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<td>PHARMACEUTICAL COMPOSITION CONTAINING CLOZAPINE</td>
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**Abstract:**

Disclosed is a slow-release solid oral pharmaceutical composition containing clozapine, and its use in the treatment of psychotic disorders.
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.
PHARMACEUTICAL COMPOSITION CONTAINING CLOZAPINE

This invention relates to a slow-release solid oral pharmaceutical composition containing clozapine, and its use in the treatment of psychotic disorders.

Background to the invention

Clozapine or 8-chlorine-11-(4-methyl-1-piperazyl)-5H-dibenzo[b,e] [1,4] diazepine is classified as an “atypical” antipsychotic drug. This class of drug is used to treat complex, heterogeneous psychotic conditions of uncertain etiology, including schizophrenia and the associated schizoaffective disorders, from which 2% of the world population currently suffer. Compared with other neuroleptics, clozapine has the following specific characteristics: it acts as a broad-spectrum antagonist with differentiated receptor affinity, both in the dopaminergic system (greater affinity for the dopamine D4 receptor and lesser affinity, in decreasing order, for subtypes D2, D1, D3 and D5) and outside that system (high affinity for serotonin and muscarinic receptors, and significant effects on the GABAergic and glutaminergic systems). The brain neurotransmitter receptor binding profile has made clozapine the drug of choice for the treatment of schizophrenic patients resistant or intolerant to the classic neuroleptics. Compared with those drugs, clozapine is practically devoid of extrapyramidal side effects, effective on both negative psychotic symptoms (apathy, blunted affect, social withdrawal, poverty of thought content) and positive symptoms (hallucinations, delirium and thought disorders), and able to reduce the risk of suicidal behaviour in schizophrenic patients.

The major side effect of treatment with clozapine is agranulocytosis, which occurs in 1% of cases. However, evaluation of the risk/benefit ratio demonstrates that the frequency of suicide in drug-resistant schizophrenics not
treated with clozapine is higher than mortality from agranulocytosis in schizophrenic patients treated with clozapine. Moreover, the introduction of monitoring by systematic differential white blood cell count (conducted weekly for the first six months of treatment and fortnightly thereafter) has reduced the incidence of agranulocytosis to 0.38%.

The absorption, distribution, metabolism and excretion profile of clozapine can be summed up as follows. After oral administration it is rapidly absorbed, and the peak concentration (Cmax) is reached in 2-4 hours (tmax). It has first-order absorption kinetics which remain linear in the plasma concentration range of 10-1000 ng/ml. The absorption rate is not affected by food. 97% of the drug bonds to plasma proteins. Before excretion it is rapidly metabolised by the liver microsomal enzymes, forming two metabolites: N-oxide and the N-desmethyl (active) derivative. During the first metabolic step, the bioavailability of clozapine is reduced by 50%.

The amount of clozapine excreted in the urine and faeces is approximately 50% and 40% respectively. Its mean half-life (t½) is approx. 12 hours. Its bioavailability and half-life present wide interindividual variability, partly dependent on the patient’s age, weight, sex and smoking habits. Considerable variability in pharmacokinetic parameters can also be found within the same patient.

Clozapine is available on the market in immediate-release oral formulations consisting of 25 and 100 mg scored tablets. The treatment commences at 12.5 mg a day. If it proves tolerable it is gradually increased, by multiple administrations, until the optimum therapeutic dose range, generally between 300 and 600 mg a day, is reached within 15 days. In some cases, daily doses of up to 900 mg need to be reached.

The relatively short half-life of clozapine causes peaks and fluctuations in its blood concentration. This situation generates problems of toxicity and
patient compliance associated with the onset of significant side effects such as
orthostatic hypotension, with a potential risk of fainting and reduction of the
convulsive threshold, on the one hand, and the need to take the drug several
times a day, with the associated risk of forgetting to take it, on the other.

Moreover, the fluctuations in blood levels of clozapine can lead the
doctor, in an attempt to optimise its efficacy, to adopt conservative or
aggressive dose regimens, with the consequent risk of failing to reach or
exceeding therapeutic blood levels.

In view of said problems of toxicity, compliance and therapeutic
efficacy, it would be desirable to have a slow-release formulation of clozapine
that reduces the frequency of daily administrations.

**Description of the invention**

The subject of this invention is a solid oral slow-release “once a day”
composition, which contains clozapine as active constituent and guarantees
constant release of the drug for 24 hours, avoiding peaks and fluctuations in
plasma levels.

In one embodiment of the invention, the composition takes the form of
granules coated with polymers or cellulose derivatives, preferably chosen
from among methyl-, ethyl- or propyl-cellulose, hydroxypropyl cellulose,
hydroxyethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl
ethylcellulose, carboxymethylcellulose, cellulose acetate or phthalate,
hydroxypropyl methylcellulose phthalate, cellulose acetate succinate, and
ethylcellulose succinate. Ethylcellulose polymer is particularly preferred.
The granules, of dimensions ranging between 500 and 1200 μm, can be
distributed or incorporated in suitable oral pharmaceutical forms, preferably
rigid gelatin capsules, tablets or sachets prepared by conventional
techniques.

In a preferred embodiment, the coated granules contain 85 to 95% (by
weight), preferably 90-95%, of clozapine, and 1 to 3%, preferably 1.5 to 2% (by weight) of ethylcellulose. The unit dose of clozapine is between 12 and 900 mg. In addition to the active ingredient and cellulose polymer, the composition according to the invention may contain pharmaceutically acceptable excipients such as lubricants (or gliding agents), diluents, dispersing agents or binders.

According to a particularly preferred embodiment, the coated granules have the following percentage composition (by weight): clozapine 90%, polyethylene glycol (carbowax) 3%, polyvinylpyrrolidone 4.5%, ethylcellulose 1.7% and talc 0.8%.

The daily dose can vary according to the patient’s characteristics, but will generally be 400-600 mg qd.

The coated granules can be prepared according to a process which basically comprises the following steps: mixing of active ingredient with binder solution; granulation of mixture; selection of granules of optimum size, for example by sieving; coating of granules by spraying with coating polymer and optionally adding a gliding agent; drying, and filling of final pharmaceutical form.

The pharmaceutical composition according to the invention is indicated for the treatment of schizophrenia and associated disorders, especially the tendency to suicide in schizophrenic patients, psychosis, Parkinson’s disease, and mood disorders in bipolar disorder.

“Once a day” oral administration of the composition according to the invention presents various advantages, including: 1) maintenance of constant therapeutic blood levels of clozapine, 2) accuracy of dose and administration of treatment, 3) reduced risk of toxic effects, 4) improved therapeutic efficacy and patient compliance.

The examples below illustrate the invention in greater detail.
EXAMPLE 1 - Preparation of 100 and 25 mg slow-release clozapine capsules

The following ingredients are required to prepare 250,000 doses:

<table>
<thead>
<tr>
<th>Dose</th>
<th>100 mg</th>
<th>25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>25 Kg</td>
<td>6.25 Kg</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone</td>
<td>1.25 Kg</td>
<td>0.312 Kg</td>
</tr>
<tr>
<td>Polyethylene glycol 4000 (carbowax 4000)</td>
<td>0.83 Kg</td>
<td>0.206 Kg</td>
</tr>
<tr>
<td>Ethylcellulose</td>
<td>0.47 Kg</td>
<td>0.116 Kg</td>
</tr>
<tr>
<td>Talc</td>
<td>0.22 Kg</td>
<td>0.056 Kg</td>
</tr>
<tr>
<td>Acetone*</td>
<td>q.s.</td>
<td>q.s.</td>
</tr>
<tr>
<td>Alcohol*</td>
<td>q.s.</td>
<td>q.s.</td>
</tr>
<tr>
<td>Deionised water*</td>
<td>q.s.</td>
<td>q.s.</td>
</tr>
</tbody>
</table>

* The solvents used during the process are removed by evaporation

Preparation of binder solution

The polyethylene glycol 4000 is placed in a stainless steel container with a pneumatic agitator. The polyvinylpyrrolidone is then sprinkled onto it in small amounts, and maintained under constant agitation until completely solubilised.

Preparation of uncoated clozapine granules

A precise quantity of clozapine is weighed and granulated in a granulator, using the previously prepared binder solution as aggregating agent.

The wet granulate is forced through netting with 840 micron mesh and dried at 40°C for 15 hours in a thermostated forced-air dryer. The granulate is then sieved through a 500 and 840 micron mesh sieve. The powder and the granules smaller than 500 microns are regranulated by the process described
above, in this case using deionised water as aggregating agent. When the granulation process has been completed, the granules are sieved with a 500 and 840 micron mesh sieve. The resulting granulate is weighed and placed in the stainless steel rack of a coating pan. To ensure sufficient rotation of the mass, the pan is rotated at approximately 12 rotations per minute. The granules are sprayed with binder solution using a spray device. Spraying is performed at intervals to allow better removal by suction of the steam generated by the water in the binder solution. At the end of the process the granulate is passed through netting with 1200 micron mesh and dried at 40°C for 15 hours in a thermostated forced-air dryer. The granulate is then sieved through an 840 and 1200 micron mesh sieve.

**Preparation of granule-coating solution**

Acetone and alcohol are placed in a stainless steel container fitted with a pneumatic agitator. The ethylcellulose is then poured in slowly, and maintained under constant agitation until completely solubilised.

**Granule coating**

The granulate obtained during the preceding stage is placed in a fluid bed and kept in suspension by a flow of filtered air. The coating solution is sprayed at intervals. To improve the glide of the granulate, small amounts of talc are scattered on the granulate in the intervals between spraying. At the end of the coating process the granulate is passed through netting with 1200 micron mesh and dried at 40°C for 15 hours in a thermostated forced-air dryer.

**Bulk granule preparation**

The dried granules are sieved through an 840 and 1200 micron mesh sieve, collected in double polyethylene bags, and placed in hermetically sealed metal containers.

**Capsule filling**

The granules are automatically distributed between capsules by a
machine programmed to fill hard gelatin capsules with predefined weights of granulate. The filled, closed capsules are collected in double polyethylene bags and placed in hermetically sealed metal containers.

**EXAMPLE 2 - Dissolution test**

The release capacity of clozapine was tested on six 100 mg samples of formulation using a HCl solution at pH 1.1 (artificial gastric juice) in a continuous flow dissolver (25 ml/min at 37°C). Samples were taken from the dissolver for 24 hours, and the percentage release was calculated on the basis of the clozapine concentrations in the samples, determined by HPLC. The individual release percentages as well as the means, standard deviations and percentage coefficients of variation, are set out in the Table.

**TABLE**

<table>
<thead>
<tr>
<th>Hours</th>
<th>Sample 1</th>
<th>Sample 2</th>
<th>Sample 3</th>
<th>Sample 4</th>
<th>Sample 5</th>
<th>Sample 6</th>
<th>MEAN</th>
<th>SD</th>
<th>% CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.1</td>
<td>9.8</td>
<td>10.7</td>
<td>9.2</td>
<td>9.2</td>
<td>11.0</td>
<td>10.0</td>
<td>0.75</td>
<td>7.5</td>
</tr>
<tr>
<td>4</td>
<td>21.8</td>
<td>20.5</td>
<td>20.6</td>
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<td>19.2</td>
<td>22.5</td>
<td>20.7</td>
<td>1.24</td>
<td>6.0</td>
</tr>
<tr>
<td>7</td>
<td>29.6</td>
<td>28.1</td>
<td>30.4</td>
<td>27.9</td>
<td>28.4</td>
<td>30.0</td>
<td>29.1</td>
<td>1.07</td>
<td>3.7</td>
</tr>
<tr>
<td>12</td>
<td>79.4</td>
<td>77.6</td>
<td>78.3</td>
<td>76.0</td>
<td>77.6</td>
<td>79.1</td>
<td>78.0</td>
<td>1.23</td>
<td>1.6</td>
</tr>
<tr>
<td>16</td>
<td>83.8</td>
<td>81.0</td>
<td>84.8</td>
<td>83.7</td>
<td>85.7</td>
<td>86.2</td>
<td>84.2</td>
<td>1.86</td>
<td>2.2</td>
</tr>
<tr>
<td>20</td>
<td>88.6</td>
<td>85.8</td>
<td>88.3</td>
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<td>24</td>
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<td>95.5</td>
<td>92.6</td>
<td>94.3</td>
<td>97.1</td>
<td>95.1</td>
<td>1.66</td>
<td>1.8</td>
</tr>
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</table>

**Comments on results**

The data shown in the table clearly demonstrate that the release of clozapine remains constant for 24 hours.

**EXAMPLE 3 - Comparative pharmacokinetic profile of the new 25 mg clozapine “once a day” capsule formulation for single administration, and the reference commercial product clozaril 25 mg tablets, half of which (12.5 mg) is administered twice a day**

A crossover study was conducted on 10 healthy volunteers, to whom a 25 mg clozapine “once a day” tablet was first administered one hour before
breakfast (7.30 a.m.). After a suitable wash-out period, treatment with the reference clozapine was performed by administering it at the dose of 12.5 mg one hour before breakfast (7.30 a.m.) and one hour before the evening meal (7.30 p.m.). The figure contains graphs based on the mean plasma concentrations of clozapine determined by HPLC.

Comments on results

If the pharmacokinetic profiles of the slow-release formulation of clozapine, administered once a day at the dose of 25 mg (CZP “once a day”), are compared with the immediate-release formulation administered at the dose of 12.5 mg twice a day, the results are as follows:

1) The peak blood concentrations (Cmax) of clozapine reached after the first administration of the two formulations can be considered equivalent, although the time taken (tmax) to obtain them is longer for CZP “once a day” (5 hours, compared with 3 hours for CZP “twice a day”).

2) The plasma concentration of clozapine obtainable with CZP “once a day” decreases by under 20% in a 24-hour period, and can consequently be considered practically constant. The same does not occur in the case of patients treated with the reference drug CPZ “twice a day”, as the clozapine concentration in the plasma declines by approximately 50% in the interval between the two peak concentrations, observed after 3 and 15 hours.

3) The plasma half-life of both formulations is around 30 hours after the first administration.

On the basis of the results reported in the above examples, the oral formulation according to the invention can be said to guarantee slow release of clozapine, so as to maintain constant levels of the drug in the plasma for at least 24 hours.
This pharmacokinetic profile, compared with that of the present immediate-release formulations of clozapine, prevents overdose, reduces the risk of some significant side effects and eliminates the need for repeated administrations during the day, leading to an improvement in therapeutic efficacy and patient compliance.
CLAIMS

1. Solid oral pharmaceutical composition for the constant release of clozapine in a period of 24 hours after single administration.

2. Pharmaceutical composition according to claim 1, in the form of granules coated with a cellulose polymer.

3. Pharmaceutical composition according to claim 2, wherein said polymer is selected from methyl-, ethyl- or propyl-cellulose, hydroxypropyl cellulose, hydroxyethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl ethylcellulose, carboxymethylcellulose, cellulose acetate or phthalate, hydroxypropyl methylcellulose phthalate, cellulose acetate succinate, and ethylcellulose succinate.

4. Pharmaceutical composition according to claim 2, wherein said polymer is ethylcellulose.

5. Composition according to claims 2-4, wherein the granules have a diameter of between 500 and 1200 μm.

6. Composition according to claims 2-5, containing 85 to 95% by weight of clozapine.

7. Composition according to claims 2-5, containing 1.5 to 2% by weight of ethylcellulose.

8. Composition according to claims 2-5, containing excipients selected from lubricants, diluents, binders and dispersing agents.

9. Composition according to claims 6-8, containing clozapine 90%, polyethylene glycol 3%, polyvinylpyrrolidone 4.5%, ethylcellulose 1.7%, and talc 0.8% (percentages in weight).

10. Composition according to claims 1-9, containing 12 to 900 mg of clozapine.

11. Composition according to any of the preceding claims, for use in the
treatment of schizophrenia and associated disorders, psychosis, Parkinson’s disease, and mood disorders in bipolar disorder.
FIGURE

PHARMACOKINETIC PROFILE

Clozapine (ng/ml)

0 3 5 8 12 15 20 24 30

Hours

CLOZAPINA ONCE A DAY 25 mg  CLOZARIL 2 x 12.5 mg