COMMONWEALTH of AUSTRALIA

APPLICATION FOR A STANDARD PATENT

X

SANDOZ LTD. of
35 Lichtstrasse,
CH-4002 Basle,
Switzerland.

We hereby apply for the grant of a Standard Patent for an invention entitled:

"IMPROVEMENTS IN OR RELATING TO ORGANIC COMPOUNDS"

which is described in the accompanying specification.

Details of basic application(s):

<table>
<thead>
<tr>
<th>Number</th>
<th>Convention Country</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>8405227</td>
<td>Great Britain</td>
<td>29 February, 1984</td>
</tr>
</tbody>
</table>

The address for service is care of DAVIES & COLLISON, Patent Attorneys, of 1 Little Collins Street, Melbourne, in the State of Victoria, Commonwealth of Australia.

Dated this 26 day of February, 1985

APPLICATION ACCEPTED AND AMENDMENTS

To: THE COMMISSIONER OF PATENTS

(a member of the firm of DAVIES & COLLISON for and on behalf of the Applicant).

Davies & Collison, Melbourne and Canberra.
COMMONWEALTH OF AUSTRALIA
PATENTS ACT 1952

DECLARATION IN SUPPORT OF CONVENTION OR NON-CONVENTION APPLICATION FOR A PATENT

In support of the Application made for a patent for an invention

entitled: BROMOCRIPTINE COMPOSITIONS

We JEAN KRAMER and HANS RUDOLF HAUS, both of
Sandoz Ltd., 35 Lichtstrasse, CH-4002 Basle, Switzerland

do solemnly and sincerely declare as follows:

1. (a) We are the applicant(s) for the patent

or (b) We are authorized by SANDOZ LTD.

the applicant.............. for the patent to make this declaration on its behalf.

2. (a) Othmar Züger, Heuwinkel 13, CH-4123 Allschwil, Switzerland

Norman Mazer, Im Lee 31, CH-4144 Arlesheim, Switzerland

are the actual inventor(s) of the invention and the facts upon which the applicant.............. is entitled to make the application are as follows:

3. The basic application.............. as defined by Section 141 of the Act was made

in ..........Great Britain.............. on the February 29, 1984

by ........SANDOZ LTD..............

in ..........on the

by ..........on the

by ..........on the

4. The basic application.............. referred to in paragraph 3 of this Declaration was

the first application.............. made in a Convention country in respect of the invention the subject of the application.

Declared at Basle this 5th day of February 1985

SANDOZ LTD.

DAVIES COLLISON, MELBOURNE and CANBERRA, Officer

Signature of declarant(s) (no attestation required)

Note: Initial all alterations.
(54) Title
SUSTAINED RELEASE BROMOCRIPTINE COMPOSITIONS

(51) International Patent Classification(s)
A61K 031/48

(21) Application No. : 39136/85
(22) Application Date : 28.02.85

(30) Priority Data
(31) Number (32) Date (33) Country
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(45) Publication Date of Accepted Application : 20.07.89

(71) Applicant(s)
SANDOZ LTD.

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(74) Attorney or Agent
DAVIES COLLISON, MELBOURNE

(56) Prior Art Documents
US 3752814
US 3752888

(57) Claim
1. A controlled release formulation for oral administration comprising
   bromocriptine
   a pharmaceutically acceptable cellulose hydrocolloid
   a pharmaceutically acceptable inert fatty acid ester and wherein the weight ratio of bromocriptine to
   the hydrocolloid is from 1:10 to 1:50 and the weight ratio of bromocriptine to the ester is from 1:1 to
   1:10.

21. A controlled release formulation comprising a granulate of bromocriptine embedded in a fatty acid
   ester, with particles of cellulose hydrocolloid surrounding the outer surface of the granulate.
Complete specification for the invention entitled:

"IMPROVEMENTS IN OR RELATING TO ORGANIC COMPOUNDS"

The following statement is a full description of this invention, including the best method of performing it known to us:

-1-
This invention relates to pharmaceutical compositions, containing bromocriptine.

Bromocriptine is the generic name for the compound 2-bromo-12'-hydroxy-2'-/1-methylethyl)-5'α-(2-methylpropyl)ergotamin-3',6'-tri-one and is listed in the Merck Index, 1976, Appendix A 2.

Bromocriptine is a well-known dopamine agonist used in the treatment of e.g. hyperprolactinemia, acromegaly and Parkinson's disease. It is usually administered in the form of the mesylate in daily dosages of e.g. 5-7.5 mg, 10-60 mg and 20-80 mg respectively. Its pharmacological and clinical properties have been recently extensively reviewed in M.O. Thorner et al.: Bromocriptine A clinical and pharmacological review, Raven Press, New York 1980. However the pharmacokinetic profile was not been established conclusively. From extensive pharmacokinetic studies we have found that bromocriptine is rapidly absorbed and rapidly eliminated from plasma after oral administration (t 1/2 = 3 to 5 hours). Although its duration of action appears to extend well beyond t 1/2 in some applications (e.g. hypoprolactinaemia effect), we have found that it is generally necessary to administer the daily doses in 2 to 4 small doses to achieve a lasting therapy and to decrease potential unwanted side effects, which are thought to be related to the rapid absorption of the drug. Some of these side effects are due to dopaminergic activity of the compound acting on dopaminergic receptors in the gastro-intestinal tract, e.g. nausea and emesis.
There exists thus a need for a controlled release formulation of bromocriptine which provides a prolonged action of bromocriptine to reduce the number of times bromocriptine has to be administered each day and to reduce certain adverse reactions.

According to the present invention there is provided a controlled release formulation for oral administration comprising:

(a) bromocriptine;
(b) a pharmaceutically acceptable cellulose hydrocolloid; and
(c) a pharmaceutically acceptable inert fatty acid ester;

and wherein the weight ratio of bromocriptine to the hydrocolloid is from 1:10 to 1:50 and the weight ratio of bromocriptine to the ester is from 1:1 to 1:10.

The preferred amounts of bromocriptine in the unit dosage form are from 2 to 20 mg, especially 5 to 10 mg. The bromocriptine may be in free base form or in the form of a pharmaceutically acceptable acid addition salt. Preferably the bromocriptine is in mesylate salt form. Reference herein to bromocriptine is intended both the free base form and such salt forms.

Hydrophilic swelling substances that can be used include one or more natural, partially or totally synthetic anionic or, preferably, nonionic hydrophilic gums, modified cellulosic substances or proteinaceous substances such as, for example, acacia, gum tragacanth, locust bean gum, guar gum,
karaya gum, agar, pectin, carrageen, soluble and insoluble alginates, methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, sodiumcarboxymethylcellulose, carboxypolymethylene, gelatin.

Preferred are cellulose hydrocolloids which include methyl cellulose, hydroxypropylcellulose and especially hydroxypropylmethylcellulose and sodium carboxymethylcellulose. Preferably the weight ratio of bromocriptine to the hydrophilic swelling substance is from 1:10 to 1:50, more preferably 1:10 to 1:35, and especially from 1:16 to 1:25.

The weight ratios refer to the amount of active substance bromocriptine, not the total weight of any salt.
Usable pharmaceutically acceptable inert fatty materials include beeswax; fatty acids; long chain fatty alcohols such as, for example, cetyl alcohol, myristyl alcohol, stearyl alcohol, glycerides such as glyceryl esters of fatty acids or hydrogenated aliphatic acids such as, for example, glyceryl monostearate, glyceryl distearate, glyceryl esters of hydrogenated castor oil and the like; oils such as mineral oil and the like. Fatty materials are preferably such with melting points between 30 and 90°C.

Most preferred fatty materials have a melting point from 45°C to 65°C and include glycerides such as glyceryl palmitates and stearates and fatty acids such as hydrogenated castor oil and fatty acid esters such as cetyl palmitate. Preferably the weight ratio of bromocriptine to the fatty material is from 1:1 to 1:10, especially from 1:6 to 1:10.

It is also convenient to incorporate in the formulation other soluble or insoluble pharmaceutical excipients such as calcium sulfate, calcium phosphate, lactose and colloidal silica. The weight ratio of bromocriptine to these other excipients is conveniently from 1:5 to 1:40, e.g. 1:15 to 1:40.

The formulation may be produced in conventional manner by mixing the ingredients together, if desired melting the fatty material. The resultant mixture is in powder form. The powder can be pressed to form a tablet, but is preferably filled into a capsule.
We have surprisingly found that the formulations possess an excellent stability, despite the fact that bromocriptine is sensitive to many chemical reagents. Moreover, the formulations have a satisfactory pharmacodynamic and pharmacokinetic profile.

The resultant retarded formulations in general have comparable bioavailability in standard clinical trials to conventional non-retarded formulations containing the same amount of bromocriptine. The formulations of the invention, even if administered once a day, can still produce a therapeutic effect for at least 24 hours and even as much as 35 hours. The formulation may thus be administered only once a day in the known indications of bromocriptine at approximately the same daily doses as employed in the conventional non-retarded forms.

Preferred formulations are such, which show in in vitro release experiments a release rate of bromocriptine of less than 50% in 2.5 hours, preferably a release rate of less than 65% in 8 hours, as measured in 0.1 n HCl solution. Most preferably, the formulation will release at least 80% of the active ingredient within 24 hours.
In the following examples all temperatures are in degrees Centigrade and are uncorrected.

Further information on the properties etc. of the pharmaceutical excipients named hereinafter may be obtained from the manufacturer, listed hereinafter, manufacturer's brochures or other sources, especially H.P. Fiedler Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete, 2nd Edition 1981, Edito Cantor Aulendorf, W. Germany.

Silica is e.g. brand Aerosil 200 available from Deutsche-Gold und Silberscheidanstalt, Frankfurt, W. Germany.

Glycerol ditripalmitostearate is e.g. brand Precirol Ato 5 available from ETS Gattefosse 929100 Boulogne-Brillancourt, France.

Hydroxypropylmethylcellulose 15000 cps and 4000 cps are e.g. brands Methocel K15M and Methocel E4M available from Dow Chemical Company, Michigan 48640 USA.

Cetyl palmitate is e.g. brand Cutina CP available from Henkel 4000, Düsseldorf, W. Germany.
EXAMPLE 1:  Composition of each capsule

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Bromocriptine mesylate</td>
<td>5.735 *)</td>
</tr>
<tr>
<td>2) Lactose (200 mesh)</td>
<td>124.265</td>
</tr>
<tr>
<td>3) Silica</td>
<td>10</td>
</tr>
<tr>
<td>4) Glycerol ditriplamitostearate</td>
<td>40</td>
</tr>
<tr>
<td>5) Hydroxypropylmethylocellulose</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>290</td>
</tr>
<tr>
<td>Capsule (Hard gelatine)</td>
<td>78</td>
</tr>
</tbody>
</table>

*) equivalent to 5 mg bromocriptine base

Preparation (Charge of 6000 capsules)

Ingredients 1), 2) and 3) are sieved and mixed. Ingredient 4) is melted by heating to 56°C (m.p. 54°C) and is added to the mixture which is heated to 55°C. The mass is stirred for 2 minutes or until it is a homogenous mixture and cooled overnight. The crushed mass is broken up and sieved (through 250 micron openings). Ingredient 5) is sieved (through 360 micron openings) and mixed in over 10 minutes. The mixture is then encapsulated.
**In vitro release**

Gastric juice 0.1 n HCl (pH 1.2)

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Release of bromocriptine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7 %</td>
</tr>
<tr>
<td>2</td>
<td>13 %</td>
</tr>
<tr>
<td>4</td>
<td>28 %</td>
</tr>
<tr>
<td>6</td>
<td>42 %</td>
</tr>
<tr>
<td>24</td>
<td>100 %</td>
</tr>
</tbody>
</table>

**EXAMPLE 2: Composition of each capsule**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Bromocriptine mesylate</td>
<td>5.735 *</td>
</tr>
<tr>
<td>2) Calcium sulfate . 2H2O</td>
<td>124.265</td>
</tr>
<tr>
<td>3) Cetyl palmitate</td>
<td>20.0</td>
</tr>
<tr>
<td>4) Hydroxypropylmethylcellulose (15000 cps)</td>
<td>120.0</td>
</tr>
<tr>
<td></td>
<td>270.0</td>
</tr>
<tr>
<td>Capsule (hard gelatine)</td>
<td>78.0</td>
</tr>
</tbody>
</table>

*) equivalent to 5 mg bromocriptine base
Preparation

Analogous to Example 1, with the difference, that now ingredients 1) and 2) are mixed, followed by addition of ingredient 3) in molten form, after which the mixture is cooled and ingredient 4) is added.

EXAMPLE 3: Composition of each capsule

<table>
<thead>
<tr>
<th>Ingredient</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Bromocriptine mesylate</td>
<td>11.47</td>
</tr>
<tr>
<td>2) Maleic acid</td>
<td>4.00</td>
</tr>
<tr>
<td>3) Lactose</td>
<td>78.53</td>
</tr>
<tr>
<td>4) Silica</td>
<td>10.00</td>
</tr>
<tr>
<td>5) Cetyl palmitate</td>
<td>40.00</td>
</tr>
<tr>
<td>6) Hydroxypropylmethylcellulose (15.000 cps)</td>
<td>130.00</td>
</tr>
<tr>
<td></td>
<td>274.00</td>
</tr>
<tr>
<td>15) Capsule (hard gelatine)</td>
<td>81.00</td>
</tr>
<tr>
<td></td>
<td>355.00</td>
</tr>
</tbody>
</table>

3*) corresponding to 10 mg bromocriptine base

Preparation

Analogous to Example 1, with the difference that now ingredients 1), 2), 3) and 4) are mixed, followed by addition of ingredient 5) in molten form, after which the mixture is cooled and ingredient 6) is added.
Comparative clinical tests

Objectives: To study in healthy volunteers the tolerability, bioavailability and the prolactine suppression effects of two oral controlled release capsules A and B according to the invention in comparison to a conventional capsule C and a placebo capsule D.

A. Composition according to the invention

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Bromocriptine in mesylate form</td>
<td>5.735</td>
</tr>
<tr>
<td>2. Lactose</td>
<td>184.265</td>
</tr>
<tr>
<td>3. Glycerol-ditripalmito stearate</td>
<td>20.000</td>
</tr>
<tr>
<td>4. Hydroxypropylmethylcellulose (4000 cps)</td>
<td>60.000</td>
</tr>
</tbody>
</table>

*) corresponding to 5 mg bromocriptine

The fatty component A3. was added in molten form to a mixture of components A1. and A2. and mixed therewith after which the mixture was cooled to room temperature and component A4. was mixed with the mixture of A1., A2. and A3.

B. Composition according to the invention

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Bromocriptine in mesylate form</td>
<td>5.735</td>
</tr>
<tr>
<td>2. Lactose</td>
<td>124.265</td>
</tr>
<tr>
<td>3. Silica</td>
<td>10.000</td>
</tr>
</tbody>
</table>
4. Glycerol-ditripalmito stearate 40.000
5. Hydroxypropylmethylcellulose (4000 cps) 110.000

The mixture was prepared analogous to the mixture under A, with the exception that instead of mixing A1. and A2., B1., B2. and B3. were mixed.

C. Conventional composition

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>mg</th>
</tr>
</thead>
</table>
| 1. Bromocriptine in mesylate form        | 2.87 | *)
| 2. Maleic acid, milled                   | 2.00 |
| 3. Lactose                               | 170.63|
| 4. Cornstarch                            | 120.00|
| 5. Silica                                | 1.50 |
| 6. Magnesium stearate                    | 3.00 |

*) corresponding to 2.5 mg bromocriptine

The ingredients 1 to 6 were mixed together

D) Conventional placebo composition

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lactose</td>
<td>190.00</td>
</tr>
<tr>
<td>2. Glycerol ditripalmito stearate</td>
<td>20.00</td>
</tr>
<tr>
<td>3. Hydroxypropylmethylcellulose (4000 cps)</td>
<td>60.00</td>
</tr>
</tbody>
</table>
The fatty component D2 was added in molten form to component D1 and mixed therewith, after which the mixture was cooled to room temperature and mixed with component D3.

Instead of 5 mg bromocriptine, as present in capsule A and B, the non-retarded capsule C contained only 2.5 mg bromocriptine to avoid a too strong influence on the healthy volunteers by expected side effects.

In a randomized double-blind design 8 healthy male volunteers received at 8.00 h in the morning either one capsule A, B, C or D in such a manner that each volunteer received the 4 different capsule types, divided over 4 administration days, separated by an interval of a week.

Prolactin inhibition

Blood samples were obtained from the 8 volunteers by an indwelling cannula, in certain time intervals from 8.00 h, the time the capsule was received, till 10.00 h on the third day (totally 50 hours), with a longer interruption from 18.00 till 8.00 h in the second night. The prolactin levels were determined by a specific radioimmunoassay.

The prolactin concentrations, measured after the administration of capsules A, B and C were plotted graphically as corresponding mean curves A (fig.1), B (fig.2) and C (fig.3).

The prolactin concentrations, determined after the administration of capsule D, were depicted as curve D in fig. 1, 2 and 3, which was compared with curves A, B and C (in nanograms/ml, time t in hours).
The prolactin curve D represents the normal prolactin concentration of healthy volunteers during night and day.

In the evening, the concentration rises, during sleep the maximum is reached and in the first wakening hours the concentration falls to a day-time "basal level" which is mantained to about 20.00 h. From curves A and B a prolactin secretion inhibition is observed 1 hour after taking the corresponding capsules A and B and lasting 35 hours.

Capsule C produces a prolactin inhibition in healthy volunteers, 1 hour after taking a capsule C and lasting only 24 hours.

Pharmacokinetics

Parallel to the prolactin concentrations, bromocriptine concentrations were measured in the blood samples obtained up till 24 hours after administration of the capsules.

The bromocriptine concentrations in the blood were plotted as mean curves A, B and C in fig. 4 (in picograms/ml, time t in hours).

The concentrations of curve C in fig. 4, caused by the 2.5 mg bromocriptine containing capsule C were doubled and plotted in fig. 5 as a curve C adapted to a double portion of capsule C, together with curves A and B, so that bromocriptine levels of equal dosages of bromocriptine (5 mg) can be compared.

From fig. 5 it is seen that the rate at which drug concentrations initially rise (i.e. absorption phase) is slightly reduced for form A and markedly reduced for form B as compared with twice form C.
It also appears from these mean curves, that the bioavailabilities (AUC*) of capsules A and B are somewhat lower than of two capsules C.

Based on the individual subjects data, the reduction in bioavailability was an average of 12% for form A and 25% for form B.

**Tolerability**

The side effects experienced by each volunteer were recorded as to type, duration and intensity (strong, moderate and weak). Overall, the following side effects were noted:

1) orthostatic hypotonia  
2) dizziness  
3) vomiting  
4) nausea  
5) nasal congestion  
6) dry mouth  
8) head pressure  
9) drowsiness  
10) tiredness  
11) weakness  
12) sweating  
13) heat sensation  
14) abdominal cramps  
15) palor

Side effects 1) to 6) are well known for dopamine agonist drugs like Bromocriptine and were used to assess the relative tolerability of the formulations in the table below:

*Area under the curve*
<table>
<thead>
<tr>
<th>Intensity</th>
<th>A (5 mg drug)</th>
<th>B (5 mg drug)</th>
<th>C (2.5 mg drug)</th>
<th>D (placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>strong</td>
<td>10</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>moderate</td>
<td>16</td>
<td>9</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>weak</td>
<td>12</td>
<td>5</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>total</td>
<td>38</td>
<td>19</td>
<td>13</td>
<td>4</td>
</tr>
</tbody>
</table>

Capsule A produced significantly more drug related side effects than all other forms.

Capsule B produced fewer drug related side effects than A, and the total number was not statistically different from the 2.5 mg conventional form C.

Capsule C produced significantly more drug related side effects than placebo D.

On the basis of tolerability, Capsule B is to be preferred over capsule A.
In in vitro experiments (USP XXI, page 1243-1244, Apparatus 1, 1000 ml 0.1 n HCl, 100 rotations per min.) the following release results were obtained with capsules A, B and C:

<table>
<thead>
<tr>
<th>Release time in hours</th>
<th>Release of bromocriptine (in percents of weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Capsule A</td>
</tr>
<tr>
<td>0.5</td>
<td>13</td>
</tr>
<tr>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
<td>81</td>
</tr>
<tr>
<td>8</td>
<td>89</td>
</tr>
<tr>
<td>10</td>
<td>94</td>
</tr>
<tr>
<td>14</td>
<td>98</td>
</tr>
<tr>
<td>24</td>
<td>100</td>
</tr>
</tbody>
</table>

From the viewpoint of pharmacokinetics capsules A and B are preferred and capsule B is especially preferred.

Summary:

- A daily dosage of two capsules of C, if administered simultaneously, would not be tolerated in clinical practice as reported before.

- Both capsules A and B, if administered once a day surprisingly cause a satisfactory therapeutically effective bromocriptine concentration for 24 hours and a prolactin suppression for 35 hours in the blood, notwithstanding a slightly decreased bioavailability in comparison with two capsules C. Capsule B is preferably used, since it causes less side effects and its controlled absorption is better.
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A controlled release formulation for oral administration comprising
   bromocriptine
   a pharmaceutically acceptable cellulose hydrocolloid
   a pharmaceutically acceptable inert fatty acid ester and wherein the weight ratio of bromocriptine to the hydrocolloid is from 1:10 to 1:50 and the weight ratio of bromocriptine to the ester is from 1:1 to 1:10.

2. A formulation according to claim 1 containing 2 to 20mg of bromocriptine per unit dosage form.

3. A formulation according to claim 2 containing 5mg bromocriptine.

4. A formulation according to claim 2 containing 10mg bromocriptine.

5. A formulation according to any of the preceding claims wherein the cellulose hydrocolloid is hydroxypropylmethylcellulose.

6. A formulation according to any of the preceding claims wherein the weight ratio of bromocriptine to the cellulose hydrocolloid is from 1:10 to 1:35.

7. A formulation according to any one of the preceding claims wherein the weight ratio of bromocriptine to the cellulose hydrocolloid is from 1:16 to 1:25.
8. A formulation according to any one of the preceding claims wherein the fatty acid ester is a hydrophobic material with a melting point between 30 and 90°C.

9. A formulation according to any one of the preceding claims wherein the fatty acid ester has a melting point from 45 to 65°C.

10. A formulation according to any one of the preceding claims wherein the fatty acid ester is a glyceride.

11. A formulation according to claim 11 wherein the glyceride is glycerol ditripalmitostearate.

12. A formulation according to any one of the preceding claims wherein the weight ratio of bromocriptine to the fatty acid ester is from 1:1 to 1:10.

13. A formulation according to claim 12 wherein the weight ratio is from 1:6 to 1:10.

14. A formulation according to any one of the preceding claims containing hydroxypropylmethylcellulose as a cellulose hydrocolloid and glycerol ditripalmitostearate as a fatty material.

15. A formulation according to claim 14, containing bromocriptine, hydroxypropylmethylcellulose and glycerol ditripalmitostearate in a weight ratio of about 1:22:8 or 1:12:4.
16. A method for the preparation of a controlled release formulation for oral administration, which comprises mixing bromocriptine, cellulose hydrocolloid and a fatty acid ester.

17. A method for treating or preventing hyperprolactinemia, acromegaly, or Parkinson's disease, which comprises administering a therapeutically effective amount of a controlled release formulation according to claim 1 to a subject in need of such treatment.

18. A formulation according to claim 1 for use in the treatment or prevention of hyperprolactinemia, acromegaly or Parkinson's disease in unit dosage form, containing 2 to 20 mg of bromocriptine.

19. A formulation according to claim 1 substantially as hereinbefore described with reference to any one of the Examples.

20. A controlled release formulation of bromocriptine according to claim 1, releasing less than 50 percent by weight of bromocriptine within 2.5 hours as measured in 0.1 n HCl in-vitro release experiments.

21. A controlled release formulation comprising a granulate of bromocriptine embedded in a fatty acid ester, with particles of cellulose hydrocolloid surrounding the outer surface of the granulate.

22. A controlled release formulation according to claim 21 in which the granulate has been obtained
by melting the fatty acid ester, mixing the 
bromocriptine with the molten fat, solidifying the 
liquid mixture and reducing the solidified mixture to 
granulate particles.

DATED this 18th day of May, 1989
SANDOZ LTD.
by its Patent Attorneys
DAVIES & COLLISON