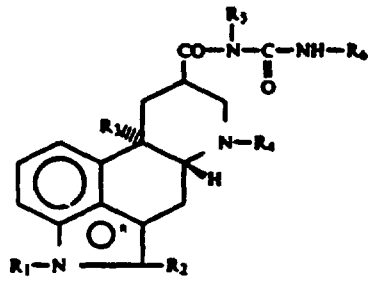
4 Claims, No Drawings

DIMETHYLAMINOALKYL-3-(ERGOLINE-8'βCARBONYL)-UREAS

This application is a continuation-in-part of application Ser. No. 06/249,995 filed Mar. 3, 1981.

The invention relates to novel ergoline derivatives, to a process for their preparation and to therapeutic compositions containing them.

The invention provides ergoline derivatives having the general formula I

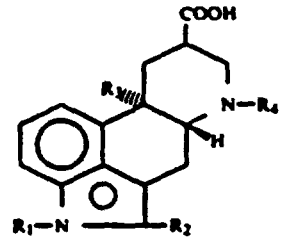


I

wherein R_1 represents a hydrogen atom or a methyl group; R_2 represents a hydrogen or halogen atom, a methyl or formyl group or a group of the formula S—R_7 or SO—R_7 wherein R_7 represents an alkyl group having from 1 to 4 carbon atoms or a phenyl group; R_3 represents a hydrogen atom or a methoxy group; R_4 represents a hydrocarbon group having from 1 to 4 carbon atoms, benzyl or phenthyl; and each of R_5 and R_6 independently represents an alkyl group having from 1 to 4 carbon atoms, a cyclohexyl group or a substituted or unsubstituted phenyl group or an acid and water-soluble group such as $(CH_2)_nN(CH_3)_2$ in which n is an integer, with the proviso that R_5 and R_6 cannot both be a said acid and water-soluble group, and the pharmaceutically acceptable addition salts with organic or inorganic acid thereof. In the general formula the term "halogen" should be construed to preferably encompass chlorine and bromine atom; nevertheless, term "halogen" also encompasses fluorine atom. In the definition of R_5 and R_6, n is preferably 1,2,3 and 4. In the definition of R_4, a hydrocarbon group having from 1 to 4 carbon atoms is intended to include alkyl, cycloalkyl and unsaturated (both ethylenically and acetylenically) groups.

Representative moieties include methyl, ethyl, n-propyl isopropyl, butyl, t-butyl, isobutyl, cyclopropyl, methylcyclopropyl, vinyl, allyl and propargyl.

The invention further provides a process for the preparation of ergoline derivatives of the general formula I as herein defined, which process comprises reacting an acid of the general formula II with a carbodiimide of the general formula III



II

III

wherein R_1, R_2,R_3,R_4,R_5 and R_6 have the meanings given above.

The reaction is suitably carried out at a temperature of from 50°-100° C. for a period of from 5 to 24 hours in a solvent such as tetrahydrofuran, dimethylformamide or dioxan, optionally in the presence of an organic base such as pyridine or triethylamine. At the end of the reaction the products can be isolated and purified following conventional procedures, for example chromatography and/or crystallization. The intermediate acids having the general formula II are either known compounds or can be prepared from the corresponding esters by saponification. Formation of the desired pharmaceutically acceptable addition salts with organic and inorganic acids is carried out by known methods, e.g. reaction with an appropriate acid. The compounds according to the invention and their pharmaceutically acceptable salts are useful antihypertensive agents, and they also display from moderate to good antiprolactinic activity and from moderate to good activity against tumors, markedly prolactin dependent tumors.

EVALUATION OF ANTI-HYPERTENSIVE ACTIVITY

Four spontaneously hypertensive male rats, strain SHR, weighing 250-300 g for each group were used. The animals were treated once a day for four consecutive days. Drugs were administered by gastric gavage, suspended in 5% gum arabic (0.2 ml/100 g body weight) and blood pressure (BP) and heart rate (HR) were measured by indirected tail/cuff method (BP Recorder W+W). Blood pressure and heart rate were measured on the first and fourth days of treatment 1 hour before and 1 and 5 hours after drug administration. Hydralazine and α-methyl-Dopa were used as reference drugs. Results are reported in Tables 1 and 2.

EVALUATION OF THE TOXICITY

The male mice for each group were orally treated with drugs at different dose levels for the determination of orientative toxicity. Mice were observed for seven days after administration. The data obtained are summarized in Table 3.

TABLE 1

Changes in blood pressure (BP) in SHR rats. The values represent the mean obtained with 4 animals

Compound of Example No.	Dose (mg/kg) os	1st day Change in BP (Δ mmHg) 1 hour after dosing	1st day 5 hours after dosing	4th day 1 hour after dosing	4th day 5 hours after dosing
10	25	−26	−41	−51	−40
	5	−11	−22	−15	−16
7	25	−30	−57	−30	−10
	5	−12	−10	−15	−7

TABLE 1-continued

Changes in blood pressure (BP) in SHR rats. The values represent the mean obtained with 4 animals

Compound of Example No.	Dose (mg/kg) os	1st day Change in BP (Δ mmHg) 1 hour after dosing	1st day 5 hours after dosing	4th day 1 hour after dosing	4th day 5 hours after dosing
9	25	−30	−37	−5	−23
1	1	−40	−37	−40	−32
	0.5	−27	−20	−20	0
12	10	−26	−37	−71	−28
	2	−17	−17	−10	−24
15	25.0	−35	−27	−47	−34
17	0.1	−5	−7	−4	−10
	1.0	−20	−19	−43	−66
	10.0	−47	−50	−59	−93
18	1.0	−15	−10	−8	−14
	12.5	−19	−19	−38	−47
Hydralazine	1	−5	−15	−5	0
	5	−40	−20	−20	−7
α-methyl-Dopa	30	−10	−20	−10	0
	100	−10	−25	−20	−25

TABLE 2

Changes in heart rate (HR) in SHR rats. The values represent the mean obtained with 4 animals

Compound of Example No.	dose (mg/kg) os	1st day Change in HR (Δ beats/minute) 1 hour after dosing	1st day 5 hours after dosing	4th day 1 hour after dosing	4th day 5 hours after dosing
10	25	−2	−12	−17	−20
	5	−5	−20	−20	+15
7	25	+5	−20	−17	−2
	5	0	−10	0	0
9	25	−20	−10	0	−20
1	1	−30	−35	−35	−30
	0.5	−20	−12	−20	−7
12	10	0	−30	+17	−10
	2	−10	−10	−20	−12
15	25	−20	−20	−27	−10
17	0.1	−2	+3	−4	−8
	1.0	−20	−23	−27	−22
	10.0	+15	−13	−2	+6
18	1.0	−22	−20	+7	−8
	12.5	−10	−13	+2	+5
Hydralazine	1	+30	+35	+25	+15
	5	+40	+45	+18	+15
α-methyl-Dopa	30	+35	+40	+45	+30
	100	+70	+40	+50	+10

TABLE 3

Compound of Example No.	Acute Toxicity Orientative toxicity in mice (mg/kg per os)
10	>800
7	>800
9	>800
1	>250 <500
12	>200 <400
15	>800
17	>100 <200
18	>200 <400
Hydralazine *	122
α-methyl-Dopa *	5300

* Data of LD_{50} from the literature

RESULTS

Antihypertensive activity

Tables 1 and 2 report the results of the activity of the compounds under study on BP and HR in spontaneously hypertensive rats, SHR strain (4 rats each group).

With the compound of Example 10, 1,3-dicyclohexyl-3-(10'α-methoxy-1',6'-dimethylergoline-8'β-carbonyl)-urea, at both the doses tried of 25 and 5 mg/kg a decrease of BP was observed; this effect was long lasting because it was still marked on the fourth day at both the first and fifth hour after dosing.

The compound of Example No. 7, 1,3-dicyclohexyl-3-(6'-methylergoline-8'β-carbonyl)-urea, was tried at the doses of 25 and 5 mg/kg; a significant decrease BP was observed with the higher dose used both on the first and fourth days of treatment; with the dose of 5 mg/kg the antihypertensive effect was less remarkable.

The compound of Example No. 9, 1,3-dicyclohexyl-3-(10'α-methylergoline-8'β-carbonyl)-urea, at the dose of 25 mg/kg produced a marked decrease of BP on the first day of treatment; the hypotensive effect was still observed on the fourth day even if less remarkable at the first hour after dosing.

The compound of Example No. 1, 1,3-diisopropyl-3-(6'-methylergoline-8'β-carbonyl)-urea, was tried at the doses of 1 and 0.5 mg/kg and it produced a marked decrease of BP in a dose dependent manner.

The compound of Example No. 12, 1,3-di-t-butyl-3-(10'α-methoxy-6'-methylergoline-8'βcarbonyl)-urea, tested at the doses of 10 and 2 mg/kg also reduced BP in a dose dependent manner; the greatest hypotensive effect was observed on the fourth day, one hour after the administration of 10 mg/kg.

All the compounds tested produced only a moderate bradycardia. The compound of Example No. 15, 1,3-dicyclohexyl-3-(6'-allylergoline-8'β-carbonyl)-urea, was administered at the dose of 25 mg/kg b.w. and produced a decrease in BP both on the 1st and 4th days of treatment but more pronounced on the 4th day. This was a long lasting activity and was still at its peak 5 hours after administration.

The dose response curve was determined in order to evaluate the hypotensive activity of the compound of Example No. 17, 1,3-di-t-butyl-3-(10'α-methoxy-1',6'-dimethylergoline-8'β-carbonyl)-urea. The tried doses were 10, 1 and 0.1 mg/kg b.w. The hypotensive effect was dose related as well as very marked with the highest dose tried (10 mg/kg b.w.) on both the 1st and 4th day of treatment. No effect was obtained with the lowest dose (0.1 mg/kg b.w.)

The compound of Example No. 18, 1,3-di-t-butyl-3-(1',6'-dimethylergoline-8'β-carbonyl)-urea, reduced BP with both the tested doses (12.5 and 1 mg/kg b.w.); this effect was dose dependent. The hypotensive activity observed with the highest dose was very remarkable on the 4th day of treatment and still lasting 5 hours after administration.

COMPARISON WITH REFERENCE DRUGS

Compounds 1,3-dicyclohexyl-3-(10'α-methoxy-1',6'-dimethylergoline-8'β-carbonyl)-urea (Example No. 10), 1,3-dicyclohexyl-3-(6'-methylergoline-8'β-carbonyl)-urea (Example No. 7) and 1,3-dicyclohexyl-3 (10'α-methoxy-6'-methylergoline-8'β-carbonyl)-urea (Example No. 9) at the dose of 25 mg/kg have a hypotensive activity comparable to that of Hydralazine at the dose

of 5 mg/kg. but show no tolerance on the 4th day. unlike Hydralazine.

The compound. 1,3-diisopropyl-3-(6'-methylergoline-8'β-carbonyl)-urea (Example No. 1) shows a greater and longer lasting hypotensive activity than Hydralazine. The compound 1,3-di-t-butyl-3-(10'αmethoxy-6'-methylergoline-8'β-carbonyl)-urea (Example No. 12) at the dose of 10 mg/kg shows comparable activity to that of Hydralazine at the dose of 5 mg/kg on the 1st day, but a greater activity on the 4th day because tolerance does not occur.

The hypotensive activity of compounds 1,3-dicyclohexyl-3-(6'-allylergoline-8'β-carbonyl)-urea (25 mg/kh b.w.) (Example No. 15), 1,3-di-t-butyl-3(10'α-methoxy-1',6'-dimethoxyergoline-8'β-carbonyl)-urea (1 mg/kg b.w.) (Example No. 17) and 1,3-di-t-butyl-3-(1',6'-dimethylergoline-8'β-carbonyl)urea (12.5 mg/kg b.w.) (Example No. 18) was comparable to that of Hydralazine (5 mg/kg b.w.) on the first day of treatment, but was much more remarkable on the 4th day.

The compound 1,3-di-t-butyl-3-(10'α-methoxy-1',6'-dimethoxyergoline-8'βcarbonyl)-urea at its higher dose (10 mg/kg b.w.) (Example No. 17) also produced an hypotensive effect larger than Hydralazine on both the 1st and 4th days of treatment.

Compared with α-methyl-Dopa tested at the dose of 30 and 100 mg/kg the tested compounds according to the invention all show a greater hypotensive effect. Considering the activity on HR, the tested compounds according to the invention do not produce any increase of HR as Hydralazine and α-methyl-Dopa do, but, on the contrary, a moderate bradycardia is observed.

TOXICITY

Finally the toxicity of the compounds according to the invention, expressed as orientative toxicity in mice (Table 3) is not greater than Hydralazine and is lower in some cases. The tested compounds according to the invention also have a better therapeutic index than α-methyl-Dopa.

EVALUATION OF ANTI-PROLACTIN ACTIVITY

The compounds of this invention have proved to possess a strong anti-prolactin activity in rats and a low emetic activity in dogs. The prolactin secretion inhibitory action of the compounds has been indirectly evaluated by determining the egg-nidation inhibitory action in rats. For the ergoline derivatives this activity is considered to be correlated with the anti-prolactin activity (E. FLUCKIGER and E. DEL POZO,Handb. exp. Pharmac. 49, 615, 1978), since prolactin is the only hypophysial hormone involved in the maintenance of the first part of pregnancy in rats (W. K. MORISHIGE and I. ROTHCHILD, Endocrinology 95, 260, 1974).

Pregnant Sprague Dawley rats weighing 200-250 g were used. The compounds to be tested, dissolved in diluted mineral acids, were administered orally to groups from six to eight rats on day 5 of pregnancy. The animals were sacrificed on day 14 and the uteri were examined. The absence of implantation sites was taken as the criterion of anti-prolactin activity. Several doses were tested for the ED_{50} evaluation. As reference standard Bromocriptine was used.

The emetic activity of the compounds was investigated by oral administration to male beagle dogs weighing 15-20 kg. The animals were observed for 6 hours after the treatment. Four to six animals per dose were employed for the ED_{50} evaluation. The results obtained are reported in TABLE 4. From Table 4 it appears that the new ergoline derivatives are 19 to 235 times more active than Bromocriptine as nidation inhibitors. The emetic activity of the compounds is similar or lower than that of Bromocriptine. The ratio between activity and tolerance of the new ergoline derivatives accordingly is very high.

From the above results it can be seen that the new derivatives may find an advantageous clinical exploitation in all the situations in which it is desirable to reduce prolactin levels such as inhibition of puerperal lactation, inhibition of galactorrhoea and treatment of infertility due to hyperprolactinaemia. The compounds, of the present invention may also find utility, like bromocriptine, for the treatment of Parkinson's disease and acromegaly.

TABLE 4

Name of Compound	Nidation Inhibition in Rats $=ED_{50}$ mg/kg p.o.	Emetic activity in Dogs $=ED_{50}$ mg/kg p.o.
1,3-diisopropyl-3-(6'-n-propylergoline-8'β-carbonyl)-urea (Example No. 5)	0.02	0.01
1-ethyl-3-(3'-dimethylaminopropyl)-3-(6'-methylergoline-8'β-carbonyl)-urea (Example No. 13)	0.3	0.01
1-ethyl-3-(3'-dimethylaminopropyl)-3-(6'-allylergoline-8'β-carbonyl)-urea (Example No. 19)	0.03	0.02
1-(3'-dimethylaminopropyl)-3-ethyl-3-(6'-allylergoline-8'β-carbonyl)-urea (Example No. 20)	0.27	—
1-ethyl-3-(3'dimethylaminopropyl)-3-(6'-n-propylergoline-8'β-carbonyl)-urea (Example No. 21)	0.02	0.02-0.04
1,3-dimethyl-3-(6'-allylergoline-8'β-carbonyl)-urea (Example No. 24)	0.5	—
2-bromo-α-ergocryptine	5.7	0.01-0.02

The following Examples illustrate preparation of some compounds of the present invention, without limiting it.

EXAMPLE 1

1,3-diisopropyl-3-(6'-methylergoline-8'β-carbonyl)urea (I: $R_1=R_2=R_3=H$, $R_4=CH_3$,$R_5=R_6=(CH_3)_2CH$)

A mixture of 5 g of 6-methyl-8β-carboxy-ergoline and 2.3 g of diisopropyl carbodiimide in 500 ml of tetrahydrofuran were refluxed, with stirring and under nitrogen, for 24 hours. The resultant solution was evaporated in vacuo to dryness and the residue taken up with chloroform and 5% sodium hydroxide solution. The organic phase was separated, dried over anhydrous sodium sulphate and evaporated in vacuo. The residue was chromatographed on silica (eluant chloroform with 1% methanol) to give 5.8 g of the title compound, m.p. 202°-204° C., after crystallization from diethyl ether.

EXAMPLE 2

1,3-diisopropyl-3-(1',6'-dimethylergoline-8'β-carbonyl-)urea (I: $R_1=R_4=CH_3$, $R_2=R_3=H$, $R_5=R_6=(CH_3)_2CH$)

Operating as in Example 1, but employing 1,6-dimethyl-8β-carboxy-ergoline in place of 6-methyl-8βcarboxy-ergoline, the title compound, m.p. 172°-174° C., was obtained in 75% yield.

EXAMPLE 3

1,3-diisopropyl-3-(10'α-methoxy-6'-methylergoline-8'β-carbonyl)urea (I: $R_1=R_2=H$, $R_3=CH_3O$, $R_4=CH_3$, $R_5=R_6=(CH_3)_2CH$)

Operating as in Example 1, but employing 10α-methoxy-6-methyl-8β-carboxy-ergoline in place of 6-methyl-8β-carboxy-ergoline, the title compound, m.p. 190°–192° C., was obtained in 79% yield.

EXAMPLE 4

1,3-diisopropyl-3-(10'α-methoxy-1',6'-dimethylergoline-8'βcarbonyl)urea (I: $R_1=R_4=CH_3$, $R_2=H$, $R_3=CH_3O$, $R_5=R_6=(CH_3)_2CH$)

Operating as in Example 1, but employing 10α-methoxy-1,6-dimethyl-8β-carboxy-ergoline in place of 6-methyl-8β-carboxy-ergoline, the title compound, m.p. 180°–182° C., was obtained in 80% yield.

EXAMPLE 5

1,3-diisopropyl-3-(6'-n-propylergoline-8'β-carbonyl)-urea (I: $R_1=R_2=R_3=H$, $R_4=CH_3CH_2CH_2$, $R_5=R_6=(CH_3)_2CH$)

Operating as in Example 1, but employing 6-n-propyl-8β-carboxy-ergoline in place of 6-methyl-8βcarboxy-ergoline, the title compound, m.p. 188°–190° C., was obtained in 82% yield.

EXAMPLE 6

1,3-diisopropyl-3-(2',6'-dimethylergoline-8'β-carbonyl)-urea (I: $R_1=R_3=H$, $R_2=R_4=CH_3$, $R_5=R_6=(CH_3)_2CH$)

Operating as in Example 1, but employing 2,6-dimethyl-8β-carboxy-ergoline in place of 6-methyl-8β-carboxy-ergoline, the title compound, m.p. 192°–194° C., was obtained in 85% yield.

EXAMPLE 7

1,3-dicyclohexyl-3-(6'-methylergoline-8'β-carbonyl-)urea (I: $R_1=R_2=R_3=H$, $R_4=CH_3$, $R_5=R_6=$cyclohexyl)

Operating as in Example 1, but employing dicyclohexyl carbodiimide in place of diisopropyl carbodiimide, the title compound, m.p. 205°–207° C., was obtained in 77% yield.

EXAMPLE 8

1,3-dicyclohexyl-3-(1',6'-dimethylergoline-8'βcarbonyl)-urea (I: $R_1=R_4=CH_3$, $R_2=R_3=H$, $R_5=R_6=$cyclohexyl)

Operating as in Example 2, but employing dicyclohexyl carbodiimide in place of diisopropyl carbodiimide, the title compound, m.p. 182°–184° C., was obtained in 83% yield.

EXAMPLE 9

1,3-dicyclohexyl-3-(10'α-methoxy-6'-methylergoline-8'β-carbonyl)-urea (I: $R_1=R_2=H$, $R_3=CH_3O$, $R_4=CH_3$, $R_5=R_6=$cyclohexyl)

Operating as in Example 3, but employing dicyclohexyl carbodiimide in place of diisopropyl carbodiimide, the title compound m.p. 229°–231° C., was obtained in 75% yield.

EXAMPLE 10

1,3-dicyclohexyl-3-(10'α-methoxy-1',6'-dimethylergoline-8'β-carbonyl)-urea (I: $R_1=R_4=CH_3$, $R_2=H$, $R_3=CH_3O$, $R_5=R_6=$cyclohexyl)

Operating as in Example 4, but employing dicyclohexyl carbodiimide in place of diisopropyl carbodiimide, the title compound m.p. 198°–200° C., was obtained in 80% yield

EXAMPLE 11

1,3-di-tert-butyl-3-(6'-methylergoline-8'β-carbonyl)-urea (I: $R_1=R_2=R_3=H$, $R_4=CH_3$, $R_5=R_6=(CH_3)_3C$)

Operating as in Example 1, but employing di-t-butyl carbodiimide in place of diisopropyl carbodiimide, the title compound, m.p. 194°–196° C., was obtained in 75% yield.

EXAMPLE 12

1,3-di-t-butyl-3-(10'αmethoxy-6'-methylergoline-8'β-carbonyl)-urea (I: $R_1=R_2=H$, $R_3=CH_3O$, $R_4=CH_3$, $R_5=R_6=(CH_3)_3C$)

Operating as in Example 3, but employing di-t-butyl carbodiimide in place of diisopropyl carbodiimide, the title compound, m.p. 138°–140° C., was obtained in 65% yield.

EXAMPLE 13

1-ethyl-3-(3'-dimethylaminopropyl)-3(6'-methylergoline-8'β-carbonyl)-urea (I: $R_1=R_2=R_3=H$, $R_4=CH_3$, $R_5=(CH_3)_2—NCH_2CH_2CH_2$, $R_6=C_2H_5$)

Operating as in Example 1, but employing N-(3-dimethylaminopropyl)—N-ethyl carbodiimide in place of diisopropyl carbodiimide, the title compound, m.p. 179°–181° C., was obtained in 75% yield.

EXAMPLE 14

1-ethyl-3-(3'-dimethylaminopropyl)-3-(10'α-methoxy-6'-methylergoline-8'β-carbonyl)urea (I: $R_1=R_2=H$, $R_3=CH_3O$, $R_4=CH_3$, $R_5=(CH_3)_2NCH_2CH_2CH_2$, $R_6=C_2H_5$)

Operating as in Example 3, but employing N-(3-dimethylaminopropyl)-N'-ethyl carbodiimide in place of diisopropyl carbodiimide, the title compound m.p. 169°–171° C. was obtained in 78% yield.

EXAMPLE 15

1,3-dicyclohexyl-3-(6'-allylergoline-8'β-carbonyl)-urea (I: $R_1=R_2=R_3=H$, $R_4=CH_2=CH—CH_2$, $R_5=R_6=$cyclohexyl)

Operating as in Example 7, but employing 6-allyl-8β-carboxy-ergoline in place of 6-methyl-8β-carboxy-ergoline, the title compound, m.p. 152°–154° C., was obtained in 80% yield.

EXAMPLE 16

1,3-dimethyl-3-(6'-methylergoline-8'β-carbonyl)urea (I: $R_1=R_2=R_3=H$, $R_4=R_5=R_6=CH_3$)

Operating as in Example 1, but employing dimethyl carbodiimide in place of diisopropyl carbodiimide, the title compound, m.p. 215°–217° C. was obtained in 74% yield.

EXAMPLE 17

1,3-di-tert-butyl-3-(10'α-methoxy-1',6'-dimethylergoline-8'β)-carbonyl)-urea (I: $R_1=R_4=CH_3$, $R_2=H$, $R_3=CH_3O$, $R_5=R_6=(CH_3)_3C$)

Operating as in Example 4, but employing di-t-butyl carbodiimide in place of diisopropyl carbodiimide, the title compound, m.p. 140°–142° C. was obtained in 60% yield.

EXAMPLE 18

1,3-di-tert-butyl-3-(1',6'-dimethylergoline-8'β-carbonyl-)urea (I: $R_1=R_4=CH_3$, $R_2=R_3=H$, $R_5=R_6=(CH_3)_3C$)

Operating as in Example 2, but employing di-t-butyl carbodiimide in place of diisopropyl carbodiimide, the title compound, m.p. 180°–181° C., was obtained in 65% yield.

EXAMPLE 19

1-ethyl-3-(3'-dimethylaminopropyl)-3-(6'-allylergoline-8'βcarbonyl)-urea (I: $R_1=R_2=R_3=H$, $R_4=CH_2=CH-CH_2$, $R_5=(CH_3)_2-NCH_2CH_2CH_2$, $R_6=C_2H_5$)

Operating as in Example 13, but employing 6-allyl-8'β-carboxy-ergoline in place of 6-methyl-8β-carboxy-ergoline, the title compound was obtained in 60% yield as diphosphate salt m.p. 153°–155° C.

EXAMPLE 20

1-(3'-dimethylaminopropyl)-3-ethyl-3-(6'-allylergoline-8'β-carbonyl)-urea (I: $R_1=R_2=R_3=H$, $R_4=CH_2=CH-CH_2$, $R_5=C_2H_5$, $R_6=(CH_3)_2NCH_2CH_2CH_2$)

Operating as in Example 19, after separation of 1-ethyl-3-(3'-dimethylaminopropyl)-3-(6'-allylergoline-8'β-carbonyl)-urea, the mother-liquor was chromatographed on silica gel using $CHCl_3$/1–2% MeOH as eluant to give the title compound in 30% yield as diphosphate salt, m.p. 149°–151° C.

EXAMPLE 21

1-ethyl-3-(3'-dimethylaminopropyl)-3-(6'-n-propylergoline-8'β-carbonyl)-urea (I: $R_1=R_2=R_3=H$, $R_4=CH_3CH_2CH_2$, $R_5=(CH_3)_2NCH_2-CH_2CH_2$, $R_6=C_2H_5$)

Operating as in Example 13, but employing 6-n-propyl-8β-carboxy-ergoline in place of 6-methyl-8β-carboxy-ergoline, the title compound was obtained in 70% yield as dichloride salt, m.p. 205°–207° C.

EXAMPLE 22

1-ethyl-3-(3'-dimethylaminopropyl)-3-(6'-isopropylergoline-8'β-carbonyl)-urea (I: $R_1=R_2=R_3=H$, $R_4=(CH_3)_2CH$, $R_5=(CH_3)_2NCH_2-CH_2CH_2$, $R_6=C_2H_5$)

Operating as in Example 13, but employing 6-isopropyl-8β-carboxy-ergoline, the title compound, m.p. 106°–108° C., was obtained in 55% yield.

EXAMPLE 23

1,3-dicyclohexyl-3-(1'-methyl-6'-allylergoline-8'β-carbonyl)-urea (I: $R_1=CH_3$, $R_2=R_3=H$, $R_4=CH_2CH=CH_2$, $R_5=R_6=$cyclohexyl)

Operating as in Example 7, but employing 1-methyl-6-allyl-8β-carboxy-ergoline in place of 6-methyl-8β-carboxy-ergoline, the title compound, m.p. 137°–139° C., was obtained in 75% yield.

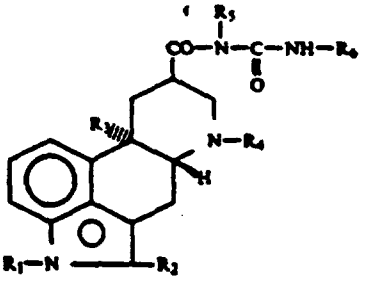
EXAMPLE 24

1,3-Dimethyl-3-(6'-allylergoline-8'β-carbonyl)-urea (I: $R_1=R_2=R_3=H$, $R_4=CH_2=CH-CH_2$, $R_5=R_6=CH_3$)

Operating as in Example 15, but employing dimethylcarbodiimide in place of dicyclohexylcarbodiimide, the title compound, m.p. 106°–108° C., was obtained in 67% yield.

What we claim is:

1. Compounds of formula



wherein R_1 is a hydrogen atom or a methyl group; R_2 is a hydrogen atom; R_3 is a hydrogen atom or a methoxy group; R_4 is an alkyl or an alkenyl group selected from methyl, allyl and propyl groups; and each of R_5 and R_6 independently is an alkyl group having from 1 to 3 carbon atoms or a group of the formula $(CH_2)_nN(CH_3)_2$ in which n is 3 with the proviso that at least one of R_5 and R_6 is said dimethylaminoalkyl group, and pharmaceutically acceptable addition salts with organic or inorganic acid thereof.

2. A compound according to claim 1 which is selected from the group consisting of:

1-ethyl-3-(3'-dimethylaminopropyl)-3(6'-methylergoline-8'β-carbonyl)-urea;

1-ethyl-3-(3'-dimethylaminopropyl)-3-(10'α-methoxy-6'-methylergoline-8'β-carbonyl)-urea;

1-(3'-dimethylaminopropyl)-3-ethyl-3-(6'-allylergoline-8'β-carbonyl)-urea; and

1-ethyl-3-(3'-dimethylaminopropyl)-3-(6'-n-propylergoline-8'β-carbonyl)-urea.

3. A pharmaceutical composition containing a therapeutically effective amount of a compound according to claim 1, in admixture with a pharmaceutically acceptable carrier for oral or parenteral administration.

4. 1-ethyl-3-(3'dimethylaminopropyl)-3-(6'-allylergoline-8'β-carbonyl)-urea.

* * * * *

CABERGOLINE NDA 20-664
Generic Drug Enforcement Act of 1992

CERTIFICATION PURSUANT TO THE GENERIC DRUG ENFORCEMENT ACT OF 1992

Pursuant to 21 U.S.C. §335a (k)(1) Pharmacia Inc. ("Pharmacia") hereby certifies that to the best of its knowledge and belief it has not used, in any capacity, the services of any person debarred under subsections 21 U.S.C. §335a(a) or (b) in connection with this Application and that it will not use, in any capacity, the services of any person debarred under 21 U.S.C. §335a(a) or (b) in connection with this Application.

Pharmacia has made a reasonable effort to list the convictions of all persons whose convictions are required to be listed under 21 U.S.C. §335a(k)(2) in connection with this Application. This effort included reviewing the Debarment List as published in the Federal Register and confirming that no employees of Pharmacia connected with this Application appear on that list. In addition, Pharmacia requires that all newly hired employees execute a certification concerning any convictions required to be listed. Finally, this effort included a requirement that all persons not employed by Pharmacia who provided significant services in connection with this Application certify to Pharmacia concerning any convictions of their organization or of any person employed by them. Relying in part on these certifications to Pharmacia, the following list of all convictions described in 21 U.S.C. §335a(a) or (b), which occurred in the previous five (5) years of Pharmacia and affiliated persons responsible for the development or submission of this Application is provided.

The listed convictions are: None.

Respectfully submitted,

By: Kenneth King
Kenneth F. King

Title: Senior Vice President, Regulatory and Scientific Affairs

Date: Dec. 20, 1995

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-664 Trade (generic) names Cabergoline (Dostinex)

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

Well-controlled studies in pediatric populations have not been completed for this drug. Such studies are not indicated due to the rarity of disease onset in childhood.

Signature of Preparer

11/22/96
Date

cc: Orig NDA
HFD-510/Div File
NDA Action Package

December 5, 1996
Division Director's Memo
To: the file NDA 20-664 Dostinex (cabergoline)
From: Solomon Sobel M.D. Director, Division of Metabolic and Endocrine Drug Products Solomon Sobel 12/6/96
Subject: Approval of NDA

The sponsor (Pharmacia/ Upjohn) has submitted an NDA for the use of cabergoline tablets for the indication of hyperprolactinemic disorders, either idiopathic or due to pituitary adenomas.

The sponsor submitted two phase 3 studies in support of the indication:

I) HPRL 007 --This study was a double blind, randomized study comparing cabergoline with placebo. The primary endpoint was biochemical(prolactin decrease)

II) ONC 26 --This study was an active control study comparing cabergoline with bromocriptine. This was a randomized double blind trial for the first eight weeks and open for the next 16 weeks. Serum prolactin and progesterone levels, occurrence of menses and pregnancy were measured.

In study ONC 026, treatment efficacy was evaluated on the basis of prolactin response and the resumption of menses and ovulation cycle.
Significant decrease in prolactin levels and resumption of menses and ovulation cycle was defined as a "global complete success."
"Complete clinical success" was defined as a resumption of ovulatory cycles or occurrence of pregnancy.
By the eighth week, at the end of the double blind portion complete clinical success had been achieved in 77% of cabergoline patients and 59% of bromocriptine patients.
Global complete success was achieved in 72% of cabergoline patients and 51% of bromocriptine patients.
Nausea was more prevalent in the bromocriptine group (50%) than in the cabergoline group 31% ($p=< o.001$)

These pivotal studies provide basis for approval although only one (ONC 02) of the studies has distinctly clinical endpoints as opposed to the biochemical endpoint of study (HPRL 007). This biochemical surrogate is sufficiently well established as to form a firm basis for efficacy.

Recommendations:
1) Approval of this NDA is recommended
2) Further discussion will resolve some labeling issues in respect to the maximum recommended dose of cabergoline and

the way the issue of lactation suppression is addressed in the label.

SD 12/5/96

Solomon Sobel M.D.

cc: Arch NDA 20-664
HFD-510
HFD-510/RHedin/SSobel/AFleming

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020664

MEDICAL OFFICER REVIEWS

Medical Group Leader Note

NDA 20-664
Dostinex™ (cabergoline)

November 30, 1996

Cabergoline appears to be equivalent if not superior to bromocriptine in tolerability, general safety, and efficacy for the proposed indication. In addition, we have some preliminary evidence that the drug is effective in shrinking macroprolactinomas and in the treatment of Parkinson's patients, but neither indication is sought by the sponsor. I agree with Dr. Gueriguain, that despite some evidence for superiority of cabergoline over bromocriptine, it is for too soon to draw that conclusion definitively. The labeling is now free of any such claim though in its presentation of the data, one might be led to conclude that the drug is superior to bromocriptine. The data, however, are appropriately presented.

The drug's very long half life appears to have some advantage but, from the beginning, has been a source of concern from the safely perspective. We do have enough pre-clinical, and dose response data from patients to feel fairly comfortable that toxicity resulting from accumulation is not likely to be a problem. Nor do we have evidence for aberrant metabolism and /or idiosyncratic responses, which are likewise concerns related to drugs with long dwell times. Animal studies are generally reassuring about potential for carcinogenicity and reproductive toxicity. There is some concern about this drug being used "off label" for physiologic lactation suppression. I have suggested some additions to the label, which I believe will reduce this occurrence.

Recommendation:

Approval of the NDA with the following modifications of the label.

[Line 36] Delete

[page 12] The title of the table should be revised to read:

The figures in the table should then be changed to reflect this different period of observation

[Insert after line 127:]

[Continuing after the above paragraph. Add:]

[Insert after line 130, from Anne Reb]

[Insert after last sentence in line 204:]

[Insert at end of sentence in line 216:]

[The following item was requested by Dr. Gueriguian but not included in the final labeling. Insert after last sentence line 266:]

[Insert after last sentence in line 270:]

In addition, Dr. Gueriguian had suggested that more emphasis be given to the relatively rare, more serious AE's seen with Parkinson's patients by moving this text up to the beginning of the

section. While agreeing with the thought behind it, this section is already very short and I do not believe this text can be moved up without appearing our of place.

11/30/96

Alexander Fleming, M.D.

cc:
HFD-510
/NDA 20-664
/div. files
/J. Gueriguian/E. Galliers/R. Hadin

Med.
APR 14 1996

NDA 20664
Sponsor:Pharmacia, Inc.
Drug:Cabergoline/Dostinex

Received: 1/29/96
Reviewed:3/28/96
Doct: N20664a/G115

MEDICAL OFFICER'S REVIEW OF NEW DRUG APPLICATION

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MEDICAL REVIEW PROPER

1 GENERAL INFORMATION

1.1 Drug Name and Structure

1.1.1 Generic name: Cabergoline

1.1.2 Proposed trade name: Dostinex

1.1.3 USAN chemical name

Available neither in the submission, nor in the USP Dictionary, 1995 edition.

1.1.4 Structure or full chemical name

N-[3-(Dimethylamino)propyl]-N-[(ethylamino)carbonyl]-6-(2-propenyl)-8-ergoline-8-carboxamide. For the exact structural formula, see Fig.1a.

1.2 Scientific Information

1.2.1 Pharmacological category

The submitted moiety is a dopamine receptor agonist (for structural formula, see Fig. 1a). The only approved drug belonging to the same category is Bromocriptine (for structural formula, see Fig. 1b). Another dopamine receptor agonist, Pergolide, has been inactive for some time due to its high level of perceived toxicity. As can be seen below, Bromocriptine, itself, is not without its occasionally severe side-effects.

Pharmacologically, the drug appears to be a rather unique moiety: While being an ergoline derivative, it distinguishes itself from its congeners through its duration of action, despite the fact that its metabolites appear to be pharmacodynamically inactive. Apparently, a large amount of unchanged drug is concentrated in various bodily compartments, especially in the hypothalamus (but also in other cerebral loci) where it can activate the dopamine receptors, eliciting there the inhibition of pituitary lactotrophs normally performed by dopamine of hypothalamic origin.Clearly, therefore, the drug crosses the blood-brain barrier. This explains why, very rarely, cerebral side-effects (e.g., dyskinesia) may appear in some patients treated with dopamine receptor agonists.

1.2.2 Proposed indication(s)

1.2.3 Dosage form(s)

Tablets, 0.5 mg.

1.2.4 Route(s) of administration: Oral.

1.3 Regulatory Information

1.3.1 Review priority rating

Bromocriptine is approved and on sale, to treat the symptomatological hyperprolactinemic population. Cabergoline

is a novel chemical entity belonging to the same pharmacological class than Bromocriptine. The fact that Cabergoline is convenient, since it should be usually administered at 0.5 mg once a week, doesn't necessarily mean that it is therapeutically superior to Bromocriptine. Hence, its introduction may or may not improve the therapeutic index within the class of dopamine receptor agonists. Only time will tell. In any event, the Team Leader and the Division Director should decide of the proper rating.

1.3.2 Related drugs

As indicated above, Bromocriptine and Pergolide are the two principal pharmacological congeners for whom we possess considerable clinical and other scientific experience and knowledge. The former has been an approved drug for quite a long-time; the latter has seen its development essentially halted by its manufacturer and owner due to some serious and unaddressed safety issues. Dopamine receptor agonists are also indicated for the treatment of Parkinson disease. As such, that additional human exposure, and the experience that goes with it, has been precious in enlarging our safety investigations and data base.

Dopamine receptor agonists siginficantly reduce plasma levels of prolactin in patients with hyperprolactinemia (and its attendant eventual consequences, e.g., galactorrhea and infertility) as well as inhibiting physiological lactation in post-partum subjects. The latter indication, originally approved for Bromocriptine, has since been withdrawn given the exceptional yet extremely worrisome existence of cerebro-vascular accidents in post-partum young women to whom the drug was administered to stop the lactating process.

Bromocriptine, the only dopamine receptor agonist presently on the market, suppresses amenorrhea and galactorrhea (completely or near completely) in about 75% of the treated patients, thus reinstituting a normal menstrual cycle in the treated patients, on average in about 6-8 weeks. Galactorrhea takes a longer time to control, and some 75% of reduction in secretion (or more) is observed, in up to 8 months of continuous treatment.

Dopamine receptor agonists have also been shown to significantly reduce Growth Hormone (GH) levels in a great number of acromegalic patients. Efficacy, here, is less pronounced than in the case of treatment of amenorrhea and galactorrhea, and questions have been raised by some as to the clinical significance of such reductions of GH on the clinical course and the ultimate outcome of the acromegalic conditions.

1.3.3 Related reviews from other disciplines

Apparently, the safety of Cabergoline has been evaluated in more than 1200 patients with Parkinson's disease in controlled and uncontrolled clinical trials, and at doses significantly higher than the ones recommended for hyperprolactinemic disorders. The following serious to severe side-effects were seen in such populations: dyskinesia, hallucinations, confusion, peripheral edema, heart failure, pleural effusion, pulmonary fibrosis, and gastric or duodenal ulcers. Though rare, such complications (which have also been observed in patients treated with Bromocriptine) should force us to maintain the recommended dosage for hyperprolactinemic disorders within reasonable bounds, as suggested from dose-response studies using Cabergoline in the appropriate populations.

1.3.4 Approval in other countries

The drug has already been approved in the following countries for the inhibition and/or suppression of lactation indication and for the hyperprolactinemic disorders indication: Australia, Austria, Belgium, Bulgaria, Denmark, Finland, Germany, Greece, Italy, Luxembourg, New Zealand, Romania, and the U.K.

Chile, Ireland, and Switzerland have approved only the hyperprolactinemic indication.

Iceland and Norway have approved only the inhibition of lactation indication.

Clearly, no country has yet approved the thus, no large scale human experience is available at higher than the doses recommended for the treatment of hyperprolactinemic disorders.

In this Reviewer's opinion, the Company has had the good sense not to request from the FDA approval of the inhibition/suppression of lactation indication.

1.3.5 Miscellaneous other information

This drug's development proceeded in a coordinated manner between Industry and the FDA. Several meetings were held in order to make sure that Industry knew what was expected of it and had a chance to respond in case of disagreements with the advisements and requirements of the FDA. As a result, it is this Reviewer's impression that the development of this drug proceeded smoothly and expeditiously.

More specifically, two pre-NDA meetings were held and the second one on During these meetings the clinical development program of Cabergoline were jointly reviewed, the pivotal trials were identified, and concurrence obtained as to the general acceptability of a plan of NDA content and submission. Discussion at both meetings also included decisions concerning the pharmacological and statistical aspects of an eventual submission.

2 LISTING OF VOLUMES REVIEWED

The following volumes were reviewed, partially or *in toto*, depending on the relative pertinence and/or importance of a given trial or topic:

Vol. 1.52
Vol. 1.53
Vol. 1.54
Vol. 1.55
Vol. 1.57
Vol. 1.58
Vol. 1.60
Vol. 1.61
Vol. 1.62
Vol. 1.64
Vol. 1.65
Vol. 1.66

Vol. 1.67
Vol. 1.69
Vol. 1.75
Vol. 1.76
Vol. 1.77
Vol. 1.78
Vol. 1.79
Vol. 1.80
Vol. 1.83
Vol. 1.103
Vol. 1.132
Vol. 1.136

3 CHEMISTRY AND MANUFACTURING CONTROLS

The drug is manufactured by
on behalf of Pharmacia. This Reviewer refers those interested with the Chemistry and Manufacturing of the drug to the expert review by our Chemist. Obviously, any medical recommendation of approval is contingent upon approval of Chemistry and Manufacturing by our colleagues in Chemistry.

As far as the Medical Reviewer is concerned, it is reassuring to see that the stability of the chemical moiety appears to be satisfactory. Again, the Chemist's recommendation ought to be followed in this and other related matters. Likewise, the dissolution figures appear to be reassuring to this Reviewer, while our Chemist's recommendation should again take precedence in such matters.

4 PRECLINICAL PHARMACOTOXICOLOGY

This Reviewer refers those interested in the extensive data base of the preclinical pharmacology of Cabergoline, contained in this submission, to its hopefully expert review by our Divisional Pharmacologist. Obviously, the approval recommendation of this Medical Officer is contingent upon a clean bill of health, so to speak, being rendered by our pharmacological Reviewer and Supervisor.

Regardless, the following preclinical findings appear to be pertinent to this Medical Reviewer, given that

Cabergoline may influence reproductive functions and organs: (1) A slight increase in the incidence of cervical and uterine leiomyomas of uterine leiomyosarcomas were observed in the mouse; and, (2) In the rat, the observation was made of a slight increase in malignant tumors of the cervix and the uterus.

But such concerns may be thoughtfully and cautiously dismissed as not being germane to conditions prevalent in the human species, as opposed to those knwon to exist in rodent species. Indeed, ovarian function in rodents is extremely peculiar, given that prolactin is needed to maintain their corpora lutea, where progesterone is synthesized during the second half of the ovarian cycle. In its absence, progesterone levels go down and estrogen levels become predominant, obviously leading to overstimulation of its target cells in the uterus and the cervix. In fact, and if memory serves, similar if not identical observations were made during preclinical studies using Bromocriptine. These observations were similarly dismissed as irrelevant to humans on the basis of the kind of considerations supplied above.

From a pharmacokinetic viewpoint, the drug's plasma half-life appear to be just as long as in the human. For example, the half-life for the elimination of radiolabeled drug from the pituitary gland after a single oral dose of tritiated-Cabergoline in rats was about 60 hrs. Of course, this figure is a composite of the clerance values for the unmetabolized drugs as well as its metabolites; even then, it gives an idea of the slowness with which the drug are eliminated, particularly after being concentrated early into cerebral sites, e.g., the hypothalamus.

5 CLINICAL BACKGROUND

5.1 Direct information

5.1.1 Human pharmacodynamics

Dopamine receptor agonists, originally ergot derivatives, activate post-synaptic dopamine receptors. The dopaminergic neurons in the tubero-infundibular hypothalamic locus modulate the secretion of prolactin from the anterior

pituitary by secreting a prolactin inhibitory factor, probably dopamine itself. This explains the endocrine effects of this class of drugs. Also, to explain its usefulness in the treatment of Parkinson disease, one should know that, in the corpus striatum, the dopaminergic-neurons are somehow involved in the control of motor function.

5.1.2 Human pharmacokinetics

It is important to note that the pharmacokinetics of Cabergoline, as a function of dose (within the studied range of mg, once a day for 18-23 days; administered to patients with Parkinson's disease) was linear and dose-proportional. Together with other studies, the present day experience suggests linear kinetics over the mg dose range.

Some 14 studies have been conducted using Cabergoline, seven of them in healthy volunteers (two of them with radiotagged drug derivatives) and the remaining seven in patients with hyperprolactinema or Parkinson's disease, or those with renal or liver insufficiency.

From a methodological viewpoint, it is reassuring to learn that the effect of sample storage conditions on the stability of Cabergoline (and, therefore, the validity of Cabergoline titer measurements during these pharmacokinetic studies) was asessed in collected human plasma and urine speciments.

Following oral administration of the drug, very low levels of unchanged drug were observed, suggesting a substantial so-called first-pass effect with a significant amount of metabolites being present in the systemic circulation.

Absorption of the drug was rapid (in about 2-3 hrs.) and didn't seem to be influenced by the dosage form (tablet or solution), or by the ingestion of food immediately prior to the oral administration of the drug.

All the available studies indicate that Cabergoline kinetics are dose-proportional, i.e., linear within the studied range of mg dosing. Urinary excretion data suggest that the terminal half-life is long (about 80 hrs.).

The volume of distribution of the drug is probably very large (see discussion immediately below) and the metabolism of residual (= what is left after rapid concentration in cellular sites) circulating drug probably extensive, with four metabolites already identified in urine extracts from treated patients. The main metabolite, dubbed FCE 21589, resulting from the hydrolysis of the acylurea residue of the drug, didn't show any D2 receptor binding activity.

Indeed, in the absence of a direct IV dosing study, the volume of distribution can only be indirectly estimated to be higher than 200 L/kg -- an unsually high number which clearly indicates that some cellular compartment(s) contain extremely high Cabergoline titer, most of which is probably protected from metabolism, the remainder (i.e., the circulating portion) eliminated is a very slow manner. The potential for overdosing and long-term unpredictable side-effects (particularly in the central nervous system) is, therefore, very real.

As a matter of fact, when drug accumulation (in the serum, mind you) was actually assessed in 12 healthy female volunteers (after single, then repeated doses of 0.5 mg of the drug, given twice weekly for no more than 4 weeks) Cabergoline showed the potential for accumulation of up to 3 times that seen following a single dose. This raises a red flag which should prompt the following precautions: (1) Give low doses once a week, shying away from the temptation to rapidly up-titrate; and, (2) as quickly as possible reduce dosing (if possible); or space dosing, whilst measuring prolactinemia; or stop giving the drug for a short while before resuming therapy -- all of this, for the purpose of giving, to individual patients, the least dose that is biochemically (and therefore clinically) effective, even at the expense of erring a bit on the conservative side rather than the other way around.

The Company's conclusion that "multiple dosing does not perturb the kinetic system and that drug accumulation to steady-state should not exceed 3-fold whern Cabergoline is administered once a week," may or may not be warranted. However, pharmacokinetic extrapolations are ordinarily so tenuous that, again, it is better to be a bit conservative, particularly in view of the following comments: (1) Since we

possess no precise measurement of the plasma half-life, we are not sure that steady-state was achieved in these studies after a twice weekly dosing for 4 weeks; (2) the study was performed in healthy volunteers, which may or may not truly reflect the kinetics in hyperprolactinemic patients; and, (3) regardless of what seems to accumulate in the serum, the action is centered on the brain -- and, there, we have no precise knowledge as to whether steady-state is achieved, not to mention our total ignorance about the actual cellular titers at that site. This Reviewer wishes to remind any Reader that Bromocriptine treatment (which results in lesser tissue accumulation than Cabergoline) nevertheless causes some severe side-effects (e.g., dyskinesia). The argument that Parkinsonians are given larger doses is negated by the possibility that small doses of Cabergoline to hyperprolactinemic patients may result in equivalent cerebral concentrations of high dose Bromocriptine.

Excretion (of drug and metabolites) occurs mainly in the feces and, to a lesser extent, through the urine. And yet, the pharmacokinetics of the drug does not appear to be affected either during renal dysfunction, or in patients with slight to moderate hepatic dysfunction. This again strongly indicates that most of the administered drug is concentrated in various cellular compartments, from which it is send back to the serum (yet, very slowly); that whatever drug exists in the circulation at any given time is (probably rapidly) metabolized into inactive derivatives; and that, thus, the very long plasma half life of the drug is an "illusion," i.e., the drug metabolizes rapidly in the serum and yet fresh amounts of unmetabolized drug are constantly released in the serum, coming from cellular sites. Again, it is important to emphasize that "the action" is in the brain as well as other cellular sites -- and, in all these sites, the drug possesses the potential to cause side-effects, particularly after prolonged dosing, which results in constantly higher titers at the cellular sites.

To summarize, it seems that following an oral administration, the drug is disposed in the body as follows: (1) Very rapidly, it is sequestered in a non-vascular compartment, in sizeable amounts; and, (2) what remains in the vascular compartment is rapidly metabolized into seemingly inactive components, while unchanged and metabolized moieties are excreted in the feces and the

urine, albeit quite slowly. The drug effect (beneficial or toxic) may, under the circumstances, be reasonably ascribed to the sequestered portions.Care must be exercized to space oral administration in function of time, or to devise an "on-off-on again" type of regimen, so as not to overload the sequestering compartments where, conceivably, too much drug may result in untoward side-effects -- this, without reducing the clinical efficacy of the drug, which can be easily assessed by strategically timed prolactinemic measurements.

5.1.3 Human clinical experience

It is clear that all the previous experience with other dopamine receptor agonists are quite useful to help apprise the benefit versus risk analysis of this particular drug, currently submitted.

5.2 Indirect information

5.2.1 Information from foreign sources

None available, at least to this Reviewer.

5.2.2 Related INDs and NDA

The following INDs have been residing in the Neuropharmacological Division of the CDER: (1) Pharmacia's IND and, (2) An individual Investigators IND Both of those have, of course, concerned themselves with the anti-Parkinsonian indication of the drug. Pharmacia's IND is housed in our Division and has concerned itself with the study of the hyperprolactinemic indications,

5.3 Other information

5.3.1 Regulatory background

As stated above, the Company has not submitted, as an indication, that of inhibition of post-partum lactation, though that indication has been approved in a number of other countries. The Company, wisely, took account of our determination (expressed in the past) that such an indication doesn't presently allow for a favorable risk vs.

benefit ratio, and has chosen not to request the approval of such an indication in the United States.

5.3.2 Directions for use

In open, informal and friendly discussions with the Company, this Reviewer has suggested that the directions for use be changed. In effect, the main suggestion was that since the drug seems to accumulate in the hypothalamus (during long-term therapy), treatment can and should be stopped for discrete periods of time, to permit the reduction of high drug titers at target sites. The data furnished by the Company strongly suggest that such periodic interruptions of treatment (followed by resumptions) are quite feasible, particularly since efficacy can be accurately gauged by performing hyperprolactinemic measurements. The Company's response was extremely favorable. They admitted that they had not thought about this possibility. They were most interested to investigate it and they promised to come out with an answer as soon as possible.

6 CLINICAL DATA SOURCES

6.1 IND and NDA Studies

6.1.1 Type of studies

The following clinical studies were performed in hyperprolactinemic patients and were included in the present submission: double-blind, placebo-controlled pivotal study HPRL-007, performed in 14 European centers; double-blind active control pivotal study 21336/ONC/26, performed in 63 European and 4 Argentinian sites; double blind placebo-controlled study APL-016, performed in Milan, Italy; open label study APL-HPRL-004, performed in Milan, Italy; open study HPRL-009 performed in 2 Italian sites; open study APL-PHKI-002, performed in Milan, Italy; open label study EM-0048, performed in Milan, Italy; open label study APL-015, performed in 12 Italian sites; open study HPRL-003, in 14 Italian sites; open study ONC/001, in 2 Japanese sites; open study ONC/002, in 5 Japanese sites; open study ONC/004, in 58 Japanese sites; open study ONC/029 in an unspecified number of European and Argentinian centers; compassionate

study performed in various European, Argentinian and New-Zealand sites; open study 93-APL-038, in 30 European sites; open study 097005-999 in 3 United States locations; open study 719i in 10 Italian sites; and open studies 097011-999 and 097014-999 in unspecified locations. Additional minor studies, too long too enumerate, were performed in healthy subjects, though important pharmacokinetic studies will be studied elsewhere in this Review. Also, we are not mentionning other clinical studies concerning puerperal lactation inhibition and Parkinson's disease. However, the importance of such studies in the safety evaluation of this drug will be included in other, more appropriate and pertinent, sections of this Review.

6.1.2 Patient populations and human exposure to date

The hyperprolactinemic patients in the pivotal endocrine clinical trials were almost all females of childbearing age. Their hyperprolactinemia was either due to microprolactinomas (55% of cases), macroprolactinomas (7%), empty sella syndromes (3%), or idiopathic (35%). All presented at least one symptom, e.g., amenorrhea.

Table 1 to 5 list the present state of human exposure to Cabergoline; namely, and for each study, the number of patients on Cabergoline, their gender, the average dose and the duration of exposure are provided for all studies exploring the endocrinological indications.

Table 6 provides the exposure of Parkinsonians to Cabergoline, in term of their total number, average dose and estimated time on treatment.

As far as the pivotal studies are concerned, the total population amounted to about 400 patients (most of them female), treated with, on average, about 1.2 mg/week Cabergoline, for 0.5 to 1.0 years; for a total estimated exposure of some 300 patient/years (not a lot, if you ask me). On the other hand, in the studies involving large numbers of Parkinsonians, some 2,500 patients (of whom 822 males) were affected, given doses ranging from mg/day, for a total exposure of some 1750 patient/years on a much higher dose regimen than for endocrine patients.

6.2 Additional sources

6.2.1 Literature

6.2.2 Foreign post-marketing experience

7 PIVOTAL CLINICAL STUDIES

7.1 First pivotal study: Trial # HPRL007

7.1.1 Description of study

7.1.1.1 Title, objective and rationale

"Double-blind, placebo-controllea, four week study, with a one year, open-label extension, in hyperprolactinemic women." The objective of the study is to investigate the possibility of a dose-response relationship for a total weekly dose of cabergoline of 0.25, 1.0, 1.5 or 2 mg., for a total of 4 weeks (with the first week at halved doses as is the case with Bromocriptine, in order to prevent serious hypotensive episodes). The rationale is straighforward enough: The new molecule is a domamine receptor agonist, other molecules of that pharmacological class have been shown to be active in the contemplated indications.

7.1.1.2 Protocolar design

Double-blind, randomized, parallel, placebo-controlled study, comprising five arms: 1 placebo, and 4 at different doses of Cabergoline, for a total of four (4) weeks. The blinded portion was followed-up by a 12-month open label extension period, during which patients were treated with 0.125-4 mg per week. The treated patients were hyperprolactinemic women with either microprolactinoma or idiopathic conditions. They were all SYMPTOMATIC.

7.1.1.3 Demographics

Some 188 (one hundred and eight eight) women were recruited into the study. Their mean age was 32.0 yrs, with a range of 16 to 46 yrs.

7.1.1.4 Safety considerations

All side-effects, routine laboratory tests, blood pressure and eart rate variable were noted and recorded.

7.1.1.5 Efficacy end-points

Measurement os serum prolactin levels, and their comparison prior to (i.e., at baseline) and at the end of the treatment period, constituted the essential of the efficacy argument. Complete effectiveness was defined as the reduction of serum prolactin levels to less than 20 ng/mL, or to less than 700 nU/mL; while partial success was defined as a reduction to less than 50% of the baseline value, though this may be greater than 20 ng/mL, or 700 nU/mL. Contrariwise, and obviously, complete failure was defined as not meeting either of the above criteria.

7.1.1.6 Statistical approaches

Data were analyzed statistically for effectiveness at any given dose, as well as dose-response relationships, using the Cochrane-Armitage test for linear trend in proportions, and Chi-Square analysis where appropriate. We would, of course, be apprised of the analysis and comments of our Statistician before forming a definitive opinion the appropriateness of these methodlogies, as well as the validity of the results reported by the Company.

7.1.2 Results and conclusions

7.1.2.1 Patient comparability

The prolactinemia values, at baseline, were not comparable, i.e., 65 ng/mL, 92, 93, 129, 69 for, respectively, placebo, 0.25 mg Cabergoline, 1.0 mg, 1.5 mg and 2.0 mg.The placebo and highest dose groups have thus the lowest baseline prolactinemic values. This would affect the interpretation of the data, particularly if conclusions are derived with respect to the dose-response activity curve of the drug.In fact, the Company agrees that the "baseline prolactin levels [shows] difference[s that are] statistically significant."

However, the overall baseline values with respect to demography, history, and clinical diagnosis variables are summarized in Table 7, from which it is clear that for any number of variables (age, race, menstrual history, frequency of microprolactinomas, and the occurrence of previous hyperprolactinemic therapy) there were no statistical differences between the groups.

7.1.2.2 Patient disposition

Only 2 out of 188 female patients withdrew prior to the completion of the blinded portion of the study; During the one-year follow-up, only five out of 162 patients withdrew, on the basis of individually intolerable side effects.

7.1.2.3 Efficacy data

Serum prolactin levels were normalized, as previously defined, in 83% of the patients receiving therapy. Menses were restored in 89% of the treated women, who otherwise entered the study as amenorrheic patients. More specifically, prolactinemia regained normal levels in 30% of patients receiving 0.25 mg. per week, 74% at 1 mg., 74% at 1.5 mg., 95% at 2 mg. In the open follow-up period, using anywhere from 0.125 to 4 mg per week (presumably through titration of dose in individual patients, normalization of prolactinemia was observed in 85% of patients, while resumption of menses or pregnancy occurred in 91% of the appropriate group treated under these conditions. Overall, the mean prescribed dose was 0.7 mg.

The following facts are important enough to warrant an emphatic mention: (1) It took 4, 3, 3, and 2 weeks to achieve optimal efficacy in, respectively, the 0.25, 0.50, 1.0 and 2.0 mg doses. Clearly, this fact may well have its place in the labeling, to guide the physician in the follow-up of treated patients; and, (2) Two to three weeks after cessation of the 4 week therapy period, euprolactinemia was seen in 12, 60, 55, and 81% of patients having received, respectively, 0.25, 0.50, 1.50 and 2.0 mg of Cabergoline (see Fig. 2 to appreciate the general tendency of prolactinemic values after cessation of treatment). This, too, is an important fact to keep in mind when deciding on the practicalities of patient treatment with Cabergoline.

Another fact to bear in mind was observed during the 12 mos., open label, follow-up treatment period. Here the beginning prolactinemic level was 46.3 ng/mL and 15.8 after 1 mo. of treatment. This value remained essentially constant throughout the 12th month of treatment. This may be interpreted in two ways: (1) the regimen was responsible for the maintenance of low values of prolactinemia; or, (2) that treatment exceeded the least dosing for effective lowering of prolactinemia, i.e., dosing had reached the plateau region of the dose-response curve. Since the mean dose in this group was 1.2 mg/week of Cabergoline, and some patients receiving more or less than that mean or average value, it follows that the second interpretation above is the more probable. Such an interpretation is also consistent with the fact that the kinetics of drug disposition in the body would allow increasing concentrations of drug in non-vascular compartments, as treatment is regularly pursued over a long period of time.

An additional observation is also of value: In the open label 12-mo follow-up study, the overwhelming majority of all patients, i.e., some 150 of them were initially given 1.0 mg x2/wk (this, based on an appreciation of their needs during the previous placebo-controlled, 4 week treatment period); but, at the end of the open period (during which titration occurred on the basis of individual responses to therapy), only 77 were still on the 1.0 mg x2/wk regimen, while 31 were normalized on 0.5 mg x1/wk; 20, on 0.25 X1/wk; and 7 on 0.5 mg x2/wk (see vol. 1.65, p. 08-0000241). This clearly indicates that the recommended initial dose may be as low as 0.5 mg/week and, in any event, should not exceed 1 mg/wk. After 3-4 weeks of therapy, this dose could be maintained or increased by 0.5 mg increments, depending on the additional serial measurements of prolactinemia.

A final factual observation: With an average dosing of 1.2 mg/week, menstrual normalization is achieved within a month in about 75% of patients and is maintained around that level during a year of continued therapy. Despite discontinuation of therapy for 2-4 weeks, it seems that euprolactinemia is maintained in most treated patients. This, also, is consistent with the hypothesis that regular, long-term therapy with Cabergoline result in continued accumulation and increasing concentrations of drug in the target compartment(s).

7.1.2.4 Safety data

During the 4-weeks of the double blind portion of the study, adverse effects were no different (in qualitative as well as quantitative terms) from those encountered during treatmenbt with Bromocriptine. Namely, the following side-effects were observed more commonly in the treated population: nausea, headache, and dizziness. The following, rather remarkable and yet puzzling, observation was made by the Company: Adverse effects were reported in 45% of placebo-treated patients, as opposed to only 29-38% (depending on dose) on subjects administered with varying weekly amounts of Cabergoline. As far as the 1 year follow-up period, the same general observations were also found to be true.

7.1.2.5 Sponsor's conclusions

The Company states: " Cabergoline significantly lowered serum prolactin levels (a biochemical endpoint) and restored normal gonadal function (clinical endpoint) in hyperprolactinemic women. Most [observed] adverse effects were graded [from] mild to moderate." In addition, the Company concludes that " 0.5 mg twice weekly appears the effective posology to start with (after one week of halved doses to minimize side effects)."

7.1.2.6 Reviewer's conclusions

This Reviewer is in agreement with the Company's conclusions.

7.2 Second pivotal study: Trial # ONC/026 (95-30703)

7.2.1 Description of study

7.2.1.1 Title, objective and rationale

"Activity and safety of Cabergoline in the therapy of hyperprolactinemic amenorrhea: Phase III, comparative (vs. Bromocriptine), randomized, parallel group, multicenter, multinational study." The objective being: To compare the efficacy of the two compounds in restoring ovulatory cycles together with normalization or lowering of PRL [prolactin]

levels and their safety and tolerability during a 24-week therapy in hyperprolactinemic women. The rational, once more, is straight forward: Bromocriptine is, presently, the only other dopamine receptor agonist on the market; and, comparing it to Cabergoline makes perfect sense, particularly if the comparisons involves not only a biochemical end-point (i.e., the effect of either drug on elevated serum prolactin levels), but also on a clinically significant end-point -- in this particular case, mostly, the restoration of normal ovulatory cycles to women previously amenorrheic because of hyperprolactinemia.

7.2.1.2 Protocolar design

The study was a randomized, parallel (vs. Bromocriptine), 8 weeks double-blind study; followed by a 16 week open end extension -- presumably, for the purpose of gathering additional safety-related information. Cabergoline was given 0.5 to 1.0 mg twice weekly against Bromocriptine at 2.5 to 5 mg bid.Some patients received twice these doses of either drug. Treatment during this blinded portion extended to eight (8) weeks, and was then followed up by an open portion lasting sixteen (16) weeks.Overall, the mean prescribed dose was 1.5 mg/week.

7.2.1.3 Demographics

Some 459 (four hundred and fifty nine) female patients, recruited because of their hyperprolactinemic (and, therefore, amenorrheic) condition. Their mean age being 31.0 years, with a range from 16 to 46 years.

7.2.1.4 Safety considerations

As already defined above (see previous study).

7.2.1.5 Efficacy end-points

As already defined above (see previous study).

7.2.1.6 Statistical approaches

As already defined above (see previous study).

7.2.2 Results and conclusions

7.2.2.1 Patient comparability

In this study, in contradistinction to the previous one, baseline prolactinemic values were comparable in the two treated groups, i.e., 106.2 and 108.4 ng/mL.The age distribution was also very comparable, i.e, centred around an average of 31 years.This assures a better comparison of the respective theraputic efficacy of Cabergoline and Bromocriptine

It should also be stated that comparability was also seen, before and during the trial, for, respectively, mean blood pressure and heart rate, and therapeutic compliance.

7.2.2.2 Patient disposition

The data show that during the blinded phase of the study, some 54% of the patients administered Cabergoline and some 57% of patients on Bromocriptine appeared to be compliant. During the open-label phase, the corresponding frequencies were 82% and 52% for, respectively, Cabergoline and Bromocriptine. Clearly, it is difficult to explain the sudden shift in favor of the present drug. One can, however, speculate that the more favorable results obtained for Cabergoline during the blinded phase were either publicized by the Company, or somehow felt by patients, or a combination of both of these factors.

7.2.2.3 Efficacy data

According to the Company, treatment efficacy was measured, using both a biochemical end-point, as well as a clinically meaningful one. The former consisted of measurements of prolactinemia before during, and at the end of the treatment period; while the latter consisted of quantitatively determing the frequency of restoration of normal ovulatory cycles in treated patients.

Complete biochemical success was defined, as in the previous study, as being the normalization of serum prolactin levels, i.e., the mean prolactinemia values should be reduced to within the normal range in the institution where the measurements were performed.

Complete so-called global success from a clinical viewpoint was defined as the restoration of menses, or resumption of ovulatory cycles as indicated either by pregnancy, or by the attainment of appropriate and normal levels of circulating progesterone in the luteal phase -- said normalization to be accompanied by a simultaneous normalization (or, at least a greather than 50% reduction from baseline values of serum prolactin levels.

Overall, the mitigated terms "partial success" was defined in terms of the completeness in meeting all of the so-called "Complete success" criteria, as defined above. Finally, the term "failure" was used when such criteria were not met at all.

Complete or partial global success was accomplishedx in 94% of the patients treated with Cabergoline, versus 73% of those treated with Bromocriptine. Complete clinical success (as defined above) was achieved in 73% of the patients treated with Cabergoline, versus 55% of those to whom Bromocriptine was administered. In the 16-week open-label extension of the study, the efficacy of Cabergoline continued to ve seen; compliance was 82.3% for Cabergoline but only 55.6% for Bromocriptine.

Again, after a month of treatment with Cabergoline, maximal efficacy is achieved and is maintained during the course of continued long-term therapy. In contradistinction, maximal efficacy is achieved after 2 mos. of treatment with Bromocriptine. It should also be noted (in comparison with the previous trial) that 0.5 mg, twice weekly (in this trial) was just as effective than 2.0 mg weekly (in the previous trial), as far as biochemical and clinical efficacies are concerned.

7.2.2.4 Safety data

According to the Company, the gathering of safety data comprised the following: recoding all side effects reported or noted during the study, conducting a battery of routine and laboratory tests, ECG, and determination of blood pressure and heart rate values -- prior to the beginning of treatment (i.e., baseline values) and at intervals thereafter, whils administering either of the tested drugs in randomly assigned subjects.

As to safety data proper, the Company makes the statement: "The incidence of patients experiencing at least one adverse event was 69% in the Cabergoline-treated group and 79% of the Bromocriptine group. Adverse events were mainly of the ergoline derivative type, such as nausea, headache, dizziness and asthenia."

With respect to cardiovascular effects, the following is stated: "During therapy, a decrease in systolic and diastolic blood pressure was observed in [about] 50% of patients in both treatment arms whereas blood pressure values increased with respect to baseline in [about] 25% of cases." Median decrease was 10 mm Hg, for systolic and diastolic pressures, in lying as well as standing positions, at almost all evaluation times (with a maximal decrease recorded in the lying position of 30-49 mm Hg for systolic, and 25-35 for diastolic). These were slightly better than the changes seen with Bromocriptine; however, they do show that Cabergoline has also a decided effect on blood pressure -- sometimes upward but more frequently downward. In all probability, there is a very small yet finite possibility of tremendous blood pressure increases in young females with some of them possibly ending up in a cardiovascular accident. Such a possibility, however remote, should force us to give (in terms of dosing) no more than is absolutely necessary to obtain the desired therapeutic effect.

There were twenty four (24)cases of pregnancies during the course of therapy with Cabergoline, while the fetal exposure was estimated to be between 12 and 57 days (median: 24 days). One patient (79/13U) elected to have a therapeutic abortion and the following abnormalities were observed in the fetus: caudal part adhering to the placenta, stumped right leg enveloped in umbilical cord vessels, deformed left leg, numerous placental abnormalities, etc. In the investigator's opinion, the leg anomalies were due to amniotic bands. The abnormalities of the placenta may explain the developmental anomalies of the fetus and, in any event, it is impossible to either exonerate or incriminate the drug as a teratogen. Nevertheless, precautions ought to be taken to diagnose any eventual pregnancy during Cabergoline therapy very early, and stop taking medication immediately after a positive diagnosis is made; this, until epidemiological data of sufficient magnitude would inform us

of the teratogenic potential of the drug, or the absence of such a potential. It is useful to remind, here, that the data base with Bromocriptine, concerning a potential teratogenicity of the drug is much more abundant than with Cabergoline, and has (so far) exonerated Bromocriptine from such a potential.

7.2.2.5 Sponsor's conclusions

The Sponsor concludes: "This study provides evidence of the superiority of Cabergoline over Bromocriptine, in the treatment of hyperprolactinemic amenorrhea, both in terms of efficacy, tolerability and patient compliance.

7.2.2.6 Reviewer's conclusions

This Reviewer has no difficulty in admitting that Cabergoline seems to be at least as good as Bromocriptine in terms of its efficacy and safety, as well as in terms of its risk versus benefit profile. On the other hand, this Reviewer does not believe that superiority of Cabergoline has been proven convincingly and conclusively, particularly when dealing with the safety profile.

After all, and to be fair, Bromocriptine has been on the marketplace for a very long period of time. As a result, most (if not all) of its "warts" are painfully evident -- e.g., its rare paroxystic hypertensive episodes as well as its portentous though equally rare pulmonary toxicity. On the other hand, such level of exposure has, of course, not been achieved with Cabergoline. Therefore, it is conceivable and still possible that the safety profile of Cabergoline may prove to be found to be, in the future, to be better or worse Bromocriptine's.

Of course, a better case can be made in terms of its putative superiority from an efficacy viewpoint. However, in the absence of long-term knowledge of its true safety profile, it is not permissible, as yet, to speak of superiority of one drug over the other. On the other hand, one may legitimately speak of added convenience and, probably, improved compliance.

8 NON-PIVOTAL CLINICAL STUDIES

8.1 First non-pivotal study: Trial # APL016 (712i)

8.1.1 Description of study

8.1.1.1 Title, objective and rationale

This study is entitled: "Prolactin lowering effect of Cabergoline administered PO for eight weeks in hyperprolactinemic patients. A double-blind, randomized, 4 [four] arm pilot trial comparing several doses and schedules." Its objective may be summarized as follows: "To evaluate the hypoprolactinemic effect of various doses ansd regiments of Cabergoline administration to patients with hyperprolactinemia. The rationale of the study is impeccable, inasmuch as an en effort should be expanded in order to try to determine the least dose that is effective in accomplishing the desired therapeutic effect. One component of such an approach is the exploration of various regimens (or schedules, as put by the Company) in order to further minimize (if at all possible) the dose needed to be administered for the purpose, again, of accomplishing a desired therapeutic goal using the least amount of administered medicine.

8.1.1.2 Protocolar design

This was randomized and placebo-controlled trial, entailing 4 (four) study arms, one of which was placebo, of course. The various drug regimen modalities were as follows: (1) 0.4 mg 2x/week; (2) 0.2 mg, 4x/week; (3) 0.4 mg, 3x/week for 3 weeks, followed by 0.4 mg, 2x/week for 5 weeks. The first and last modalities were the ones actually accompanied by a parallel placebo administration. The mean prescribed dose, overall, was 0.7 mg.

8.1.1.3 Demographics

Some 24 women were enrolled in the study, with an average age of 29 years at entrance, and a range of 18 to 43 years. Six (6) patients were randomly allocated to each group -- three (3) to individual therapeutic groups and one (1) to placebo. Seventeen (17) completed eight (8) weeks of therapy.

8.1.1.4 Safety considerations

The safety profile, as previously described, was defined as follows: through the performance of a battery of laboratory tests, ECGs and recording of all observed or recalled adverse events.

8.1.1.5 Efficacy end-points

Efficacy, according to the Company, was evaluated following measurements of prolactinemic levels (biochemical endpoint), at baseline, at weekly intervals during the study, and two weeks after the discontinuation of drug administration. The absence or occurrence of menses were also noted.

8.1.1.6 Statistical approaches

Data were analyzed by ANOVA (all patients) after three weeks of treatment. The results were as follows: All three Cabergoline regimens were signficantly diufferent from placebo, with a p value of less than 0.05, but not significantly different from one another. In other words, the three drug treatment regimens were equivalent.

8.1.2 Results and conclusions

8.1.2.1 Patient comparability

Not at issue.

8.1.2.2 Patient disposition

In the open-label prolongation of the study five (5) patients out of 162 hyperprolactinemic females withdrew from the study because of one or more of the following: dizziness, nausea, vertigo, dyspnea, and facial edema.

8.1.2.3 Efficacy data

Of the seventeen (17) evaluable patients, all had a prolactinemia measurement performed at baseline, after eight weeks of therapy, and after two weeks following cessation of said therapy. Of these, 82% were judged as showing a good

response to therapy (in the treated groupe) while no improvement was visible in all of these who had been given placebo. The effective dose was anywhere between 0.8 mg to 1.2 mg, once a week. In nine (9) of these patients, prolactinemic values were still within the normal range, a full 2 weeks after cessation fo treatment.In clear, after some 2 mos. of treatment, prolactinemic levels remain within normal in many patients up to 2 weeks after cessation of therapy (see vol. 1.66, p. 08-0000243).

8.1.2.4 Safety data

The observed adverse events were mild-to-moderate ones, as far as intensity was concerned. They included dizziness, nausea, constipation, dyspepsia and somnolence, i.e., again rather run of the mill and known responses to dopamine receptor agonists.

8.1.2.5 Sponsor's conclusions

The Company concluded as follows: "Results of this placebo-controlled study in hyperprolactinemic women indicate the prolactin-lowering efficacy and long-duration of action of Cabergoline administered at low doses twice a week. The data also indicate that a given dose of Cabergoline is equally effective whether administered in two or four divided weekly doses."

8.1.2.6 Reviewer's conclusions

This Reviewer accepts the Company's conclusions.

8.2 Second non-pivotal study: Trial #APL-HPRL-004 (704i)

8.2.1 Description of study

8.2.1.1 Title, objective and rationale

The Company entitled this study as follows: "Efficacy of Cabergoline (0.3 mg) and Bromocriptine (2.5 mg), administered as a single dose in lowering serum prolactin levels in hyperprolactinemic patients." The objectives of the study were defined to be: To evaluate the prolactin lowering activity of a single oral dose of cabergoline (0.3

mg) or of Bromocriptine (2.5 mg) in terms of the maximal decrease seen in serum prolactin levels, and the duration of the prolactin-loweriung effect. The study would permit both an appreciation of the prolactin lowering effect of a single dose of Cabergoline, as well as permit (perhaps) some comparison between its effects and those associated with a single dose administration of a roughly therapeutically equivalent dose of Bromocriptine.

8.2.1.2 Protocolar design

The study was an open, cross-over one, comparing a single Cabergoline dose of 0.3 mg, p.o., to a single Bromocriptine dose of 2.5 mg, p.o. A single week washout period was used prior to any cross-over.The mean prescribed dose was 0.3 mg.

8.2.1.3 Demographics

Three (3) males and fourteen (14) females were included in the trial. The mean age of the subjects was 40.4 years, with a range of 19 to 70 years.

8.2.1.4 Safety considerations

No special precautions were taken, given the short-term nature of the study. Instead, the general observations described for earlier studies were also performed here, to make sure to be able to record any notable and important side-effect.

8.2.1.5 Efficacy end-points

Only the biochemical end-point, i.e., prolactinemic levels, were utilized. Under the circumstances, i.e., since the study had a short-term duration, this seems quite appropriate and sensical.

8.2.1.6 Statistical approaches

Not applicable, since this was an open study.

8.2.2 Results and conclusions

8.2.2.1 Patient comparability

On the main, conditions of comparability seem to have been met in this relatively small study, particularly concerning age and the basal levels of prolactinemia.

8.2.2.2 Patient disposition

The Company states that "all 17 patients who were enrolled in the study completed the study."

8.2.2.3 Efficacy data

According the Company, "the study confirmed the potent and long-lasting prolactin [lowering] activity of Cabergolinem [during] hyperprolactinemic disorders." More specifically, serum prolactin levels dropped on average some 65% following single-dose Bromocriptine treatment (the maximum decrease occurring at six-hours post-admnistration); while the drop due to Cabergoline was 52% with a maximum decrease seen after 48 hours following the single administration. A noteworthy comment: In this single-dose comparative study, Bromocriptine (2.5 mg) was successful in normalizing prolactinemia in 65% of cases -- a better result than that shown by a single dose Cabergoline at 0.3 mg. Clearly, the 0.3 mg would seem a lower than necessary average to-be-recommended dose. On the other hand, it should be reminded at this point that 0.5 mg was quite effective in about 3/4 of treated subjects. Under the circumnstances, it would appear that 0.5 mg, once per week, would be the best recommended average dose -- one that should be the initial dose administered to most if not all patients.

It should be noted that, after cessation of therapy for 120 hrs (i.e., 5 days), prolactinemic levels in patients treated with Cabergoline were still below baseline, in contradistiction to what occurred in patients treated with Bromocriptine. This clearly emphasizes that the important and pertinent kinetic parameters are not those concerning the vascular compartment, but those involving the non-vascular (i.e., target sites for efficacy as well as for side-effects) compartments. There, we can only infer the degree and time course of accumulation of repeated weekly doses, as well as the clearance of drug from such sites, after cessation of continuous long-term therapy. Again, such inferences have important practical consequences and they

will allow us to determine how patients ought to be treated in order to maximize the benefits of therapy and minimize its risks.

8.2.2.4 Safety data

One severe adverse event was reported (a transient amaurosis) at 0.3 mg Cabergoline. The other common side-effects were, as usual, dizziness, headache, nausea and somnolence.

8.2.2.5 Sponsor's conclusions

The Sponsor writes: "In this controlled, single-dose study in 17 hyperprolactinemic patients, Cabergoline was well tolerated at doses that were effective in lowering serum prolactin levels."

8.2.2.6 Reviewer's conclusions

This Reviewer is not sure that it can be stated that Cabergoline was well tolerated in this study, given that a single case (out of 17 patients) of amaurosis -- a not too inconsequential event -- was noted. In any case, it would seem prudent to include this case of amaurosis in the labeling.

The results of this study, together with data obtained from other pertinent studies, strongly suggest a modality of treatment of the average patient which would decrease risks without loss of benefits (see discution, above, in previous subsections).

8.3 Third non-pivotal study: Trial # HPRL009 (705i)

8.3.1 Description of study

8.3.1.1 Title, objective and rationale

The Company defines its objective as: "Compare the prolactin-lowering activity of two different doses of Cabergoline." The objective, I presume, is to help define the least dose that is effective in the average patient; and its rationale, that minimizing the dose results in less

toxicity for equivalent efficacy. It is also to help define equivalent dosing of Bromocriptine and Cabergoline.

8.3.1.2 Protocolar design

The study is a randomized, controlled but open label, during which the effect of a single dose of Cabergoline are to be determined, either 0.3 mg, or 0.6 mg, p.o. In addition, certain subjects were given 2.5 mg of Bromocriptine. The mean prescribed dose was 0.45 mg.

8.3.1.3 Demographics

Three (3) males and forty-eight (48) females were studied, with a mean age of 32.2 years, and a range of from 17 to 46 years.

8.3.1.4 Safety considerations

As in previous studies.

8.3.1.5 Efficacy end-points

The biochemical endpoint was defined, in this particular case, as the percent decrease of serum prolactin levels, following a single oral administration of either 0.3 mg or 0.6 mg of Cabergoline.

8.2.1.6 Statistical approaches

The analysis was performed as a repeated measure analysis of variance of a two-period cross-over. The treatment effectiveness was measured as percent decrease of prolactinemic levels from baseline values at each time and, before performing the analysis, the data were standardized to have zero mean and unit standard deviation. See our Statistician's presentation and discussion for further, detailed, analysis of methodology and conclusions.

8.3.2 Results and conclusions

8.3.2.1 Patient comparability

The treatment groups were comparable with respect to age, weight, height; but, due to etiological heterogeneity,

a great individual variability in baseline prolactinemic levels was observed -- inevitable, I should think, in such a small group. Still, the median prolactinemic values were 36 ng/ml and 50.3 ng/ ml for, respectively Cabergoline- and Bromocriptine-treated patients.

8.3.2.2 Patient disposition

All fifty-one (51) patients that entered the study completed it.

8.3.2.3 Efficacy data

The results show a dose-effect relationship for the two tested doses of Cabergoline, with respect to both the maximum decrease of prolactinemia and the duration of action. In addition, the study found out that the lowering effect of 0.6 mg of Cabergoline resulted in a maximum lowering of hyperprolactinemia equivalent to that seen with a single 2.5 mg dose of Bromocriptine, with the caveat that the former's effect lasted much longer that the latter's.

Specifically, Cabergoline lowered prolactinemia a maximum of 63% at the 0.3 and 0.6 mg dosings, whilst 2.5 mg of Bromocriptine lowered serum prolactin by 72%. Again it can be seen that 0.3 mg of Cabergoline does not seem to be an adequate dose in many cases, whilst the 0.5 mg dose would seem to be the ideal initial dose, to be included as the recommended intial dose for most if not all patients.

Following Cabergoline treatment, effects lingered on for 5 to 7 days after cessation of therapy, again highlighting the very peculiar kinetics of the drug: It rapidly disappears from the blood stream, whilst being concentrated in the target cells, i.e., either pharmacological or toxic-effects sites.

8.3.2.4 Safety data

The safety precautions were essentially similar to those taken in previous studies (see details above). Fifteen (15) adverse events were recorded in eight (8) patients during the course of the study, six of which after Bromocriptine administration, one (1) following 0.3 mg Cabergoline, without any adverse event being seen in the 0.6

mg. dosing -- a not too surprising finding in such a small cohort. The adverse events were the ones traditionally observed following administration of dopamine receptor agonists, both in qualitative or broadly quantitative terms.

8.3.2.5 Sponsor's conclusions

The Company concludes: " The study confirms the potent and log-lasting prolactin-lowering activity as well as the good tolerability of Cabergoline, supporting the potential of this compound in the management of hyperprolactinemic disorders."

8.3.2.6 Reviewer's conclusions

This Reviewer agrees with the general gist of the Company's conclusions, as stated above. However, it may be fair to state that given the narrow scope of this trial, one didn't obtain a conclusive and convincing comparison between Cabergoline and Bromocriptine equivalent dosing. Still, the results obtained in this trial possess practical value, particularly since a strict pharmacodynamic comparison between the two drugs is extremely difficult, given the peculiar kinetics of Cabergoline. All things considered, we do know how much Cabergoline should be prescribed if a given patient is transferred from Bromocriptine to Cabergoline -- an event likely to occur often, if only because of the advantages of a once weekly administration of the new drug.

8.3 Other non-pivotal studies

Ten (10)open-label, uncontrolled studies were conducted to further obtain information for the indications proposed in the present submission.

Single doses of Cabergoline (0.5-1.0 mg), administered to hyperprolactinemic patients significantly reduced serum prolactin levels by up to 92% with a duration of effect of about a week.

Single doses of Cabergoline (0.5, 0.75, or 1.0 mg), administered to lactating females significantly reduced serum prolactin levels and inhibited/suppressed lactation, with the hypoprolactinemeic effect lasting for about three

week. This clearly supports the notion that most of the administered drug is being concentrated, among other places, in target cells from whence it dissociates very slowly.

Multiple dosing in hyperprolactinemic populations (0.3 to 3.0 mg, once a week), administered over varying periods of time (eight, nine and 48 weeks), resulted in the normalization of the prolactinemia in 70-100% of the treated patients, depending on dose and duration of treatment. It is noteworthy to observe that following cessation of treatment with Cabergoline, prolactin levels were normalized for up to three (3) weeks following such cessation -- this, again, has clear pharmacokinetic and therapeutic implications, since the clear inference is one of long lasting effect after multiple dosing, which itself implies continuous accumulation of drug in cryptic compartments (many of them very definitely in the central nervous system) with a slow disposition of that active material through a slow shifting, over time, towards the vascular compartment, where metabolism and excretion can occur. It also begs the question: Wouldn't it be wiser to periodically stop Cabergoline treatment (say every six months) for, say, two weeks to a full month? If efficacy would still be present during that period of cessation of therapy (as clearly implied here) then that would be the prudent thing to recommend in the labeling. Tumor shrinkage was observed in 29 out of 57 (i.e., in 51% of cases) of patients with microprolactinoma. Notice is made that this is the first time that tumor shrinkage is measured and it only refers to microprolactinomas. Under the circumstances, a reasonable case can be made that the safety and effectiveness of tumor shrinkage of macroprolactinomas (and particularly in cases when impingement of the optic nerve, or other intracranial structures, creates a criticial or an emergency situation) has not been addressed so far in the present submission.

Finally, a total of ninety-eight (98) patients with macroprolactinoma (adenomas woth a diameter greater than 10 mm), sixteen (16) of whom were males, were treated with 0.125-5.0 mg of Cabergoline per week.In the general population, prolactinemia was significantly lowered -- suggesting a tumoral regression, though there is no mention of radiographic evidence to that effect. In a male population of eight (8), where testosterone levels were measured, seven (7) of those showed a clear increase in

circulating testosterone. Two (2) of three (3) impotent males reported an increase in sexual potency -- whatever that means, given the highly subjective and suggestible nature of male impotence. The Company asserts that "data are being accumulated to assess the effect of [Cabrergoline] on the size of macroprolactinomas." Given the size of the study and the lack of scanning data, it would be wise to exclude, at least at present, the treatment of macroprolactinomas from the list of approved indications.

Efficacy data from six addional studies in hyperprolactinemic patients treated with Cabergoline are in the process of being analyzed by the Company.

Additional studies not related to the treatment of hyperprolactinemic disorders comprises the following: (1) Cabergoline treatment of healthy subjects (0.05 to 2.0 mg per week) resulted in significant reductions in prolactinemia, sometimes to below detection levels; 2) Eleven (11) Cabergoline treatment studies (with 0.4 to 1.0 mg., single dose) in a total of 1152 subjects with puerpueral lactation, with the resulting expected inhibition of lactation; (3) A study during which wight (8) acromegalic patients were treated with a single dose of Cabergoline (0.3 to 0.6 mg.), resulting in reduced circulating GH as well as prolactin concentrations; (65) Cabergoline treatment in 98 patients with macroprolactineoma, the results of which have not been analyzed yet. Clearly, then, the treatment of macroprolactinomas should be contraindicated at the present; and, (6) Sundry other minor studies essentially insignificant little studies with precious few useful information in them.

9 OVERVIEW OF EFFICACY

Cabergoline has been shown to be very effective in reducing serum prolactin levels, with the following biochemical efficacy : Complete effectiveness is defined as the reduction of serum prolactin levels to less than 20 ng/mL, or to less than 700 nU/mL; while partial success was defined as a reduction to less than 50% of the baseline value, when this results in prolactinemic values greater than 20 ng/mL, or 700 nU/mL. Such a normalization was achieved in a large majority of treated patients with weekly

doses of 1 mg. Most other would be normalized with 2 mg. per week. Only 0.5 mg is recommended for the first week of treatment in order to minimize the dose effects encountered upon initiation of therapy with a dopamine receptor agonist.

In a majority of women experiencing normalization (or near normalization) of prolactinemia, such reduction as was obtained was accompanied by the resumption of menstrual cycles; and, in some of these cases, occurrence of pregnancy.

Shrinkage of microprolactinomas was observed in 29 out of 57 cases, i.e., in 51% of the studied cases. The Company has not m,ade any claims to include the treatment of macroprolactinomes as an indication.

In hyperprolactinemic men, it is reported Cabergoline treatment increased libido and sexual potency -- results notoriously difficult to ascertain in objective terms, and, in any event, two few men were studied to really make a case that safety and effectiveness has been established for this gender-linked indication.

10 OVERVIEW OF SAFETY

10.1 Significant events or leads

10.1.1 Deaths during drug use

The only death during the trials for the indications on hand (i.e., hyperprolactinemia) occurred when a 39 year-old woman was killed in a traffic accident. In the treatment of Parsinson's disease, one death was also directly attributed to the drug (and was due to pulmonary fibrosis well known to occur, albeit exceptionally, during dopamine receptor agonist therapy), while the overall mortality was not significantly different from that expected from this kind of elderly and more brittle population, i.e., 2.3%. (See Tables 8 and 9 for additional details).

10.1.2 Severe to serious drug effects

In studies to appreciate the safety and effectiveness of the hyperprolactinemic indications, the following rare events of a serious nature were observed during the various trials submitted for review: one case of somnolence severe enough to lead to the patient's premature discontinuation from the study, a single case of transient amaurosis in a hyperprolactinemic patient, a case of syncope judged to be severe in nature, and a few cases of dizziness severe enough to warrant a cautionary discontinuation of drug treatment. Tables 10 and 11 list the adverse events observed during the two pivotal, well-controlled clinical trials).

In the some 200 patients treated for Parkinson's disease, and who received 15 to 20 times higher weekly doses of Cabergoline than hyperprolactinemic patients, while also representing an older and more brittle population, the following low-frequency events appeared to be related to Cabergoline therapy: severe cases of orthostatic hypotension, dyskinesias, (three cases of) pulmonary fibrosis, and hallucinations.

Long-term treatment with Bromocriptine has been associated with the occurrence of the following low-frequency events: dyskinesia, hallucinations, confusion, peripheral edema, heart failure, pleural effusion, pulmonary fibrosis, and gastric or duodenal ulcers. Given the relatively limited human exposure to Cabergoline, we cannot eliminate the possibility that such events might also occur with Cabergoline, particularly when thinking of the implications of its pharmacokinetic peculiarities.

10.1.3 Potential toxicities

Bromocriptine, and other dopamine receptors agonists, have been shown to induce in most patients an hypotensive effect, particularly at the initiation of therapy, often in the form of orthostatic hypotension. Much more rarely, a hypertensive effect has been observed -- a phenomenon which is thought to be the causative mechanism of cerebro-vascular accidents observed in some young female patients during treatment with bromocriptine for the purpose of inhibiting physiological lactation at term.

Another worrisome feature of Bromocriptine therapy is the infrequent occurrence of respiratory tract pathologies,

i.e., pulmonary infiltrates, pleural effusion and thickening of the pleura. These rare events are seen during long-term therapy, i.e., 3-6 months or more.

In addition, the following most frequent side-effects have been observed during treatment with Bromocriptine: nausea, headache, dizziness, fatigue, lightheadedness, vomiting, abdominal cramps, nasal congestion, constipation, diarrhea and drowsiness.

10.2 Other drug-related safety issues

10.2.1 ADR incidence

In the eight multiple-dose, open label studies within the proposed indication, 52 out of 2244 patients (2.3%) reported adverse events rated as severe in intensity, including: dyspepsia, palpitation, hypotension, renal pain, gastritis, dyspnea, erythematous dermatitis and itchy scalp. A case of viral encephalitis occurred in one patient. Fifteen (0.7%) of studied patient population were prematurely discontinued due to adverse events of enough severity or concern to warrant such termination. Most of these side effects are known to be specific to dopamine receptor agonist therapy (e.g., hypotension), suggesting that the overall incidence of adverse events due to Cabergoline treatment is around 1 to 2% of the treated populations.

10.2.2 Clinical findings

All pertinent issues that could have been put under this subheading have already been fully discussed elsewhere.

10.2.2.1 Routine laboratory results

No clear abnormalities observed, except that some patients show a reduction in hemoglobin values.

10.2.2.2 Vital signs

Some patients experienced hypotension -- a feature widely expected from dopamine receptor agonists.

10.2.2.3 Specialized tests

No findings with any clinical significance observed. Beside the lactrotophs, no other effects were seen on the other hormonal functions of the ovary.

10.2.3 Additional safety issues

None that have not been already fully addressed in other sections of this review.

11 LABELING REVIEW

11.1 Drug description

This section is brief, clear and to the point.

11.2 Clinical pharmacology

The "Mechanism of action" section clearly summarizes the present knowledge pertaining to dopamine receptor agonists, in a physiopathologically meaningful and useful manner.

The "Clinical Studies" section summarizes the trials which have been conducted to ascertain the safety and efficacy of the drug. The data is presented usefully and factually, without hard-to-justify or self-serving interpretations. Nevertheless, the sentence "Distinex was superior to bromocriptine...." ought to be replaced by "Distinex is more convenient to use than other presently marketed dopamine receptor agonists." The term "superior," an OVERALL superiority, i.e., one that concerns a global assessment of both safety and efficacy. The relatively smaller human experience with Cabergoline precludes us to make an even implied claim of such a putative superiority. It is possible that, though Cabergoline is (weight for weight) more potent than Bromocriptine, its toxicity may rise faster than its efficacy. The Company may simply state the comparative merits of Cabergoline: e.g., its reduced dosage needed for an equivalent pharmacodynamic effect,and also its longer duration of action.

An example will illustrate why it is not permissible (and even dangerous) to imply a SUPERIORITY of one drug over

another on the basis of the fact that one is more active on either a ponderal or a molar basis. Phenformin, a oral hypoglycemic, was much more active on a ponderal basis than Metformin, a pharmacological congener. For that reason, Phenformin was developed and introduced in the marketplace first. But when sufficient experience was developed, it appeared that Phenformin was INFERIOR to Metformin when a GLOBAL assessment could be performed on the basis of their respective benefit-versus-risk analysis.

Indeed, Cabergoline's greater efficacy and longer duration of action may be later found to be a dangerous combination. Because, as in the case of Phenformin, we may find in the future that its "toxic potency" may be greater than its "pharmacodynamic potency".

In all, a more cautious approach to labeling would benefit all concerned, since the incorrect implications of the term "Superior," may lead to heightened expectations on the part of patients and physicians alike, and tort actions and malpractice suits may be initiated when a few people experience severe side-effects -- as always happens with any drug used for long enough in largem enough populations.

The "Pharmacokinetics" section is clear, factual and informative.

11.3 Indications and usage

The submission appears to support the Company's recommendation that Cabergoline "is indicated for the treatment of [symptomatic] hyperprolactinemic disorders, either idiopathic or due to pituitary adenomas," except that the following comments appear to be reasonable under the circumstances.

One can argue that added emphasis may be put to satisfy the following comments: (1) The main indication should more strongly state that only hyperprolactinemia with significant pathological consequences ought to warrant treatment; and, (2) that a question remains as to whether the safety and efficacy of the treatment of hyperprolactinemic disorders in males has been established, since very few males have been included in the clinical trials, particularly the pivotal ones. Under the circumstances, it is very difficult to

pointedly and clearly exclude such a population from the indication section. Let it be reminded that hyperprolactinemia in the male may lead to impotence, loss of libido, infertility and galactorrhea. In all these case, save perhaps in galactorrhea, it is difficult to assess the clinical efficacy of treatment regimen. This implies that long-term treatment would have to be instituted in such individuals. To these medical concerns, we may add a regulatory one: Is it permissible to approve an indication (i.e., hyperprolactinemia in the male) with highly inadequate data base in that population?

This Reviewer does not find compelling reasons to espouse such comments as the ones maid immediately above. As a result, the Reviewer agrees with the indications proposed by the Company.

11.4 Contraindications

The Company believes that Cabergoline is contraindicated only in patients with known hypersensitivity to ergot derivatives.

And yet, as a matter of reference, it should be stated that Bromocriptine labelling lists the following contraindications: Uncontrolled hypertension, toxemia of pregnancy and sensitivity to any ergot alkaloids. Needless to say, and since of the withdrawal of the post-partum lactation inhibition indication, the latter condition is also a *de facto* contra-indication. The pharmacological and chemical similarities and affinities between Bromocriptine and Cabergoline beg the question: Ought not the same warnings be present in the labelling of both drugs, at least until longer experience in humans assure us that such a warning is not warranted in the case of Caberrgoline?

Also, given the known facts of its metabolic disposition, this Reviewer believes that Cabergoline ought to be contra-indicated in subjects with severe hepatic insufficiency.

11.5 Warnings

Again as a matter of reference, the Bromocriptine labeling provides the following warnings: (1) A thorough

evaluation of the pituitary is warranted prior to the treatment of hyperprolactinemic patients with amenorrhea and/or galactorrhea; (2) A pregnancy obtained as a result of bromocriptine treatment has to be carefully monitored, though epidemiological studies have not, so far, shown any potential for teratogenic effects on the fetus. This, of course, does not mean that the safety of bromocriptine to the fetus has been conclusively established (in fact, the bulk of the available evidence poits strongly to the contrary opinion); and (3) During pregnancy following bromocriptine treatment, there may be a rapid increase in adenomatous size, which may result in serious impingements on the optic or other cranial nerves, thus necessitating a surgical intervention.

Given the extremely long serum half-life of Cabergoline, and given the knowledge about the high-level accumulation during multiple dosing, a warning statement appears warranted to advise not to either increase dosage beyond the prescribed dose, or increase the frequency of administration, or both.

Also, the pharmacokinetic data make it clear that women on the drug should either avoid lactating their infants, or stop taking the drug for a sufficient period of time prior to lactating.

11.6 Precautions

11.6.1 General

The labeling proposed by the Company states:

A change should be found to combat the implication that 1.0 mg is an acceptable initial dose, or even a final dose in most patients, since 0.5 mg appears to be a most effective dose for most patients; therefore, that's the recommended initial dose for most people, even though some of them may be upward titration later.

11.6.2 Information for patients

A note is inserted here to the effect that "A patient should be instructed to notify her physician if she becomes or intends to become pregnant during therapy." Two comments

appear to be in order: (1) Clearly, the Company doesn't intend to request the indication of restoration of fertility in hyperprolactinemic-amenorrheic patients. Under the circumstances, this should be stated more clearly: That the indication of restoration of fertility has not been investigated and, therefore, its safety and effectiveness has not been determined; and, (2) Under the warning section, a statemnent should be included, to inform physicians and patients that the lack of teratogenicity of Cabergoline has not been conclusively established. As of October 1994, 226 pregnancies had occurred in women treated with Cabergoline with the following observed anomalies: 2 cases of Down's syndrome; and one case each of leg deformation and adherent placenta, hydrocephalus, transient respiratory distress with umbilical and inguinal hernia, intra-atrial communication, monolateral mega-ureter, Mongolian spot and mild chordee of the penis; labiognathopalatoschisis, talipes with hip dysplasia, and dolicocephaly with premure fontanella closure. Given the limited and preliminary nature of our information, we cannot be sure that the observed incidence of anomalies and malformations is similar to that seen in the genral population. Accordingly, women being treated with Cabergoline should be instructed to avoid pregnancy. If pregnancy does accidentally occur, fetal exposure to Cabergoline should be minimized through an early diagnosis of pregnancy followed by interrutopn of Cabergoline treatment.

11.6.3 Laboratory tests

No specific laboratory tests are recommended by the Company. The Reviewer would suggest that serial prolactinemic measurements are essential for the proper treatment of individual patients, particularly to know when to stop therapy (for a while) and when to resume it and for how long.

11.6.4 Drug interactions

The following drugs are listed as able to interact with the effects of Cabergoline: Phenothiazines, butyrophenones, thioxanthines, or metoclopramide -- all of them Dopamine D2 receptor antagonists.

11.6.5 Carcinogenesis, mutagenesis, fertility

11.6.6 Pregnancy

The statement by the Company that "no adequate and well-copntrolled studies [exist] in pregnant woman," is warranted under the circumstances. On the other hand, this Reviewer feels that this statement should be printed at the top of the Pregnancy heading, and not at its end. In addition, we feel that the statement that "this drug should be used during pregnancy only if clearly needed," ought to be more explicit. For example, it could be stated that, since one cannot rule a possible teratogenic effect of the drug, Cabergoline may be prescribed to pregnant women only when other therapies appear contra-indicated or have been proven to be ineffective.

11.6.7 Labor and delivery

No pertinent comments.

11.6.8 Nursing mothers

Again, the Company's statement that because "many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infant from cabergoline, a decision should be made to discontinue nursing or discontinue the drug," is all right as far as it goes. This Reviewer feels that it doesn't go far enough. A better approach would be to state that "under such circumstances, it is currently highly advisable to discontinue nursing, unless it is possible to discontinue the drug without serious consequent to the mother." Also, a reasonable and well defined wash-out period ought to be given, providing the average discontinuation-of-therapy length of time before nursing can be resumed without the risk of having circulating levels of the blood harm the infant.

11.6.9 Pediatric use

No additional comments besides what has already been said in the preceding subheading.

11.7 Adverse reactions

The statement that "treatment with DOSTINEX was well-tolerated at doses up to 4.5 mg/week," is not acceptable without some qualification. We may not have observed visible cases of severe side-effects in the relatively small exposure currently available, but that doesn't mean that the drug will be well tolerated at high doses when large numbers of people may be exposed to the drug for long periods of time. If the recommended dose is 0.5 mg, such a statement is an invitation for impatient and careless practitionners to rapidly (and needlessly as well as heedlessly) titrate the dose upward in patients who are slow to normalize their prolactin levels with otherwise adequate dosing. This propensity is generally observed with the often overdosed sulfonylureas and, therefore, it could be argued that our concern is neither overdramatic or unrealistic.

This section should also contain statements as to low frequency serious-to-severe events associated so far with Bromocriptine use that may or may not be seen when Cabergoline is prescribed to large populations for long periods of time, i.e., paroxystic cerebrovascular accidents and pulmonary organic pathologies (e.g., pleural thickenings or effusions). The company has made appropriate statements to that effect. However, they are relegated at the end of "Adverse reactions" section. In fact, such statement should immediately follow the list of adverse events seen during the hyperprolactinemic trials using Cabergoline.

11.8 Drug abuse and dependence

The Company's statement appears to be adequate.

11.9 Overdosage

The Company's statement appears to be adequate.

11.10 Dosage and administration

The Company's statement that the recommended initial dose of 0.5 mg per week "may be increased... to a maximum of 4.5 mg, is not supported by the company's own study, which rather clearly shows a plateau-ing of the dose-response curve of Cabergoline roughly above 1.5 to 2.0 mg. The most that can be said is: "Most people will be effectively treated with no more than 2 mg a week. Only a rare patient

may need more than that; in which case, treatment may be pursued to up to 3.0 to 4.0 mg per week, but with extreme caution; and, if such a regimen remains inefficacious, other therapeutic avenues, if available, should be sought."

11.11 How supplied

Adequate information supplied by the Company.

12 CONCLUSIONS

The Reviewer recommends approval of the drug while requesting that his suggestions be communicated to the Company, to permit proper modifications of the labeling. It should be stated, here, that during an informal meeting with the Company's top Clinicians. the gist of the Reviewer's suggestions were communicated to the them, in clear scientific language. A full discussion ensued during which the Company representatives gracefully accepted most of this Reviewer's suggestions. They also promised to send back a corrected labeling section. It is worthy of note that said meeting was extremely cordial and pleasant.

13 REVIEWER'S RECOMMENDATIONS

The drug is recommended for approval after suitable modifications to the labelling have been submitted, reviewed, and found acceptable by the HFD-510 and ODE2.

John L. Gueriguian
Medical Officer
3/28/96

cc.
The File
Dr. Troendle
Dr. Fleming
Dr. Gueriguian

Superb review!
4/14/96

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FIGURE 2

CAD TABLETS TWICE A WEEK SCHEDULE DOSE FINDING STUDY IN HYPERPROLACTINAEMIA - HPRL 007

FIGURE 2. PERCENT VARIATION OF SERUM PRL VALUES DURING THE STUDY PERIOD

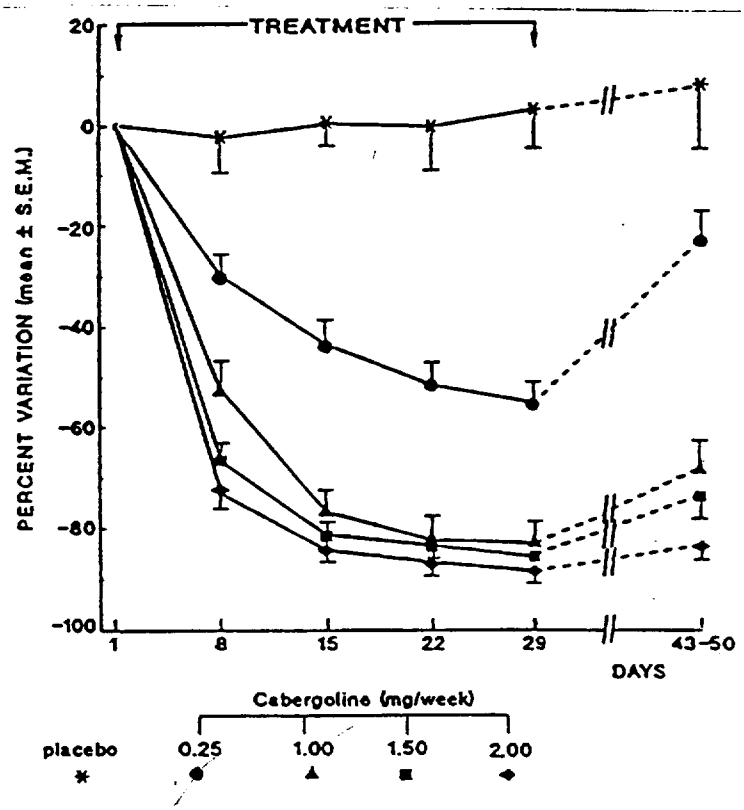


TABLE 1

Information on Patient Population from Clinical Studies with Cabergoline

Group	Total # Subjects	Sex	Age (Yrs) Approx. Mean (Range)	# Subjects Treated with Cabergoline
Pathologic Hyperprolactinemia (Two Pivotal Studies)	647	647 F	31.5 (16-46)	389
Pathologic Hyperprolactinemia (13 Additional Studies)	2,429	10 M[1] 2,439 F	32.0[1] (15-70)[1]	2,377
Healthy Subjects (13 Studies)	160	136 M 24 F	27.3 (19-39)	142
Puerperal Lactation (11 Studies)	1,070	1,070 F	28.8[3] (14-45)[3]	887
Premenstrual Mastalgia (One Study)	82	82 F	NS	82
Macroprolactinoma (Four Studies)	98	98 M/F	NS	98
Acromegaly (Three Studies)	71	71 M/F	NS (21-81)	71
Renal Insufficiency (One Study)	12	6 M 6 F	53.3 (34-70)	12
Hepatic Insufficiency (One Study)	12	9 M 3 F	48.6 (39-67)	12
Parkinson's Disease (21 Studies)	2,004	1,234 M 770 F	61.7 (29-85)	1,282

[1] Calculated from seven studies with 522 patients for whom these data are available.
[2] Calculated from 12 studies with 154 subjects for whom these data are available.
[3] Calculated from seven studies with 623 subjects for whom these data are available.
NS = not stated

TABLE 2

SUMMARY TABLE OF CLINICAL STUDIES WITH CABERGOLINE (HEALTHY SUBJECTS)

Report No.	Study No.	Double Blind or Open Duration	No. of Subjects in Study/Sex	No. of Subjects Treated with CAB/Sex	Mean Dose of CAB (mg, Final Dose)	Detailed Report Vol./Pg. No.
602i	FCE 21336/602i	Double Blind - Single Dose	9 M	9 M	0.2	1.53/0000080
EM-0027	-	Double Blind - Single Dose	6 M	6 M	0.5	1.53/0000136
617i	097003-000	Double Blind - Single Dose	49 M	37 M	1.0	1.58/0000161
618i	097004-000	Double Blind - 2 Weeks	24 M	18 M	1.5 / day	1.60/0000141
612iCL	APL-PHKI-005	Open - Single Dose	12 M	12 M	0.5	1.54/0000270
EM-0047	-	Open - Single Dose	7 M	7 M	0.6	1.53/0000373
605i	FCE 21336/605i	Open - Single Dose	3 M	3 M	0.6	1.47/0000278
604i	FCE 21336/604i	Open - Single Dose	3 M	3 M	0.6	1.47/0000293
611iCL	APL-PHKI-001	Open - Single Dose	12 M	12 M	1.0	1.53/0000142
613iCL	APL-PHKI-004	Open - Single Dose	12 F	12 F	1.0	1.53/0000376
610iCL	APL-PHKI-009	Open - Single Dose	5 M	5 M	1.0	1.54/0000180
609iPK	APL-PHKI-003	Open - Single Dose	12 F	12 F	1.0	1.48/0000355
606i	21336/MPK/001	Open - Single Dose	6 M	6 M	1.0	1.47/0000318

TABLE 3

SUMMARY TABLE OF CLINICAL STUDIES WITH CABERGOLINE (ENDOCRINOLOGICAL INDICATION)

Report No. (Patient Type)	Study No.	Double Blind or Open Duration	No. of Subjects in Study/Sex	No. of Subjects Treated with CAB/Sex	Mean Dose of CAB (mg, Final Dose)	Detailed Report Vol./Pg. No.
717i (P)	21336/ONC/30	Open - Single Dose	49 F	49 F	0.5	1.82/0000120
709i (P)	APL-BLLA-013	Open - Single Dose	11 F	8 F	0.7	1.80/0000285
608iPK (H)	APL-PHKI-002	Open - Single Dose	18 F	18 F	0.75	1.48/0000590
97-30704 (P)	CG-OB-251	Open - Single Dose	46 F	46 F	0.75	1.83/0000298
615i (RI)	PHKI-022	Open - Single Dose	6 M, 6 F	6 M, 6 F	1.0	1.49/0000802
616i (HI)	PHKI-021	Open - Single Dose	9 M, 3 F	9 M, 3 F	1.0	1.50/0001091
EM-0128 (P)	-	Open - Single Dose	36 F	18 F	1.0	1.82/0000073
720i (P)	21336/ONC/32	Open - 2 Days	115 F	115 F	0.5 / day	1.82/0000319
706i (H)	APL-015	Open - 4 Weeks	2 M, 214 F	2 M, 214 F	0.9 / week	1.76/0000025
EM-0048 (H)	--	Open - 4 Weeks	6 F	6 F	0.9 / week	1.76/0000019
EM-0048 (H)	--	Open - 9 Weeks	1 M, 30 F	1 M, 30 F	0.45 / week	1.76/0000019
728i (MA)	097005-999	Open - 48 Weeks	7 M, 8 F	7 M, 8 F	1.6 / week	1.78/0000078
-- (H)	ONC/029	Open - 48 Weeks	323 M/F	323 M/F	2.0 / week	1.76/0000015
719i (MA) --	097005-999 and Compassionate	Open - 6-28 Months	9 M, 24 F	9 M, 24 F	1.6 / week	1.79/0000146 , 1.76/0000016

H = hyperprolactinemia P = puerperal lactation RI = renal insufficiency HI = hepatic insufficiency MA = macroprolactinoma

TABLE 4

SUMMARY TABLE OF CLINICAL STUDIES WITH CABERGOLINE (ENDOCRINOLOGICAL INDICATION)

Report No. (Patient Type)	Study No.	Double Blind or Open Duration	No. of Subjects in Study/Sex	No. of Subjects Treated with CAB/Sex	Mean Dose of CAB, (mg, Final Dose)	Detailed Report Vol./Pg. No.
708i (P)	APL-BLLA-011	Double Blind - Single Dose	24 F	16 F	0.7	1.80/0000057
710i (P)	APL-SPLA-005	Double Blind - Single Dose	140 F	120 F	0.75	1.80/0000127
93-30704 (P)	CG-OB-261	Double Blind - Single Dose	185 F	185 F	0.75	1.83/0000299
711i (P)	APL-SPLA-006	Double Blind - Single Dose	271 F	136 F	1.0	1.80/0000323
95-30702 (and 713i and 715i) (H)	HPRL-007	Double Blind: 4 weeks Open: Approx. 1 year	188 F	168 F	1.2 / week	1.62/0000018 1.64/0000001 1.65/0000183
95-30703 (and 721i) (H)	21336/ONC/26	Double Blind: 8 Weeks Open: 16 Weeks	459 F	226 F	1.5 / week	1.67/0000001 1.69/0000001
712i (H)	APL-016	Double Blind: 8 Weeks	24 F	18 F	0.9 / week	1.66/0000238
– (M)	93-APL-036	Double Blind - 3 mos.	82 F	≤82 F	1.0 / week	1.78/0000017
704i (H)	APL-HPRL-004	Open - Single Dose	3 M, 14 F	3 M, 14 F	0.3	1.75/0000048
707i (P)	APL-007	Open - Single Dose	11 F	11 F	0.4	1.82/0000077
-- (A)	EM-0071	Open - Single Dose	2 M, 6 F	2 M, 6 F	0.45	1.84/0000102
705i (H)	HPRL-009	Open - Single Dose	3 M, 48 F	3 M, 48 F	0.45	1.75/0000126

P = puerperal lactation H = hyperprolactinemia M = mastalgia A = acromegaly

TABLE 5

SUMMARY TABLE OF CLINICAL STUDIES WITH CABERGOLINE (ENDOCRINOLOGICAL INDICATION)

Report No. (Patient Type)	Study No.	Double Blind or Open Duration	No. of Subjects in Study/Sex	No. of Subjects Treated with CAB/Sex	Mean Dose of CAB (mg, Final Dose)	Detailed Report Vol./Pg. No.
714i (H)	HPRL-003	Open - 49-85 Weeks	1 M, 164 F	1 M, 164 F	0.75 / week	1.76/0000364
EM-0197/Compassionate (A)	--	Open - 3 mo. - 8 yr.	63 M/F	63 M/F	1-7 / week	1.78/0000022
Compassionate (H)	--	Open - 7 mo. - 8 yr.	1,279 M/F	1,279 M/F	≤ 1.0 / week	1.76/0000016
ONGOING 9530704 (P)	ONC/005	Double Blind - Single Dose	189 F	189 F	0.75	1.77/0000461
ONGOING (P)	93-APL-037	Double Blind - 2 Days	178 F	≤178 F	0.5 / day	1.78/0000019
ONGOING 9530704 (H)	ONC/001	Open - Single Dose	20 F	20 F	0.72	1.77/0000461
ONGOING 9530704 (P)	ONC/003	Open - Single Dose	46 F	46 F	0.75	*
ONGOING 9530704 (H)	ONC/002	Open - 18 Weeks	34 F	34 F	0.6 / week	1.77/0000461
ONGOING 9530704 (H)	ONC/004	Open - 26 Weeks	125 F	125 F	< 1.25 / week	*
ONGOING (H)	93-APL-038	Open - 7-10 mo.	126 M/F	126 M/F	≤ 4.5 / week	1.76/0000017
ONGOING (MA)	097011-999	Open - Since 12/91	14 M/F	14 M/F	≤5 / week	1.78/0000004
ONGOING (MA)	097014-999	Open - Since 1/93	36 M/F	36 M/F	≤5 / week	1.780000004

H = hyperprolactinemia MA = macroprolactinoma A = acromegaly P = puerperal lactation

TABLE 6

PARKINSONISM CLINICAL STUDIES WITH CABERGOLINE (COMBINED DATA)

No. of Studies	Mean Study Duration (SD) Range	Mean Final Dose (SD) Range	Total No. of Patients in Studies	No. of Patients Treated with Cabergoline
21	Mean = 202 Days (176) Range = 1-600 Days	Mean = 3.2 mg/day (2.5) Range = 0.25 - 12 mg/day	Total = 2,004 1,234 M 770 F	Total = 1,263 * 822 M 441 F

* Corrected number (19 fewer than stated in NDA)

TABLE 7

SUMMARY OF DEMOGRAPHIC, HISTORY, AND CLINICAL DIAGNOSIS CHARACTERISTICS

	Cabergoline (mg)					
	Placebo	0.25	1.00	1.50	2.00	
Number of Patients Randomized:	20	42	42	42	42	
Age (years)						
N	20	42	42	42	42	
Mean	34.8	30.4	31.7	31.0	32.5	=5.87 (a)
Median	38.0	29.0	33.0	28.5	31.5	p =0.21
Std. Deviation	9.32	7.85	7.25	7.79	7.05	
Range						
Race, N(%)						
Caucasian	19(95%)	41(98%)	42(100%)	42(100%)	42(100%)	p =0.20 (b)
Asian	0(0%)	1(2%)	0(0%)	0(0%)	0(0%)	
Other	1(5%)	0(0%)	0(0%)	0(0%)	0(0%)	
Menstrual History, N(%)						
Primary Amenorrhoea	0(0%)	1(2%)	0(0%)	1(2%)	1(2%)	=17.00 (c)
Secondary Amenorrhoea	7(35%)	12(29%)	19(45%)	23(55%)	18(43%)	p =0.65
Oligomenorrhoea	9(45%)	13(31%)	12(29%)	8(19%)	11(26%)	
Normomenorrhea	4(20%)	14(33%)	10(24%)	8(19%)	12(29%)	
Polimenorrhoea	0(0%)	1(2%)	1(2%)	2(5%)	0(0%)	
Not Specified	0(0%)	1(2%)	0(0%)	0(0%)	0(0%)	
Previous Hypoprolactinaemic Therapy, N(%)						
No	6(30%)	17(40%)	20(48%)	18(43%)	20(48%)	p =0.71 (b)
Yes	14(70%)	25(60%)	22(52%)	24(57%)	22(52%)	
Hyperprolactinaemia Due to: N(%)						
Microprolactinoma	11(55%)	25(60%)	24(57%)	26(62%)	27(64%)	p =0.82 (b)
Idiopathic Disease	8(40%)	17(40%)	16(38%)	13(31%)	13(31%)	
Other	1(5%)	0(0%)	2(5%)	3(7%)	2(5%)	
CT Scan, N(%)						
No	6(30%)	6(14%)	11(26%)	8(19%)	8(19%)	p =0.55 (b)
Yes	14(70%)	36(86%)	31(74%)	34(81%)	34(81%)	
Magnetic Resonance (MR), N(%)						
No	13(65%)	35(83%)	28(67%)	28(67%)	29(69%)	p =0.34 (b)
Yes	7(35%)	7(17%)	14(33%)	14(33%)	13(31%)	

(a) Kruskal-Wallis Test (b) Fisher's Exact Test (c) Pearson Chi-Square Test

TABLE 8

DEATHS IN PARKINSONIAN PATIENTS RECEIVING CABERGOLINE

Case #	Age	Sex	Cause of Death	Cabergoline Dose (mg/day)	Treatment Duration	Drug Related?	Study #
–	76	M	congestive heart failure	1.0	14 days	P	Pre-IND
09791014	73	F	pulmonary edema	1.5 or L-dopa 200	50 days	P	PKDS-009
09792002	68	M	cardiogenic shock	5.0	> 4 months	P	PKDS-012
09792032	70	M	C.O.P.D.	0.5	> 4 months	NO	TOPD-002
09790019	U	M	intracranial hemmorr.	5.0	> 4 months	P	PKDS-014
09792003	63	F	sudden death	1.5 or L-dopa 200	> 4 months	P	PKDS-009
09792067	38	M	suicide	U or L-dopa U	17 weeks	P	PKDS-009
09790020	67	M	sudden death	3.5	19 weeks	P	PKDS-014
09792077	63	M	heat stroke	6.0	20 weeks	P	PKDS-012
09790010	39	M	general deterioration	4.5	5 months	P	PKDS-014
09792006	53	M	suicide	2.0	> 5 months	NS	PKDS-009
09793001	64	M	pneumonia	5 or BRC 30	> 6 months	P	U
09792035	67	F	sudden death	6.0	> 7 months	P	PKDS-012
09793002	67	M	congestive heart failure	4.0	> 10 months	P	PKDS-012
09793016	75	M	aortic aneurysm	2.0 or L-dopa 100	> 10 months	NO	PKDS-009
09793039	79	F	suicide	4 or B 25	> 11 months	NO	PKDS-012
09790009	65	M	acute renal failure	18	14 months	P	PKDS-007
09792048	79	M	congestive heart failure	3.5	> 14 months	NO	97009
09793010	72	M	pulmonary fibrosis	3.0	> 14 months	PR	017
09793019	64	M	pneumonia	3.0	> 15 months	NO	MN-91601
09794071	63	M	death	5	16 months	P	097013
09793009	53	F	pulmonary embolism	6.0	> 16 months	P	PKDS-012
09792058	65	M	sudden death	6.0	> 16 months	P	PKDS-012
09794065	69	M	myocardial infarct	3.5	> 16 months	UNL	097015
09792033	77	M	congestive heart failure	4.0 or L-dopa 600	> 17 months	NO	PKDS-009

P = Possible NS = not stated PR = Probable U = unknown BRC = bromocriptine

TABLE 9

DEATHS IN PARKINSONIAN PATIENTS RECEIVING CABERGOLINE

Case #	Age	Sex	Cause of Death	Cabergoline Dose (mg/day)	Treatment Duration	Drug Related?	Study #
09793038	65	M	pulmonary embolism	4 or BRC 25	> 18 months	NO	PKDS-012
09792039	74	M	pulmonary embolism	2.5 or L-dopa 400	> 23 months	NO	PKDS-009
09793037	73	F	peritonitis	U or Dopa	> 2 years	P	009
09794054	66	M	myocardial infarct	5	> 2 years	UNL	016
09794020	70	M	sudden death	6	> 2 years	UNL	012
09795028	72	M	pulmonary carcinoma	4	> 2 years	UNL	009/1
09794062	60	M	sudden death	6	2.5 years	UNL	PKDS-012
09792079	68	M	sudden death	4.0	> 33 months	P	018
09793083	58	M	suicide	4.5	> 3 years	NO	PKDS-018
09793008	71	M	brain lesion	2	> 3 years	P	006
09795062	80	M	cardiac failure	NS	4 years	UNL	PKDS-009
09794084	73	F	pneumonia	4	4 years	NO	PKDS-009
09794074	67	M	pneumonia	5	> 4 years	UNL	PKDS-018
09794055	82	M	pneumonia	4	> 4 years	UNL	PKDS-009
09795002	66	M	neoplasm	5	> 4 years	UNL	PKDS-018
09793050	56	F	sudden death	6.0	> 4 years	P	PKDS-018
09794085	77	M	pneumonia	5	> 5 years	UNL	PKDS-018
09795009	71	F	pneumonia	3.5	> 5 years	UNL	PKDS-018
09795022	81	M	hepatic neoplasm	4	5.5 years	UNL	PKDS-018
09791001	66	F	sudden death	9.0	U	P	PKDS-014
09794028	73	F	cerebrovasc. disorder	4.5	U	UNL	PKDS-018

P = possible NS = not stated PR = Probable U = unknown UNL = unlikely BRC = bromocriptine

TABLE 10

Number of All Reported Adverse Experiences by Body System (Study HPRL-007)

	Placebo	0.25 mg	1.0 mg	1.50 mg	2.0 mg
Autonomic NS	0	0	1 (2%)	1 (2%)	0
Body as a Whole	2 (10%)	6 (14%)	3 (7%)	2 (5%)	4 (10%)
CV (General)	0	1 (2%)	0	0	0
CNS/PNS	4 (20%)	10 (24%)	8 (19%)	9 (21%)	8 (19%)
Gastrointestinal	3 (15%)	3 (7%)	4 (10%)	6 (14%)	7 (17%)
Heart Rate	0	2	0	0	0
Metabolic/Nutritional	0	1 (2%)	0	0	0
Psychiatric	0	3 (7%)	0	2 (5%)	2 (5%)
Reproductive (Female)	2 (10%)	3 (7%)	1 (2%)	2 (5%)	1 (3%)
Respiratory	1 (5%)	0	0	1 (2%)	3 (7%)
Skin/Appendages	0	1 (2%)	1 (2%)	0	1 (2%)
Vasc. (extracardiac)	1 (5%)	0	0	2 (5%)	1 (2%)
Vision	0	0	0	0	1 (2%)

NS=Nervous system CV=Cardiovsacular CNS=Central nervous system
PNS=Peripheral Nervous System

Most of these AE involved the gastrointestinal system or the central/peripheral nervous systems. The table above presents data on the ten specific AE with the highest incidence.

TABLE 11

Adverse Experiences, by Event, Reported During Study No. ONC/026

Adverse Experience	Cabergoline No. of Reports	Bromocriptine No. of Reports
Nausea	69 (31%)	115 (50%)
Headache	66 (30%)	70 (30%)
Dizziness	42 (19%)	56 (24%)
Abdominal pain	20 (9%)	28 (12%)
Asthenia	17 (8%)	23 (10%)
Constipation	17 (8%)	21 (9%)
Fatigue	11 (5%)	22 (10%)
Emesis	11 (5%)	22 (10%)
Vertigo	14 (6%)	12 (5%)
Breast pain	11 (5%)	12 (5%)

The incidence of AE were similar except for nausea, which was reported more often by BRC patients (50%) than by those receiving CAB (31%). The body systems most often affected were the gastrointestinal system (CAB 100 AE=45%; BRC 144 AE=62%), and the central and peripheral nervous system (CAB 99 AE=45%; BRC 111 AE; 48%).

NOV 19 1996

NDA 20664
Sponsor: Pharmacia & Upjohn
Drug: Cabergoline/Dostinex

Received: 11/19/96
Reviewed: 11/21/96
Doct: N20664B/G116

MEDICAL OFFICER'S REVIEW OF LATEST SAFETY UPDATE

I. Introductory Statement

Thus NDA Amendment, dated November 13, 1996, is a safety update covering the period from August 1, 1995 to July 31, 1996. During that one-year period of time, and according to the company's statement, no new studies were completed either in the United States or in Europe.

The update consists of reports of serious spontaneous adverse reactions from two different indications: Hyperprolactinemia and inhibition or suppression of lactation. Since the latter indication is not approved in the United States, it is clear that reports emanating from the physicians of such patients come from outside our country. The submissions also supplies end-of-study reports for numerous trials during which patients with Parkinson's disease were treated with cabergoline and other dopamine receptors agonists.

What now follows is a quick introduction to the drug: Cabergoline is a dopamine receptor agonist with effects similar to those of bromocriptine mesylate (Parlodel). However, it differs from bromocriptine in one singular way: Its peculiar pharmacodynamics makes it a very long-acting drug. The practical consequence of that fact is the useful regimen it allows, i.e., a once-a-week administration is enough to correct hyperprolactinemic disorders in most cases. Of course, this advantage may have its drawbacks, since there is indirect evidence that, on the chronic course, it can accumulate in various bodily compartments and particularly the central nervous system.

The latter concern was communicated to the company representatives at an informal meeting during which labeling changes were suggested that improve the safety of the drug as labeledz. The company accepted these suggestions, changed its labeling accordingly and -- as a result -- the issue is now practically moot. It is our opinion that this drug is now proven to be safe and effective as indicated.

II. A Review of Submitted Adverse Reaction Data

We shall now review single adverse reaction reports but would only present and discuss those that are perceived to be original and contributory to the best understanding of the drug's safety profile.

A. Fetal anomalies

1. Case 9547162: In utero exposure to drug for 23 days was followed by the diagnosis of trisomy after an amniotic fluid withdrawal and analysis.
2. Case 9649213: A female subject became pregnant and still followed through till delivery, despite protocolar advice to the contrary. A macerated fetus was eventually delivered.
3. Case 9651131: An in-utero exposure was followed by an abortion to deliver a fetus with a "prune-belly syndrome."

B. Nervous system reactions

1. Case 9647573: After a 1-year chronic exposure to cabergoline, the patient suffered from tonic-clonic convulsions. Drug involvement is possible given the slow build-up of drug concentrations in the central nervous system.
2. Case 9649213: A fetus with an in-utero exposure to cabergoline (via administration to the mother) suffered from an epileptic condition shortly after birth.
3. Case 9438401: A 35 year-old female patient treated with cabergoline eventually developped paresthesias and visual disturbances. Dechallenge and rechallenge confirmed the drug's involvement in this symptomatology. This observation suggests a wider than thought distribution and concentration of the drug in the nervous system, certainly during long-term therapy.

C. Cardiovascular system reactions

Case 9649612: Supraventricular tachycardia was observed in a 52 year-old man during long-term cabergoline therapy. However, the simultaneous administration of a great number of other drugs tended to complicate the interpretation of the data as to the possible invovement of cabergoline in

this cardio-rhythmic incident.

III. Report on Adverse Reactions during Treatment for Parkinson's Disease

Theis section of the safety update contains numerous reports summarizing the safety-related occurrences during several studies during which patients with Parkinson's disease were treated with dopamine receptor agonists, with high doses and for long periods of time.

A careful analysis of the supplied data seem to support the following conclusion: That there is no visible modification in the safety profile of cabergoline when a comparison is made with the safety data provided in the original NDA and the data submitted in the present documentation. Specifically, one doesn't find any statistically significant difference between patients treated with cabergoline and those treated with either bromocriptine or Dopa. If anything, there is a slight but consistent edge of cabergoline over the other treatment modalities. No visible trend of gradual increase of adverse reaction frequencies can be discerned with prolonged treatment periods. Also, the kinds of adverse reactions seen are essentially the same than those reported in the original NDA, or those listed in the labeling of bromocriptine.

IV. Conclusions

With respect to the possible causal relationship between the drug and fetal abnormalities, it is prudent to continue to avoid administration (or continued administration) of cabergoline to women who are or become pregnant. This doesn't mean that there is an established causality between cabergoline administration and fetal abnormalities. It simply means that under the present conditions of knowledge it is prudent to avoid, as much as possible and as soon as possible, in-utero exposure to cabergoline. Additional support for this position comes from a published report about 226 cases of pregnancies in women taking cabergoline, show 42 (forty-two) miscarriages and three abortions because of major malformation -- one Down syndrome, one limb-body wall complex, and one hydrocephalus (Robert L. et al., Reproductive Toxicology 10:333-7, 1996).

Overall, it can be concluded that the information provided in this safety update deoes not seem to be able to alter the safety profile observed in the original NDA-submission. Thus, as far as this Reviewer is concerned, the recommendation to approve the drug stands. In addition, the Reviewer also accepts, as more than adequate, the latest labeling proposed by the company, one that was reviewed earlier.

V. Regulatory recommendation

The drug ought to be approved as safe and effective as indicated. The latest labeling supplied by the Company is also acceptable. It does offer the prescribing physician with all the needed information to enable him/her to administer the drug in a safe way and under conditions of maximum efficacy.

John L. Gueriguian, M.D.
11/21/96

cc:

The File
Dr. G. A. Fleming
Dr. J. L. Gueriguian

Excellent update, provided ahead of schedule.

11/14/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020664

STATISTICAL REVIEWS

STATISTICAL REVIEW AND EVALUATION

NDA : 20-664 **DRUG CLASS:** 1S

NAME OF DRUG: Dostinex (Cabergoline)

SPONSOR: PHARMACIA INC

INDICATION: Hyperprolactinemic Disorders, Either Idiopathic or Due to Pituitary Adenomas.

DOCUMENTS REVIEWED: Volumes 1.137 - 1.152 of NDA 20-664 Dated December 26, 1995.

MEDICAL REVIEWER: John L. Gueriguian M.D., HFD-510. This review has been discussed with the medical reviewer.

I. INTRODUCTION AND A BRIEF SUMMARY:

I.1. The sponsor has submitted two Phase III , double-blind, randomized, multi-center, multinational trials in Europe and Argentina in support of Dostinex in the treatment of hyperprolactenemic disorders, either idiopathic or due to pituitary adenomas.

I.2. The two studies are identified as HPRL 007 and ONC 026. Study 007 is a double blind, randomized trial comparing Cabergoline(CAB) with placebo. It has **five** arms and a sample size of 188(placebo has 20 subjects; each of the arms, 0.25 mg, 1.0 mg, 1.5 mg and 2.0 mg has 42 subjects) at the beginning of the experiment (Day 1). On Day 29, the end of the double blind portion of the trial, 186 of the subjects remained in the study. The primary efficacy end-point for 007, which is also the biochemical end-point, is the prolactin level (PRL) in the blood serum which was measured on Day 1, Day 8, Day 15, Day 22 and Day 29. Additionally, PRL was measured on Day 43 in order to assess the 'long-term' efficacy of CAB, after suspending treatment on Day 29. **Criteria for success:** As defined in the protocol, (A) 'Complete Success' (CS) = PRL < 20 ng/ml; (B) Partial Success (PS) Not a CS but PRL<50% of base-line value; (C) Failure (F) = neither CS nor PS. The protocol called for assessing the efficacy of CAB by comparing the proportion of completely successful patients in each active dose arm with the corresponding proportion in the placebo arm on Day 29. An important issue of this trial is the existence of a significant between-treatment baseline difference with regard to the primary efficacy parameter. This was reported by the sponsor.

I.3. Study ONC 26 is an active control study, comparing Dostinex with Bromocriptine (BCP). This is a randomized trial, double-blind for the first eight weeks and open the next 16 weeks. The double-blind during the first eight weeks was maintained by assigning drug and/or matched placebo twice daily, using the double-dummy technique. The study involves 452 patients with 221 in the CAB arm and 231 in the BCP arm. One dose is administered in each arm, with 0.5 mg of CAB given **twice a week** and 2.5 mg of BCP given **twice daily**. There are no significant baseline differences between the arms in this trial.

I.4. **The Sponsor's Goal**: To establish that Dostinex is safe and efficacious compared to: (1) The placebo; (2) the open control, Bromocriptine; (3) Its Adverse Effects are fewer and less intense than those of BCP.

SECTION II. REVIEWER'S DISCUSSION OF THE CLINICAL TRIALS:

The following discussion will address only the two pivotal studies mentioned in Section I.

II.1 **STUDY HPRL 007**: This is a Phase-III, multi-center (20 centers, with number of recruited patients ranging from one to four in each arm) multinational, randomized one-year efficacy study comparing CAB with placebo which was double-blind for the first four weeks. The blind was broken after Day 29. As mentioned above, it has five arms: Placebo (0.0 mg/wk), Dose 1 (0.25 mg/wk), Dose 2 (1.0 mg/wk), Dose 3 (1.5 mg/wk) and Dose 4 (2.0 mg/wk). The initial, Day 1 sample sizes for the five groups were 20 in the placebo arm and 42 for each of the other four arms, in all 188 female subjects. The dosages were administered over two days in half doses to minimize initial reactions, mainly, nausea and vomition.

Inclusion criteria: Hyperprolactinemic (HPRL) caucasian women between the ages 16 and 45. The biochemical end-point is the serum prolactin level (PRL). Definition of HPRL disorder is, any woman with PRL level greater than 20 ng/ml. The indication is for nonpregnant women only. **Exclusion Criteria:** Patients with a high-risk profile such as weak pulmonary, renal, etc., conditions.

Complete Success (CS) for this trial is defined as PRL < 20 ng/ml; Partial Success (PS) is PRL < 50% of the base-line value but not in the category CS; Failure (F) is, neither of the categories CS, PS. The success/failure assessments were done on Day 29, the last day of the four week double-blind portion of the trial. Safety assessments which include ECG, BP and standard clinical laboratory variables were conducted at each visit. PRL values and the safety assessment variables were measured once every week, on Day 1 (baseline), Day 8, Day 15, Day 22 and Day 29. In addition, as a measure of the long-term efficacy, PRL level and safety variables were measured on day 43, after a washout period of 2 weeks.

Sponsor's Analysis:

In addition to routine measurement of the selected variables, creating and maintaining the data base, tabulation and cross-checking the entries, computing the descriptives, the following statistical analyses have been performed to support their claims (see 'Sponsor's Goal' above in Section I above):

1. Two-tailed tests for baseline differences of the prognostic variables.
2. Treatment group comparisons that are based on Qualitative variables are conducted using frequencies. Treatment group comparisons are tested using the Kruskall-Wallis Test.
3. The Cochran-Armitage Linear Trend is used to test for differences in categorical proportions. No adjustments are made for multiple comparisons.
4. Safety analysis focuses on a study of the vital signs such as BP, pulse rate, clinical lab examinations and adverse effects (AE). The sponsor has used the K-W test.

II.1.1 DISCUSSION OF RESULTS OF STUDY 007:

The following results were filed by the sponsor:

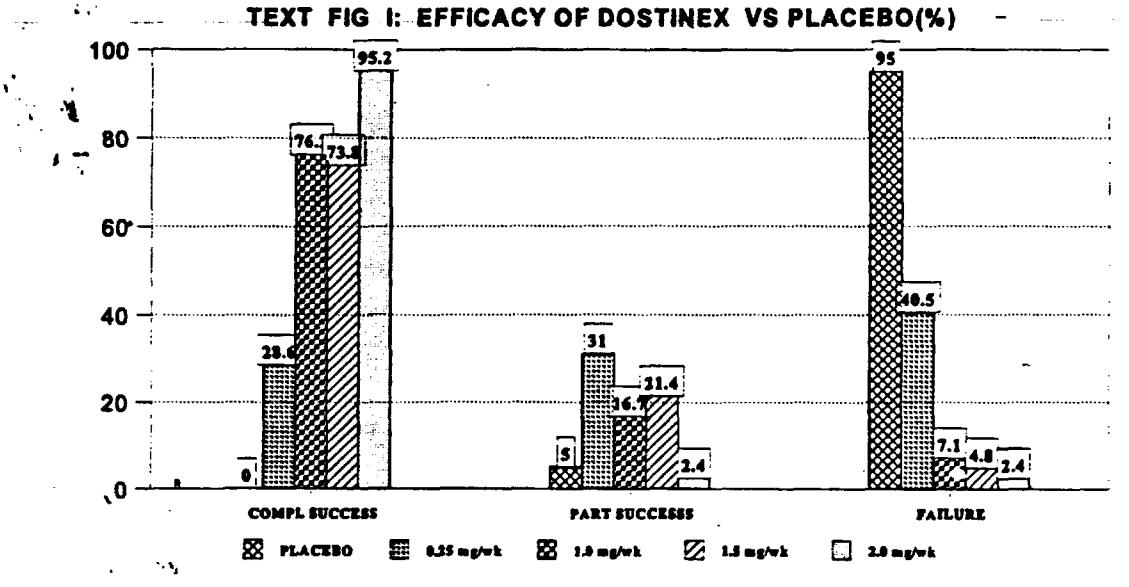
1. There was an overall significant baseline difference in the variable Day 1 PRL values with p = 0.018 (K-W). See Table 1 in the Appendix.
2. 186 out of 188 subjects stayed on the trial (99%) until Day 29. Of the 186 that completed the double-blind portion of the trial 162 (81%) entered the uncontrolled open phase of the trial, after the 43rd day, with CAB as treatment.

CAB VS PLACEBO: EFFICACY ON DAY 29

DOSE	COMPL SUCCESS	PART SUCCESS	FAILURE	NA*
PLACEBO	0 (0%)	1 (5%)	18 (90%)	1 (5%)
0.25 mg/wk	12 (29%)	13 (31%)	14 (33%)	3 (7%)
1.0 mg/wk	32 (76%)	7 (17%)	2 (5%)	1 (2%)
1.5 mg/wk	31 (74%)	9 (21%)	1 (2%)	1 (2%)
2.0 mg/wk	40 (95%)	1 (2%)	1 (2%)	0 (0%)

Note: 1. This table was adopted from the sponsor's NDA submittal.

* = Not Applicable. The sponsor reports that these patients could not be classified into



any one of the three categories for various reasons. The sponsor decided to consider all the subjects in this category as failures.

3. The Cochran-Armitage Trend Test was used by the sponsor to test for a dose-response relationship. They report that on the basis of Complete Success (CS) rates, that there was a statistically significant relationship when calculated across all groups, with $p < 0.001$. The sponsor has also compared all groups excluding placebo and the results were identical. This is in keeping with their protocol. See Section I.2 above.

II.1.2 REVIEWER'S ANALYSIS OF THE STUDY 007:

Text Figure I above (created by this reviewer), compares the performance of Dostinex with placebo. One may note that the two arms with dose levels 1.00 mg/wk and 1.5 mg/wk bear close resemblance in regard to each of the categories CS, PS and F. It is also obvious that the 0.25 mg/wk arm is relatively inadequate. The 2 mg/wk arm is the most efficacious. This dosage would be desirable provided the Adverse Effects profile of this arm is satisfactory. Pairwise t-test comparisons which were performed to test for significant differences in the mean PRL values on Day 29 between the 2 and 1.5 mg/wk arms and the 2 and 1.0 mg/wk arms showed only a trend, indicating no statistically significant differences. Figure 1 and Table 1 in the Appendix of this report pertain to Study 007 (created by this reviewer).

II.1.3 A Key Issue: It was pointed out earlier in Section I.2 that the sponsor reported significant baseline differences in the primary efficacy parameter. Apart from mentioning this baseline difference, the sponsor has not addressed the issue. A natural question that would arise here is,

how does this significant baseline difference influence the outcome on Day 29? One should, indeed, expect this difference to account for part, if not the whole, of the differences at the end of the experiment. The vital question then is: Does there exist a statistically significant difference in the primary efficacy parameter, PRL on Day 29, the last day of the trial, even after 'accounting' for the initial differences? Statistically speaking, this question would translate to: Are the PRL values for the treatment groups on Day 29, even after *covarying* with respect to baseline values significantly different from corresponding values for the placebo group? The following discussion will address this issue:

A one-way ANOVA covarying for Day 1 PRL values was performed by this reviewer with 'Outcome', as the dependent variable. Outcome had three values: 1 = Complete Success, 2 = Partial Success, 3 = Failure. The independent predictor was 'Medication' having five values: 1 = the 0.25 mg arm, 2 = the 1.0 mg arm, 3 = the 1.5 mg arm, 4 = 2.0 arm and 5 = placebo arm. The analysis indicated that the variable, Day 1 PRL, was significant at $p = 0.007$ with an F-value of 7.533; it also indicated that the treatment effect was significant even after covarying, at $p < 0.0001$, with an F-value of 43.251.

An exact ANOVA was also performed by this reviewer using the software StatXact, testing for differences at Day 29 in the five arms. The exact probability that the five arms were identically distributed was also < 0.00001.

This reviewer also tested for a significant trend in dose-response: The double-ordered Jonckheere-Terpstra test of the five treatment arms in terms of the three possible out-comes was performed. As is well-known, this is a non-parametric test. The asymptotic p-value was 0.000 for testing the null hypothesis that the groups have no significant dose-response relationship. A Monte-Carlo estimate of the exact probability of the homogeneity of the five arms was also computed. This reviewer used the exact testing procedures of StatXact. The computed M-C estimate was also <0.0001 and the 99% confidence interval for p was (0.000, 0.0005).

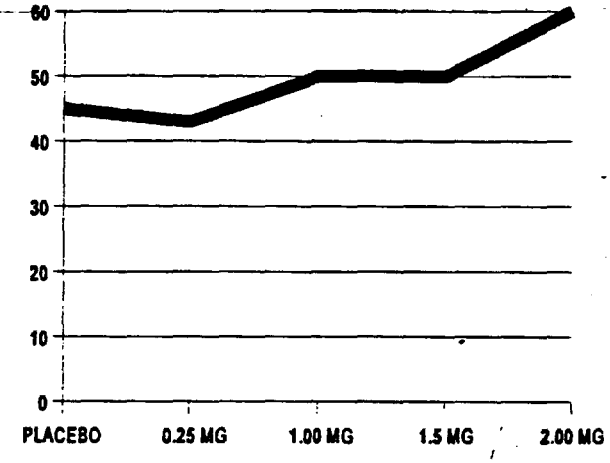
The above discussion allows one to conclude that the contribution of medication to reduction in PRL values on Day 29 was significantly different from the placebo, in spite of significant baseline group differences in the PRL levels of the subjects. In other words, the sponsor's claim regarding the efficacy of Dostinex in comparison to the placebo is supported by the independent statistical analyses of this reviewer.

II.1.4 The Adverse Effects Profile:

ARM	PLACEBO	0.25 MG	1.00 MG	1.5 MG	2.00 MG
SUBJECTS	9 (45%)	18 (43%)	21 (50%)	21 (50%)	25 (60%)

The above table gives the frequencies (and percents) of adverse effects suffered by the subjects

TEXT FIG II: ADVERSE EFFECTS(%



in each treatment arm. The Text Figure II (by reviewer) presented above describes the above table graphically. The AE has a range of 15% across all arms and there is no difference in the 1 mg and 1.5 mg arms as far as the AE is concerned. The adverse experiences of the patients in each arm were counted and actual frequencies were used to test for differences in AE. Pearson's Chi-squared test was performed on the frequencies and the asymptotic, as well as Monte-Carlo estimate of the exact probabilities were computed using Exact Test Procedures. The probability of obtaining the observed Chi-squared was 0.72.

The non-parametric Cochrane-Armitage trend test for a stratified 2 x c table was also performed by the reviewer. The test did not point to any significant trend. Thus although there is an increasing trend of AE's, it does not attain statistical significance. Specific AE's were then examined for significant differences. Nausea differences were statistically significant in the different arms: Kruskal-Wallis test (two-sided) was significant with p = 0.046 (asymptotic prob) with a Monte-Carlo estimate of the exact probability of 0.044. The 99% confidence interval was (0.0391 0.0497). The Cochran - Armitage Trend test was also performed for confirmation. The corresponding figures were p = 0.0491 (asymp.), M-C estimate = 0.0475, the 99% confidence = (0.0042 0.053). Headache was not significant. Other specific AE differences were so small as not to warrant tests. Table 46, Vol138, p0000112, submitted by the sponsor was used in this context. The software StatXact was used for performing these nonparametric tests. This reviewer therefore concludes that with the *exception* of nausea (the CAB patients suffering more), that CAB does not significantly differ from the placebo arm in regard to Adverse Effects.

SECTION II.2: THE STUDY 026:

II.2.1 This was a Phase III, randomized, multicenter(67 centers, number of patients recruited ranging from one to four in each arm) study to compare the efficacy of Cabergoline (CAB) versus Bromocriptine (BCP) in the treatment of HPRL women. A total of 67 centers were involved in this study. The mean durations of amenorrhea were respectively 16 and 18 months in the CAB and BCP arms. The mean baseline PRL values were respectively 106.6 ng/ml and 104.8 ng/ml in the CAB and BCP arms. Of the 452 subjects that entered the study, 221 were randomized to CAB and 231 to BCP. The treatments were double-blind during the first eight weeks and open thereafter for a further 16 weeks. During the double-blind phase, patients received test treatments at fixed doses; CAB 0.5 mg twice weekly and BCP 2.5 mg twice daily. Thus the dose was fixed for each arm, one mg/wk of CAB, 5 mg daily of BCP. Blind was maintained during the first eight weeks of the trial by assigning drug and/or matched placebo twice daily, using the double-dummy technique. Doses were adjusted at the end of the eight weeks and/or sixteen weeks if PRL values were still above normal (>20 ng/ml). Serum PRL and progesterone levels, occurrence of menses and pregnancy, BP, pulse rate in supine and standing positions and AE's were measured and monitored at baseline, and weeks 2, 4, 6, 8, 12, 14, 16, 20, 24. Hematology and blood chemistry were obtained at baseline and on weeks 4,8,16 and 24. ECG was done at baseline and at the end of the therapy.

II.2.2 Treatment efficacy was evaluated on the basis of **both** the serum PRL during therapy (biochemical endpoint) and resumption of menses and ovulation cycle (clinical criteria). The achievement of stable PRL normalization (i.e., PRL < 20 ng/ml) or PRL reduction by at least 50% from baseline with resumption of ovulatory cycles was **defined as global complete success. Complete Clinical Success** was: Resumption of ovulatory cycles or occurrence of pregnancy. The sponsor's **protocol** calls for a comparison of the proportion of global successes, as well as, of complete successes in the two treatment arms to demonstrate the efficacy of CAB over BCP at the 8th and at the 24th week.

II.2.3 The sample size of 452 was based on the following: There was a desire to detect a difference of at least 10% in the proportion of complete successes for the 'global criteria of efficacy' intent to treat analysis. From a clinical perspective, a difference between the proportion of success between the two treatment groups less than 10% was considered small enough to render the two therapies equivalent. Assuming 80% success for both CAB and BCP, at alpha level = 0.05, a sample size of at least 200 in each arm was required.

II.2.4 Sponsor's Statistical Analyses: Efficacy analyses include summaries and analyses for biochemical and clinical efficacy for patients included in the intent-to-treat population. Patients were classified, in each analysis, into one of the three groups: CS, PS, F, NA. For inferential tests, patients **classified as Not Applicable were considered treatment failures.**
After classification, the Kruskall-Wallis Test was performed to compare the response between the two treatment groups. A Wilcoxon Rank Sum was computed at each visit to compare serum PRL values between the two treatment groups. An analysis of biochemical efficacy was

performed at the end of the double blind segment. Clinical efficacy was also performed by comparing the two treatment groups with respect to number of patients who successfully completed the ovulatory cycle using the Exact Test of Fisher. The same test was also used to compare the number of patients with at least one regular menstrual cycle.

II.2.5 Sponsor's Statistical Results:

1. The baseline serum PRL values (see Table 2 in the Appendix), between the two arms were not significantly different (Wilcoxon test, $p = 0.09$).

2. In both groups, a marked, statistically significant decrease in PRL values occurred within the first two weeks of therapy. See Figure 2 in the Appendix created by this reviewer, and also the comments of the reviewer in the section 'Reviewer's Analyses'.

3. Recall that in Section II.2.2, a description of the sponsor's efficacy evaluation methodology for Study 026 was given. The protocol calls for both global complete success and complete clinical success. By the 8th week, at the end of the double-blind portion of the study, complete clinical success had been achieved in 172 (77%) of CAB patients, whereas, 140 (59%) had achieved complete clinical success in the BCP group (Kruskal-Wallis, $p<0.001$).

4. Global complete success occurred in the two groups as follows: 160 (72%) -- CAB vs 120 (51%) -- BCP (Krukal-Wallis: $p < 0.001$).

5. Adverse Effects: 159 (69%) vs 181 (79%) for CAB and BCP. $p = 0.018$. Most AE's reported were related to GI, the nervous system or body as a whole in both the groups. Nausea was more prevalent in the BCP group than in the CAB group -- 50% vs 31%, $p < 0.001$.

II.2.6 Reviewer's Analyses: This reviewer carried out several types of analyses: Computation of many descriptives and several non-parametric tests. The sponsor's categorical assessment of outcome was based on the Last Observation Carried Forward (LOCF) procedure. The reviewer carried out analyses, selecting only subjects whose data were not missing *en block*; in other words, this meant, excluding those subjects whose data were missing in all the contiguous cells after the 2nd or 4th week. However care was taken to include subjects who had one or two cells missing with no observable pattern. The distribution of the mean PRL values for this group are presented in Table 2 (in the Appendix) by medication and week number. Figure 2 in the Appendix, describing the mean values for the two groups by the week number, is also presented.

II.2.7 Comments on the Sponsor's Analyses in II.2.5: The following table summarizes the results computed, and also the charts appended at the end of the Review, present the reviewer's assessment of the sponsor's analyses.

CABERGOLINE VERSUS BROMOCRIPTINE (MEAN PRL VALUES):
Presenting the Probabilities of Non-parametric Tests Results (by Reviewer)

MEDICATION BY WEEK	WILCOXON TEST	KOLMOGOROV-SMIRNOV TEST
DAY 1 PRL	0.1981	0.2101
WEEK 2 PRL	0.6270	0.6220
WEEK 4 PRL	0.0041	0.0303
WEEK 6 PRL	0.0005	0.0097
WEEK 8 PRL*	<0.00001	0.0001
WEEK 12 PRL	<0.00001	0.0004
WEEK 14 PRL	<0.00001	<0.00001
WEEK 16 PRL	<0.00001	<0.00001
WEEK 20 PRL	<0.00001	<0.00001
WEEK 24 PRL**	<0.00001	<0.00001

* = End of double blind portion of the study. ** = End of the clinical trial.

Comments on the Table: Beginning with the 4th week, the differences in the mean PRL values are all highly significant, in favor of CAB over BCP. The reviewer holds the view that using the LOCF, if one were to perform the above analyses using all the data again, the results would be the same, as omission of *en block* missing data from analyses makes the results only more conservative.

Based on the above analyses, the reviewer agrees with the sponsor in their claim that Cabergoline is more efficacious than Bromocriptine.

SECTION III: REVIEWER'S CONCLUDING REMARKS:

- Study 007: The statistical analyses performed by the reviewer supports the sponsor's claims regarding the efficacy of Cabergoline over placebo. However patients in the CAB group suffered more from nausea than the placebo group. The difference was statistically significant.

- Study ONC 026: There is statistical evidence which supports the claims made by the sponsor regarding the efficacy of Cabergoline over Bromocriptine.

This reviewer agrees with the statistical findings of the two studies, with minor disagreements, none of them serious. Some of the data tables were sloppy and inconsistent. These were resolved by going to various other sources in the statistical volumes and data discs.

Ananda V. Gubbi Ph.D.
Mathematical Statistician.

Concur: Mr. Marticello
Team Leader Division II

Dr. Nevius 9/1/96
Director, Division II

CC:
Archive: NDA 20-664
HFD-510
HFD-510/S Sobel, A Fleming, J Gueriguian, E Galliers, R Hedin
HFD-344/A Lisook
HFD-715/Division File, Marticello
Chron.
This review consists of 10 pages of text, two pages of tables and 2 pages of charts.

:APPENDIX PAGES:

TABLE 1: OVERALL DESCRIPTIVES: CABERGOLINE VERSUS PLACEBO.

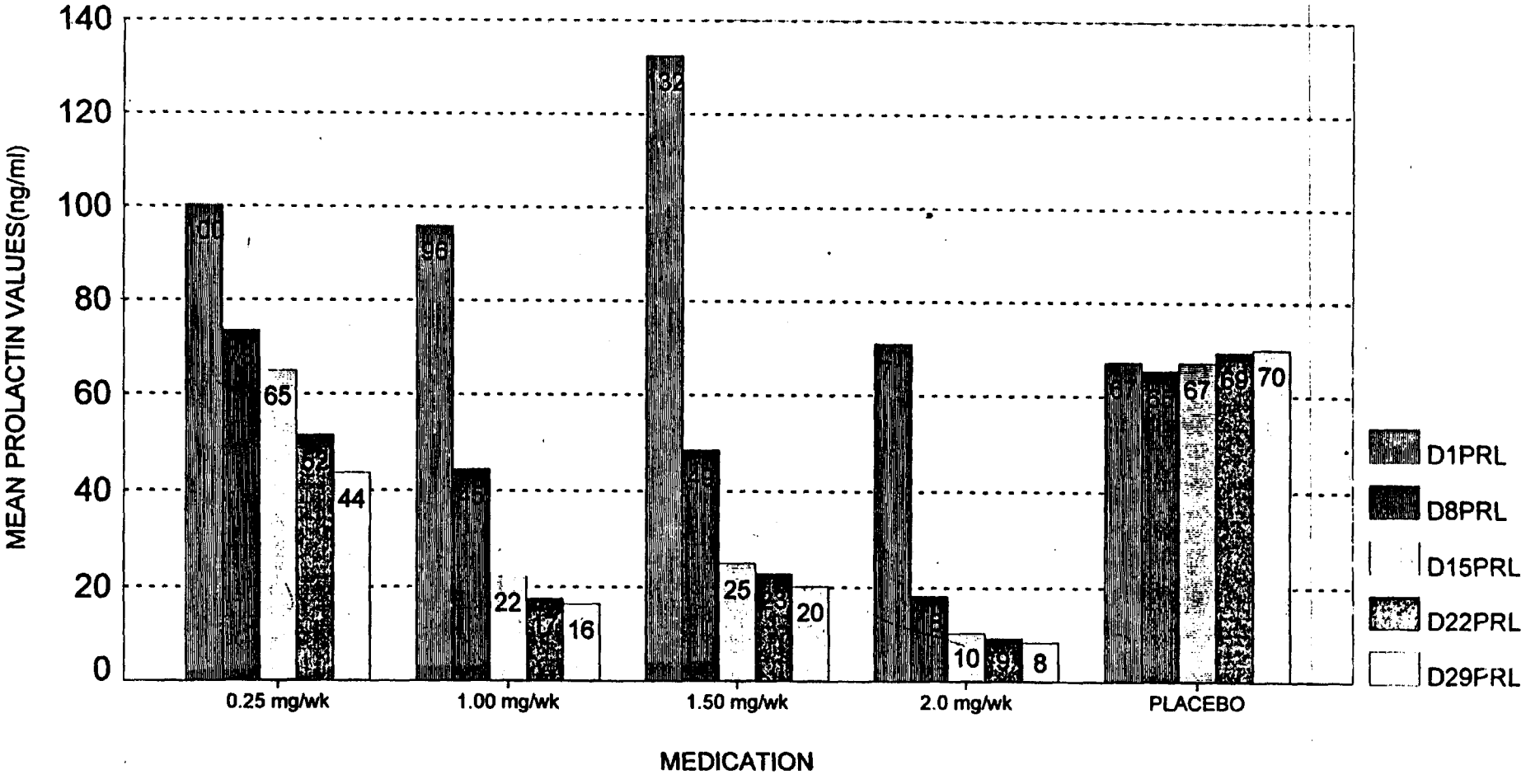
Variable	Mean	Std Dev	Kurtosis	S.E. Kurt	Skewness	S.E. Skew	Range	Minimum	Maximum	N
MEDCN: 1 = 0.25 MG/WEEK										
D1PRL	99.79	107.65	12.52	.74	3.38	.38		30.0	593.5	39
D8PRL	72.85	101.79	21.87	.74	4.38	.38		6.9	613.0	39
D15PRL	64.70	97.68	19.34	.74	4.08	.38		3.0	569.0	39
D22PRL	51.30	59.45	10.60	.74	2.88	.38		.0	319.0	39
D29PRL	49.06	45.61	6.46	.74	2.31	.38		.0	223.0	39
D43PRL	73.70	79.44	7.89	.75	2.76	.38		7.4	389.0	38
MEDCN: 2 = 1.00 MG/WEEK										
D1PRL	95.07	87.91	13.54	.72	3.52	.37		27.0	500.0	41
D8PRL	45.03	53.20	6.10	.72	2.40	.37		.9	241.0	41
D15PRL	21.94	27.57	6.12	.72	2.43	.37		.3	119.3	41
D22PRL	17.29	29.64	18.54	.72	4.02	.37		.0	170.0	41
D29PRL	16.38	24.43	8.43	.73	2.87	.37		.0	112.0	40
D43PRL	31.36	41.03	6.49	.74	2.50	.38		.5	188.0	39
MEDCN: 3 = 1.50 MG/WEEK										
D1PRL	132.45	113.53	3.52	.72	1.88	.37		25.0	500.0	41
D8PRL	48.52	69.84	15.57	.72	3.51	.37		1.2	398.4	41
D15PRL	25.03	31.97	10.96	.72	2.89	.37		1.7	172.9	41
D22PRL	22.88	35.08	19.59	.72	3.94	.37		.0	208.0	41
D29PRL	20.26	36.27	24.31	.72	4.53	.37		.1	221.2	41
D43PRL	34.36	45.58	10.44	.74	2.76	.38		.2	241.3	39
EDCN: 4 = 2.0 MG/WEEK										
D1PRL	70.99	38.60	2.67	.72	1.67	.37		26.2	200.0	42
D8PRL	18.20	15.11	-.53	.72	.84	.37		.8	52.0	42
D15PRL	10.37	10.16	3.16	.72	1.63	.37		.5	43.5	42
D22PRL	9.25	11.61	10.62	.72	2.85	.37		.4	63.0	42
D29PRL	8.34	12.22	18.77	.72	3.89	.37		.0	72.5	42
D43PRL	12.92	16.39	7.64	.73	2.58	.37		.7	80.0	40
EDCN: 5 = PLACEBO										
D1PRL	67.59	29.16	-.64	1.01	.47	.52		25.0	126.1	19
D8PRL	66.97	30.05	-.33	1.01	-.08	.52		7.1	125.4	19
D15PRL	67.46	30.25	-.47	1.01	.68	.52		24.3	130.3	19
D22PRL	68.75	51.00	9.15	1.01	2.79	.52		23.5	250.0	19
D29PRL	68.92	45.02	9.41	1.01	2.74	.52		24.0	230.0	19
D43PRL	76.37	54.59	4.89	1.01	1.99	.52		23.8	250.0	19

TABLE 2: CABERGOLINE VERESUS BROMOCRIPTINE: DESCRIPTIVES BY MEDICATION

MEDCN: 1 = CABERGOLINE

Variable	Mean	Std Dev	Kurtosis	S.E. Kurt	Skewness	S.E. Skew	Minimum	Maximum	N
DAY1PRL	101.99	67.45	8.76	.35	2.51	.17	30.1	498.3	193
W2PRLNG	23.52	28.80	30.47	.35	4.27	.18	1.0	274.0	191
W4PRLNG	15.14	17.36	6.44	.35	2.21	.17	.3	106.8	196
W6PRLNG	13.19	17.27	13.62	.35	3.09	.17	.1	131.5	196
W8PRLNG	12.21	16.75	15.22	.35	3.23	.17	.1	131.5	196
W12PRLNG	11.22	16.24	20.51	.35	3.81	.17	.1	134.2	193
W14PRLNG	10.86	15.77	24.45	.36	4.05	.18	.0	137.0	178
W16PRLNG	9.56	14.07	19.58	.35	3.76	.18	.1	115.1	191
W20PRLNG	9.23	13.26	20.96	.35	3.77	.17	.1	112.3	194
W24PRLNG	10.21	15.67	19.47	.35	3.80	.18	.0	117.8	189
MEDCN:	2 =	BROMOCRIPTINE							
DAY1PRL	103.54	88.85	18.94	.36	3.57	.18	23.5	767.3	184
W2PRLNG	26.24	33.42	12.81	.36	3.11	.18	.8	233.0	182
W4PRLNG	23.45	30.22	9.11	.36	2.75	.18	.2	185.3	184
W6PRLNG	21.93	28.53	10.29	.35	2.77	.18	.2	199.0	187
W8PRLNG	23.18	29.60	13.27	.35	2.91	.18	.0	230.0	189
W12PRLNG	20.71	26.13	9.64	.36	2.67	.18	.6	178.0	183
W14PRLNG	19.32	24.23	14.63	.38	3.24	.19	.0	176.0	165
W16PRLNG	25.04	42.62	32.69	.36	4.97	.18	.1	375.7	182
W20PRLNG	20.83	27.52	11.12	.36	2.94	.18	.0	180.0	178
W24PRLNG	22.42	34.39	21.43	.37	4.00	.19	.0	272.0	168

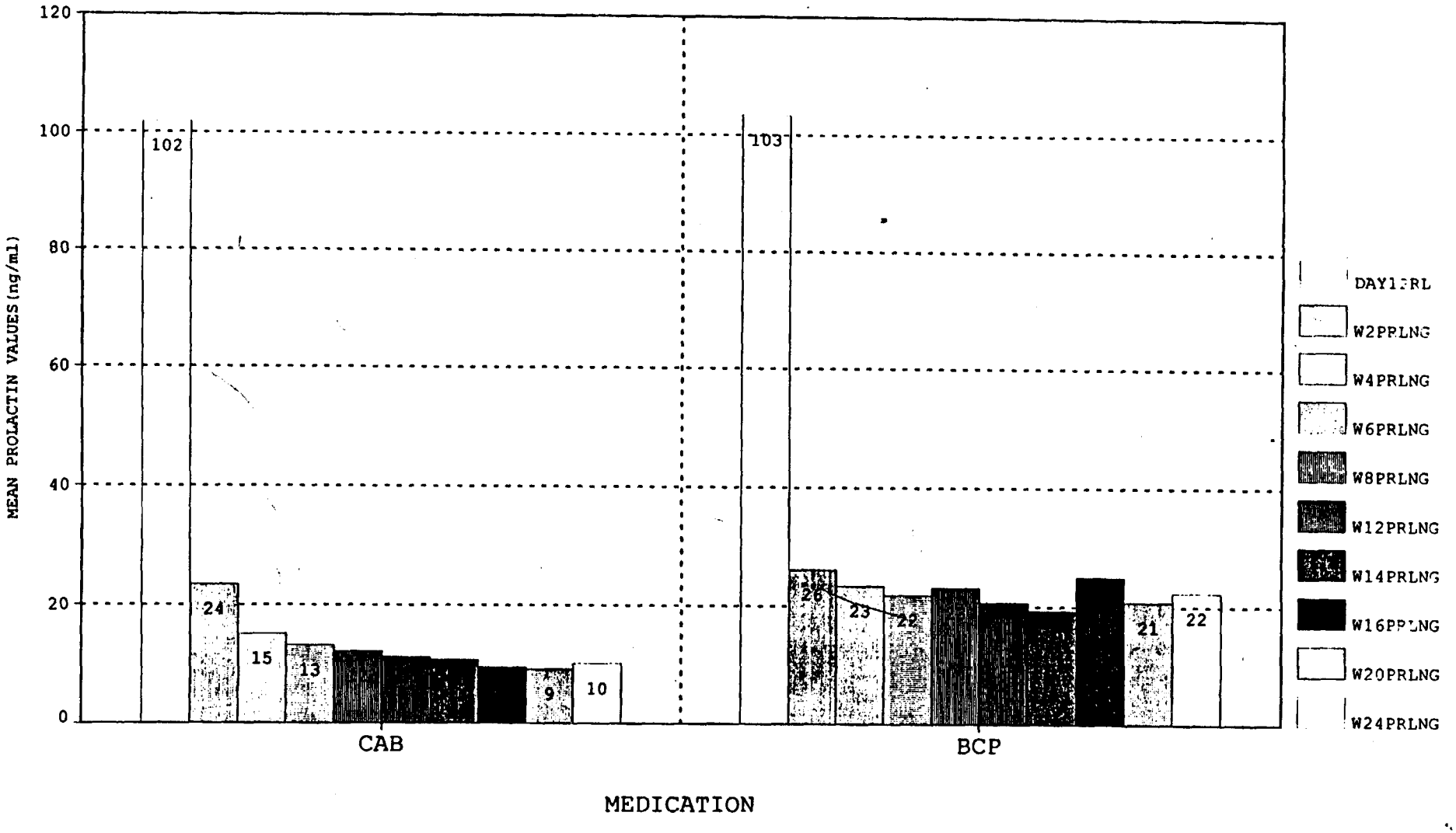
FIGURE I: DOSTINEX VS PLACEBO --- DOSE EFFICACIES



N.B. 1. Chart Represents Subjects with Almost Complete Data

N.B. 2. The 1.5 mg/wk Arm Has a Couple of Outliers

FIGURE II: EFFICACIES OF DOSTINEX AND BROMOCRIPTINE



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020664

PHARMACOLOGY REVIEWS

NOV 14 1996

NDA 20-664 13 Nov 1996

Pharmacia, Inc.
P.O. Box 16529
Columbus, OH 43216

Submission: 31 Oct 96; Rec'd. 4 Nov 96

Pharmacology Recommendations for Labeling Changes
Revised Package Insert

Dostinex (Cabergoline) [FCE 21336]

Long-acting dopamine (D_2) receptor agonist with antiprolactin activity.

Indicated Use: Treatment of hyperprolactinemic disorders, either idiopathic or due to pituitary adenomas.

Dosage and Administration: —

Labeling: Precautions section.
Labeling needs revision.

Multiples of the human dose should be based on a 50 kg human rather than a 60 kg human. For consistency in labeling, multiples of the human dose were calculated on the basis of body surface area (mg/m^2) rather than on the basis of AUC. (Conversion factors were those supplied by the sponsor, presumably based on the weights of their animals.)
Double spacing after each sentence is for clarity only and not necessary for labeling.

Delete lines 142 through 156 and replaced with the following:

Delete lines 175 through 178 and replace with the following:

Delete lines 181 through 209 and replace with the following:

Cabergoline has been reported to reduce plasma progesterone concentrations below that necessary to maintain pregnancy in dogs, resulting in termination of pregnancy at a dose of 0.002 mg/kg/day subcutaneously for 5 days. In cats, pregnancy has been terminated at a dose of 0.005 to 0.015 mg/kg/day in the diet.

David H. Hertig
Pharmacologist

R W Steigerwalt 11/14/96

HEDINI

NDA 20-664

19 Sep 1996

Pharmacia, Inc.
P.O. Box 16529
Columbus, OH 43216

Submission: 21 Aug 96

Pharmacology Recommendations for Labeling Changes
Package Insert

Dostinex (Cabergoline) [FCE 21336]

Long-acting dopamine (D_2) receptor agonist with antiprolactin activity.

Indicated Use: Treatment of hyperprolactinemic disorders, either idiopathic or due to pituitary adenomas.

Dosage and Administration:

Labeling: Precautions section.
Labeling needs revision.

1) Multiples of the recommended dose for humans appear to be based on mg/kg. When plasma drug levels are available, maximum human exposure should be expressed in terms of multiples of the AUC observed in preclinical studies. In the absence of plasma drug levels, drug exposure comparisons between preclinical and clinical doses should be based on surface area (mg/m^2) rather than on mg/kg. The method of comparison should be stated.
   [Please provide calculations, but do not include in labeling. - Freireich, E. J., et al., Cancer Chemother. Repts. 50 (4):219-244, 1966 may be used as a reference to determine calculations.]

2) Since the clinical dose is in mg, preclinical doses should be expressed in mg/kg not µg/kg.

3) The heading for the Pregnancy section should be changed to read:

4) The sentence,

should be corrected to mg/kg and to the proper multiple of the maximum human dose and moved from the Pregnancy section to the last sentence in the Carcinogenesis, Mutagenesis, Impairment of Fertility section.

5) The species should be included in the following sentence:

This sentence should be corrected as stated above and moved to a position after that of the rat and rabbit teratology findings.

6) The sentence,

found in the Pregnancy section should be changed to read: Cabergoline has been reported to reduce plasma progesterone concentrations below that necessary to maintain pregnancy resulting in termination of pregnancy ~~in dogs~~ at a dose of .002 mg/kg/day s.c. for 5 days. Pregnancy has been terminated in cats given .005 to .015 mg/kg/day in the diet. [If the multiple of the maximum human dose is determinable, it should be included.]

7) Also in the Pregnancy section the word in the following sentence should be changed to

8) The rat and rabbit teratology section should be changed to read as follows:

David H. Hertig
Pharmacologist

Ronald W. Stiegwart
7/19/96