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(54) PREPARATIONS PHARMACEUTIQUES A LIBERATION CONTROLEE CONTENANT UN INHIBITEUR DE L’ENZYME DE CONVERSION DE L’ANGIOTENSINE COMME PRINCIPE ACTIF

(54) CONTROLLED RELEASE PHARMACEUTICAL PREPARATION WITH ACE INHIBITOR AS ACTIVE AGENT

(57) L’invention concerne une préparation pharmaceutique à libération contrôlée contenant les constituants suivants ou constituée de ceux-ci: (i) une dose initiale de principe actif, contenant, outre des additifs facultatifs, le principe actif, (ii) un premier type de granulés à libération contrôlée, dans lequel le principe actif ainsi que les additifs facultatifs sont enrobés d’un revêtement, et (iii) une deuxième type de granulés à libération contrôlée, dans lequel le principe actif ainsi que les additifs facultatifs sont de nouveau enrobés d’un revêtement. Le principe actif est constitué par un inhibiteur de l’enzyme de conversion de l’angiotensine, et les masses des revêtements selon (ii) et (iii) se situent dans des rapports en poids compris entre 1:2 et 1:7.

(57) The invention relates to a pharmaceutical preparation containing or consisting of the following components: (i) an initial dose of active agent containing the active agent and optional auxiliary agents (ii) a first type of controlled release pellet in which the active agent and the optional auxiliary agents are coated, and (iii) a second type of controlled release pellet in which the active agent and optional auxiliary agents are also coated. The active agent is an ACE inhibitor and the weight ratio of the masses of the coatings in (ii) and (iii) is between 1:2 and 1:7.
Title: CONTROLLED RELEASE PHARMACEUTICAL PREPARATION WITH ACE INHIBITOR AS ACTIVE AGENT

Abstract

The invention relates to a pharmaceutical preparation containing or consisting of the following components: (i) an initial dose of active agent containing the active agent and optional auxiliary agents (ii) a first type of controlled release pellet in which the active agent and the optional auxiliary agents are coated, and (iii) a second type of controlled release pellet in which the active agent and optional auxiliary agents are also coated. The active agent is an ACE inhibitor and the weight ratio of the masses of the coatings in (ii) and (iii) is between 1:2 and 1:7.

Zusammenfassung

Die Erfindung betrifft eine pharmazeutische Zubereitung, die folgende Komponenten umfasst oder aus ihnen besteht: (i) eine Wirkstoff-Initialdosis, die durch den Wirkstoff neben fakultativen Hilfsstoffen vorgesehen wird, (ii) eine erste verzögert freisetzung Art Pellets, bei denen der Wirkstoff sowie fakultative Hilfsstoffe von einer Beschichtung umhüllt sind, und (iii) eine zweite verzögert freisetzende Art Pellets, bei denen der Wirkstoff und fakultative Hilfsstoffe wiederum von einer Beschichtung umhüllt sind, wobei der Wirkstoff ein ACE-Hemmer ist und wobei die Massen der Beschichtungen gemäß (ii) und (iii) auf Gewichtsbasis im Verhältnisbereich von 1:2 bis 1:7 vorliegen.
Our ref.: 9369
New international patent application
Hexal AG
Fischer & Klokkers & Oppelt; Preparation comprising an ACE inhibitor

Controlled-release pharmaceutical preparation comprising an ACE inhibitor as active ingredient

The present invention relates to a pharmaceutical preparation with which it is possible to achieve improved release of active ingredient as a function of time and of the pH value of the surroundings. The invention relates especially to such a preparation comprising an ACE (angiotensin converting enzyme) inhibitor as active ingredient, especially comprising captopril.

Slow-release pharmaceutical dosage forms for the controlled and delayed release of captopril are known. For example, US-A-5 158 777 describes a composition in which a portion of the active ingredient (captopril) is released immediately and a second portion is released in a delayed manner. That is achieved, according to Example 2, by the provision of two different types of pellet, of which one type of pellet, containing active ingredient, is uncoated, while the other type, containing active ingredient, has a core comprising, inter alia, captopril and ascorbic acid, the core being coated with a methacrylic acid polymer (Eudragit RS) which causes the active ingredient to be released in a delayed manner.
Other slow-release forms of captopril include, for example, according to US-A-4 666 705 an uncoated tablet containing an acrylic acid polymer; according to US-A-5 738 850 a preparation containing captopril in combination with chitosan; and according to US-A-4 756 911 a coated tablet comprising a core containing, for example, captopril as active ingredient (column 4, line 57), one or more water-soluble or water-swellable primary hydrocolloidal swelling agents containing methoxy groups, one or more secondary hydrocolloidal swelling agents, one or more non-swellable binders and/or waxes, and one or more lubricants.

It has been found, however, that the prior art is in need of improvement in that the active ingredient is released prematurely according to the prior art and thus leads to a therapeutic plasma level that has too short a duration. In addition, in some slow-release forms the coatings may not have dissolved sufficiently to release the active ingredient when the tablet has reached the intestine so that the active ingredient is excreted before it is absorbed from the stomach/intestinal tract, since no further absorption takes place in the large intestine.

Investigations underlying the invention have shown that although formulations according to the prior art exhibit retarding effects *in vitro*, it is not possible *in vivo* to obtain a constant and therapeutically effective blood level concentration over a prolonged period, or to achieve prolonged ACE inhibition.

The problem underlying the invention is to provide a pharmaceutical preparation, especially a preparation comprising an ACE inhibitor as active ingredient, for example comprising captopril, that permits controlled release of the active ingredient, especially in the case of a single dose, and thus ensures over a prolonged period a therapeutically effective blood level with minimal variations in the blood level concentration, and that meets the requirement that the action should begin immediately and, furthermore, that permits prolonged ACE inhibition.

To that end there is provided according to the invention a pharmaceutical preparation which comprises or consists of the following components:
(i) an initial dose of active ingredient, which is provided by the active ingredient as desired in the form of a powder, granules and/or pellets, in each case together with optional excipients,

(ii) a first delayed-release type of pellet, in which the active ingredient and optional excipients are covered with a coating, and

(iii) a second delayed-release type of pellet, in which the active ingredient and optional excipients are again covered with a coating,

- wherein the active ingredient is an ACE inhibitor, and

- wherein the amounts of the coatings according to (ii) and (iii) are present in a ratio, based on weight, within the range of from 1:2 to 1:7.

With the preparation according to the invention it has been found, with captopril as active ingredient, that blood level concentrations with extremely small variations can be established in vivo and, moreover, that the action of the medicament begins almost immediately. Surprisingly, the active ingredient is released from the preparation according to the invention in such a manner that pronounced blood level peaks at the beginning are avoided and yet therapeutically effective blood concentrations are maintained over a long period of time. Above all it has been found, surprisingly, that ACE inhibition of above average duration can be achieved.

In the preparation according to the invention, the amounts of the coatings according to (ii) and (iii) may be present in a ratio, based on weight, of approximately 1:5.

The active ingredient is, therefore, an ACE (angiotensin converting enzyme) inhibitor, especially captopril, moexipril, perindopril, quinapril, ramipril, spirapril, tandolapril, mixtures thereof and/or their pharmaceutically acceptable salts, for example hydrochlorides, for example perindopril erbumin.
The active ingredient content of the initial dose may be from 5 to 30% by weight of the total active ingredient content.

In the initial dose, the active ingredient may be in the form of a powder, granules and/or in the form of a pellet, it being possible for granules and pellets to contain customary excipients.

Pellets of the first and second delayed-release types can be obtained by providing pellets which may have been prepared for an initial dose with the respective coating.

The coating for the first and second types of delayed-release pellet may be a coating that is resistant to gastric juices, especially based on polymethacrylic acid, more especially on Eudragit S. In a preferred embodiment, the same coating material is chosen for the first and second types of delayed-release pellet.

In a preferred embodiment, the coating for the first and second types of delayed-release pellet has, apart from polymethacrylic acid, no other component of equal or greater acidity.

The coating for the first and/or second type(s) of delayed-release pellet may comprise customary film-forming agents and/or excipients, especially dibutyl phthalate, polyethylene glycol, triethyl citrate (Citroflex), ethyl cellulose (Aqua coat), titanium dioxide and/or hydroxypropylmethyl cellulose. Microcrystalline cellulose and/or lactose may come into consideration as excipients.

The ratio by weight of initial dose to first type of delayed-release pellet to second type of delayed-release pellet may be within the range of from 1:1:1 to 1:10:10 and may be especially approximately 1 : approximately 1 : approximately 2.

The preparation according to the invention can be characterised by the following proportions by weight:

initial dose: from 10 to 30% by weight,
first type of delayed-release pellet: from 20 to 40% by weight, and
second type of delayed-release pellet: from 40 to 60% by weight,

the sum of all three components being 100% by weight; it can be characterised especially by

initial dose: approximately 22.9% by weight,
first type of delayed-release pellet: approximately 25.8% by weight, and
second type of delayed-release pellet: approximately 51.3% by weight,

the sum of all three components being 100% by weight.

The preparation according to the invention may be in the form of a capsule, especially a gelatin capsule, the capsule comprising all three components. Such a capsule may comprise an amount of active ingredient required for a daily dose or for a single dose. For example, a capsule may comprise an amount of captopril required for the daily dose or single dose, especially in the range of from 25 to 300 mg, more especially from 50 to 200 mg and very especially from 75 to 150 mg.

The initial dose of captopril, based on a daily dose or a single dose, may be from 5 to 30 mg.

The active ingredient content of the pellets may be from 10 to 50%, it being possible to use customary excipients for pellet formation, such as microcrystalline cellulose and/or lactose, and it being possible for the pellets of the three components to have different active ingredient contents.

The ratio of the active ingredient contents is from 1:3:3 to 1:10:10, especially 1:2.5:4.

The invention is explained in greater detail below with reference to Examples and Figures. In the Figures
Figure 1 shows the retarding effect of a captopril capsule according to Example 1 in comparison with a rapid-release captopril tablet;

Figure 2 shows a plasma captopril level in relation to the ACE inhibition corresponding to Figure 1; and

Figure 3 shows a plasma captopril level in relation to the ACE inhibition corresponding to Example 2 and Figure 4 and

Example 1

A) Preparation

The following three types of pellet were provided for captopril slow-release capsules:

Pellet 1; the composition was as follows:

captopril 5 mg
Avicel (microcrystalline cellulose) 3 mg
Tablettose 2 mg

Pellet 2; 700 g of pellets of type 1 were first film-coated with 40.48 g of OPADRY II and 250 g of water. The solution for a second film coating had the following composition:

Eudragit S 100 62.5 g
dibutyl phthalate 6.25 g
96% ethanol 350.00 g
purified water 87.5 g

Pellet 3; 700 g of pellets of type 1 were provided with an initial film coating of 40.48 g of OPADRY II and 250 g of water. The solution for a second film coating had the following composition:
Eudragit S 100 192.5 g
dibutyl phthalate 19.25 g
96% ethanol 1078 g
purified water 269.5 g

For the preparation of captopril slow-release capsules, 100 mg of pellets of type 1, 700 mg of pellets of type 2 and 700 mg of pellets of type 3 were introduced into a gelatin capsule. This produced a total active ingredient concentration of captopril of 150 mg.

B) Pharmacokinetic and pharmacodynamic tests

Plasma levels and ACE inhibition were determined in an open cross-over study based on individual doses. The test subjects received either a capsule according to the invention comprising 150 mg of captopril or a reference product comprising 50 mg of captopril. Figure 1 shows the retarding effect of the captopril capsule according to the invention in comparison with a rapid-release captopril tablet. Figure 2 shows plasma captopril levels in relation to ACE inhibition.

Example 2

Preparation:

The following three components were provided for captopril slow-release capsules:

Component 1 (initial dose):
captopril (powder) 20 mg

Component 2 (first type of delayed-release pellet):
captopril 50 mg
microcrystalline cellulose 49.37 mg
Opadry, white, consisting of lactose H$_2$O 2.07 mg
hydroxypropylmethyl cellulose 1.61 mg
<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>titanium dioxide</td>
<td>1.49 mg</td>
</tr>
<tr>
<td>Macrogol 4000</td>
<td>0.58 mg</td>
</tr>
<tr>
<td>Eudragit S 100</td>
<td>6.13 mg</td>
</tr>
<tr>
<td>dibutyl phthalate</td>
<td>0.61 mg</td>
</tr>
</tbody>
</table>

Component 3 (second type of delayed-release pellet):

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>captopril</td>
<td>80 mg</td>
</tr>
<tr>
<td>microcrystalline cellulose</td>
<td>81.64 mg</td>
</tr>
<tr>
<td>Opadry, white, consisting of lactose H₂O</td>
<td>3.37 mg</td>
</tr>
<tr>
<td>hydroxypropylmethyl cellulose</td>
<td>2.62 mg</td>
</tr>
<tr>
<td>titanium dioxide</td>
<td>2.43 mg</td>
</tr>
<tr>
<td>Macrogol 4000</td>
<td>0.93 mg</td>
</tr>
<tr>
<td>Eudragit S 100</td>
<td>50 mg</td>
</tr>
<tr>
<td>dibutyl phthalate</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

The active ingredient concentration of captopril per capsule is 150 mg.

Example 3

The following three components were provided for captopril slow-release capsules:

Component 1 (initial dose): 50% captopril

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>captopril</td>
<td>20 mg</td>
</tr>
<tr>
<td>microcrystalline cellulose</td>
<td>20.12 mg</td>
</tr>
</tbody>
</table>

Component 2 (first type of delayed-release pellet): 50% captopril

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>captopril</td>
<td>50 mg</td>
</tr>
<tr>
<td>microcrystalline cellulose</td>
<td>49.36 mg</td>
</tr>
<tr>
<td>Opadry, white, consisting of lactose H₂O</td>
<td>2.06 mg</td>
</tr>
<tr>
<td>hydroxypropylmethyl cellulose</td>
<td>1.61 mg</td>
</tr>
<tr>
<td>titanium dioxide</td>
<td>1.50 mg</td>
</tr>
<tr>
<td>Macrogol 4000</td>
<td>0.58 mg</td>
</tr>
<tr>
<td>Eudragit S 100</td>
<td>6.14 mg</td>
</tr>
<tr>
<td>dibutyl phthalate</td>
<td>0.61 mg</td>
</tr>
</tbody>
</table>
Component 3 (second type of delayed-release pellet): 50% captopril

captopril  
80 mg
microcrystalline cellulose  
81.64 mg
Opadry, white, consisting of lactose H₂O  
3.37 mg
hydroxypropylmethyl cellulose  
2.62 mg
titanium dioxide  
2.43 mg
Macrogol 4000  
0.93 mg
Eudragit S 100  
50 mg
dibutyl phthalate  
5 mg

In this Example too, the active ingredient concentration per capsule is 150 mg of captopril.

Example 4

Composition of the captopril slow-release capsules:

Component 1 (initial dose):
captopril  
20 mg
lactose D80  
56 mg
microcrystalline cellulose  
24 mg

Component 2 (first type of delayed-release pellet):
captopril pellets 50%  
99.93 mg
Opadry  
5.78 mg
Eudragit S 100  
6.17 mg
dibutyl phthalate  
0.62 mg
water  
44.33 mg
96% ethanol  
34.54 mg

Component 3 (second type of delayed-release pellet):
captopril pellets 50%  
160.21 mg
Opadry  
9.27 mg
<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit S 100</td>
<td>49.56 mg</td>
</tr>
<tr>
<td>dibutyl phthalate</td>
<td>4.96 mg</td>
</tr>
<tr>
<td>water</td>
<td>126.61 mg</td>
</tr>
<tr>
<td>96% ethanol</td>
<td>277.56 mg</td>
</tr>
</tbody>
</table>

The total active ingredient concentration of a slow-release capsule is 150 mg of captopril.
August 5, 1999

Our ref.: 9369

New International patent application

_Fischer & Klokkers & Oppelt: Preparation comprising an ACE inhibitor_

Claims

1. Pharmaceutical preparation which comprises or consists of the following components:

   (i) an initial dose of active ingredient, which is provided by the active ingredient together with optional excipients,

   (ii) a first delayed-release type of pellet, in which the active ingredient and optional excipients are covered with a coating, and

   (iii) a second delayed-release type of pellet, in which the active ingredient and optional excipients are again covered with a coating.

   - wherein the active ingredient is an ACE inhibitor,
   - wherein the amounts of the coatings according to (ii) and (iii) are present in a ratio, based on weight, within the range of from 1:2 to 1:7, and
   - wherein the first delayed-release type of pellet and the second delayed-release type of pellet consist of the same coating material.

2. Preparation according to claim 1, characterised in that the amounts of the coatings according to (ii) and (iii) are present in a ratio, based on weight, of approximately 1:5.
3. Preparation according to claim 1 or 2, characterised by captopril, moexipril, perindopril,quinapril, ramipril, spirapril, tandolapril, mixtures thereof and/or their pharmaceutically acceptable salts, especially hydrochlorides, especially perindopril erbumin, as ACE (angiotensin converting enzyme) inhibitor.

4. Preparation according to any one of the preceding claims, characterised in that the active ingredient in the initial dose is in the form of a powder, granules and/or pellets.

5. Preparation according to any one of the preceding claims, characterised in that the pellets of the first delayed-release type and/or the pellets of the second delayed-release type have been obtained by providing the initial dose in the form of pellets with the respective coating.

6. Preparation according to any one of the preceding claims, characterised in that the coating for the first and second types of delayed-release pellet is a coating that is resistant to gastric juices, especially based on polymethacrylic acid, more especially Eudragit S.

7. Preparation according to claim 6, characterised in that the coating has, apart from polymethacrylic acid, no other component of equal or greater acidity.

8. Preparation according to any one of the preceding claims, characterised in that the coating comprises customary film-forming agents and/or excipients, especially dibutyl phthalate, polyethylene glycol, triethyl citrate (Citroflex), ethyl cellulose (Aquacoat), titanium dioxide and/or hydroxypropylmethyyl cellulose.

9. Preparation according to any one of the preceding claims, characterised in that the active ingredient content of the initial dose of active ingredient is from 5 to 30% by weight of the total active ingredient content of the preparation.

10. Preparation according to any one of the preceding claims, characterised by a ratio (based on weight) of first component to second component to third component.
in the range of from 1:1:1 to 1:10:10, and especially by a ratio (based on weight) of
approximately 1 : approximately 1 : approximately 2.

11. Preparation according to any one of the preceding claims, characterised in that the active
ingredient content of the initial dose (especially in the form of pellets) of the first delayed-release
pellets and/or of the second delayed-release pellets is from 10 to 50% (based on weight), it
being possible for the active ingredient contents of the three components to be the same or
different.

12. Preparation according to any one of the preceding claims, characterised in that the ratio of
the contents of the active ingredient of initial dose: first delayed-release pellets: second
delayed-release pellets is in the range of from 1:3:3 to 1:10:10 and may especially be about 1 :
2.5 : 4.

13. Preparation according to any one of the preceding claims, characterised by

initial dose: from 10 to 30% by weight,
first type of delayed-release pellet: from 20 to 40% by weight, and
second type of delayed-release pellet: from 40 to 60% by weight,

the sum of all three components being 100% by weight.

14. Preparation according to any one of the preceding claims, characterised by

initial dose: approximately 22.9% by weight,
first type of delayed-release pellet: approximately 25.8% by weight, and
second type of delayed-release pellet: approximately 51.3% by weight,

the sum of all three components being 100% by weight.

15. Preparation according to any one of the preceding claims in the form of a capsule,
especially a gelatin capsule, the capsule comprising all three components.

16. Preparation according to claim 15, characterised in that the capsule comprises an amount of
active ingredient required for a daily dose or for a single dose.
17. Preparation according to claim 15 or 16, characterised in that the capsule comprises an amount of captopril required for the daily dose or single dose, especially in the range of from 25 to 300 mg, more especially from 50 to 200 mg and very especially from 75 to 150 mg.

18. Preparation according to any one of the preceding claims, characterised in that, based on a daily dose or a single dose, with captopril as active ingredient, the initial dose is from 5 to 30 mg.

19. Preparation according to any one of the preceding claims, characterised by microcrystalline cellulose and/or lactose as excipients.
**PLASMA CAPTOPRIL CONCENTRATIONS**

Arithmetische mean values

(n = N)

**Dose:** 1 x 50 mg captopril IR tablet
**Dosis**
**LOPRIN**
(Squibb)

**Dose:** 1 x 150 mg captopril IR capsule
**Dosis**
**CAPTOPRIL**
(Hexal)

![Graph showing plasma concentrations over time](image-url)
Mean captopril concentrations (left axis, open symbols) and mean ACE activities (right axis, filled symbols) and average curve fits after PK/PD data analysis.

Fig. 2: mittlere Captopril-Konzentrationen (linke Achse: offene Symbole);
mittlere ACE-Aktivitäten (rechte Achse: gefüllte Symbole);
angepaßter mittlerer Verlauf nach PK/PD-Analyse;
Vergleichsprodukt: offene und gefüllte Quadrate
Testprodukt: offene und gefüllte Kreise
Fig. 3: Mean total plasma captopril concentration in ng/ml on day 5 (open squares)
Mean ACE inhibition in mU/ml (open stars: day 2; open circles: day 5)
Fig. 4: Mittlere Plasmakonzentrationen des freien Captoprils (ng/mL) am 2. Tag (F) und am 5. Tag (R)
Mean plasma concentrations of free captopril (ng/ml) on day 2 (F) and on day 5 (R)

F - First Dose on Day 2
R - Repeated Dose on Day 5

Concentration (ng/mL)  Mittelwerte  Mean data

Konzentration

0 50 100 150 200 250 300
0 2 4 6 8
Time (h) Zeit

Treatment  F  R