(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International publication date
31 July 2003 (31.07.2003)

PCT

(10) International publication number
WO 03/061669 A1

(51) International patent classification[7]: A61K 31/685, A61P 33/02

(21) International application number: PCT/EP03/00072

(22) International filing date: 7 January 2003 (07.01.2003)

(25) Language of filing: German

(26) Language of publication: German

(30) Data relating to the priority:
102 03 195.9 25 January 2002 (25.01.2002) DE

(71) Applicant: ZENTARIS AG [DE/DE]; Weismüllerstrasse 45, 60314 Frankfurt (DE).

(72) Inventor: ENGEL, Jürgen; Erlenweg 3, 63755 Alzenau (DE).

(74) Attorney: ZENTARIS AG; Patentabteilung, Meissner Strasse 35, 01445 Radebeul (DE).

(81) Designated states *(national)*: AU, BR, CA, CN, CO, ID, IL, IN, JP, KE, MX, NZ, PH, SD, SG, ZA.

(84) Designated states *(regional)*: European Patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR).

Published:
- *With the International Search Report.*
- *Before expiry of the period provided for amending the claims, will be republished if such amendments are received.*

For an explanation of the two-letter codes and the other abbreviations, reference is made to the explanations ("Guidance Notes on Codes and Abbreviations") at the beginning of each regular edition of the PCT Gazette.

As printed

WO 03/061669 A1

(54) Title: USE OF ALKYLPHOSPHOCHOLINES FOR THE PREVENTATIVE TREATMENT OF PROTOZOAN DISEASES

(54) Bezeichnung: VERWENDUNG VON ALKYLPHOSPHOCHOLINEN IN DER PRÄVENTIVBEHANDLUNG VON PROTOZOENERKRANKUNGEN

(57) Abstract: The invention relates to pharmaceutical compositions containing alkylphosphocholines, especially hexadecylphosphocholine or octadecyl-(1, 1-dimethyl-piperidinio-4-yl)-phosphate for the preventative treatment of protozoan diseases, especially leishmaniasis. The invention also relates to a dosing scheme of said compositions for the preventative treatment of said illnesses.

(57) Zusammenfassung: Die Erfindung bezieht sich auf pharmazeutische Zusammensetzungen, enthaltend Alkylphosphocholine, insbesondere Hexadecylphosphocholin bzw. Octadecyl-(1, 1-dimethyl-piperidinio-4-yl)-phosphat für die präventive Anwendung bei Protozoenerkrankungen, insbesondere Leishmaniase. Die Erfindung beschreibt auch ein Dosierungsschema von genannten Zusammensetzungen zur präventiven Anwendung genannter Erkrankungen.

Use of alkylphosphocholines in the preventive treatment of protozoal diseases

Introduction

The present invention relates to pharmaceutical compositions comprising alkylphosphocholines, especially hexadecylphosphocholine (miltefosine), or octadecyl 1,1,-dimethylpiperidino-4-yl phosphate (perifosine, D-21266) for oral administration in the preventive treatment of protozoal diseases, especially of leishmaniasis, furthermore a dosage schedule for the oral administration of this pharmaceutical composition in the preventive treatment of protozoal diseases, especially leishmaniasis, and a combination which comprises this pharmaceutical composition, an antiemetic and/or an antidiarrhoeal.

Prior art

Leishmaniasis is a name for various tropical diseases caused by flagellates of the genus Leishmania and transmitted by various blood-sucking insects. The manifestations of leishmaniasis may be visceral (kala-azar), mucocutaneous (espundia) or cutaneous (Aleppo sore or diffuse cutaneous leishmaniasis). The incubation time is from weeks to months. A very high mortality rate is observed especially in untreated cases of kala-azar and of espundia.

The known agents in the standard therapy for treating cases of leishmaniasis, i.e. pentavalent antimony compounds (e.g. sodium stibogluconate) and aromatic diamidines, have had to be administered by parenteral injection, which not only led to severe side effects because of their high toxicity but also entailed a risk of infection.

The fact that alkylphosphocholines, especially hexadecylphosphocholine (miltefosine), are suitable for the oral and topical treatment of leishmaniasis was described for the first time by Eibl et al. in the patent application DE-A 4132344, which was filed in 1991, and in EP-A 534445.

Numerous other authors describe the treatment of leishmaniasis with alkylphosphocholines as a new class of medicaments with remarkable antiprotozoal activity. Thus, T. Jha et al., Miltefosine, an oral agent, for the treatment of Indian visceral leishmaniasis, N. Engl. J. Med. (1999), 341(24), 1795-1800 report on a study with 120 patients on whom between 50 and 150 mg of miltefosine were used each day for several weeks. S. Sundar et al., Oral treatment of visceral leishmaniasis with miltefosine, Ann. Trop. Med. Parasitol. (1999), 93(6), 589-597, observe the oral use of from 100 to 200 mg of miltefosine per day for visceral leishmaniasis in a pilot trial.

Miltefosine is difficult to handle, although it is obtainable in dry form as crystalline platelets with a defined melting point above 200°C, because it is very hygroscopic. The uptake of water molecules may lead to a weight gain of up to 30% by weight, to a melting point depression and to a caking and clumping of the crystals. The processability of the water-containing miltefosine is inadequate for further processing to solid pharmaceutical compositions such as tablets, capsules or sachets. In particular, the flowability of water-containing miltefosine is inadequate. However, satisfactory flowability is one of the indispensible prerequisites for the production of pharmaceutical compositions on an industrial scale.

In addition, anhydrous miltefosine shows a considerable tendency to electrostatic charging, especially when it is stirred in the dry state. The flowability of

electrostatically charged miltefosine is also inadequate for further processing to solid pharmaceutical compositions. Moreover, electrostatic charges are always associated with considerable safety concerns because of the risks, associated therewith, both of explosions and of damage to sensitive electronic components.

In order to get round the abovementioned problem in the production of solid, miltefosine-containing pharmaceutical compositions, Eibl et al. proposed that miltefosine be applied to the surface of silicon dioxide particles by evaporating to dryness a suspension of 1 part by weight of silicon dioxide in a solution with 1 part by weight of miltefosine. The flowability of the solid dispersion obtained as proposed by Eibl et al. is in fact sufficient for packing into capsules, at least on the laboratory scale. However, the process described by Eibl et al. is based on the use of a highly volatile and, at the same time (because of the electrostatic charging), non-flammable solvent. The only solvents which meet these requirements for all practical applications in the prior art are methylene chloride and chloroform. However, halogenated hydrocarbons, especially chloroform, are categorized as toxic and carcinogenic compounds. In addition, halogenated hydrocarbons accumulate in adipose tissue and are broken down only slowly.

The patent WO 99/37289 has already described the possibility of solving the abovementioned problem by physically mixing an alkylphosphocholine, especially hexadecylphosphocholine, at least one flow-control agent and/or lubricant, selected from the group consisting of fine-particle silicon dioxide, talc, magnesium stearate and mixtures thereof, and at least one filler from the group consisting of lactose, microcrystalline cellulose and mixtures thereof.

According to WO 99/37289, it is possible by simple physical mixing of alkylphosphocholines, especially miltefosine, a flow-control agent and/or lubricant and at least one filler to obtain a solid pharmaceutical mixture with a flowability which is sufficient for further processing, for example to capsules, tablets or sachets.

According to this WO publication, the solid pharmaceutical composition can be used to fill capsules, preferably hard gelatin capsules, or be compressed to tablets or effervescent tablets or - as drinkable blend or effervescent blend - be packed in sachets.

The miltefosine content per dose unit is in the range from 10 to 800 mg, preferably in the range from 10 to 500 mg, and particularly preferably in the range from 50 to 250 mg. The most preferred content is in the range from 50 to 150 mg.

The preparation of miltefosine is described in detail in the examples for hexadecylphosphocholine in German patent application DE-A 4132344. Further methods for the production and purification of miltefosine are described, for example, in the German patent applications DE-A 2752125, DE-A 3641379, DE-A 3641491, DE-A 4013632 and DE-A 3641377.

Description of the invention

Surprisingly and unexpectedly, it has been found according to one aspect of the application that alkylphosphocholines, especially hexadecylphosphocholine (miltefosine), and octadecyl 1,1,-dimethylpiperidinio-4-yl phosphate (perifosine, D-21266) are suitable for preventive treatment of protozoal diseases, especially leishmaniasis. A pharmaceutical

use of alkylphosphocholines, especially hexadecylphosphocholine, and octadecyl 1,1,-dimethylpiperidinio-4-yl phosphate for the prevention of protozoal diseases, especially leishmaniasis, is neither described in nor obvious from the communications of the prior art.

According to one aspect of the present invention, a dosage schedule is provided for the preventive treatment of leishmaniasis in humans by oral administration of the pharmaceutical composition.

In a preferred embodiment, the following dosage schedule is suitable for the preventive treatment of leishmaniasis in humans by oral administration:

total daily dose: 10-250 mg of miltefosine active ingredient, preferably 20-150 mg, in particular 30-100 mg;
daily single or multiple dose: a total daily dose of 10-50 mg of active ingredient is preferably administered as a single daily dose;
a dose of 50-250 mg of active ingredient, preferably of 50-150 mg of active ingredient, is administered each day orally as a daily multiple dose, preferably as two doses per day (total daily dose 100 mg of active ingredient) or as three doses per day (total daily dose 150 mg of active ingredient). With regard to the compliance of patients, a daily dose divided into 4-5 doses is generally regarded as the upper limit. However, for preventive purposes, it is also possible to administer the agent divided otherwise than in 1-5 doses per day.

In a preferred embodiment, multiple doses of the same size are administered each day (e.g. 100 mg of active ingredient/day = 2 × 50 mg of active ingredient/day or 150 mg of active ingredient/day = 3 × 50 mg of active ingredient/day).

Prophylaxis is also possible with an initial dose followed by maintenance doses, administering as initial dose for example 100 mg of active ingredient or more, followed by maintenance doses of, for example, 30 mg of active ingredient.

Duration of use for prophylaxis: 2 weeks to 6 months, preferably for the duration of the risk of infection.

According to a further aspect of the invention, a dosage schedule is provided for the preventive treatment of leishmaniasis in mammals which are not humans by oral administration of the pharmaceutical composition of the invention.

It is possible to treat all mammals. Use of the dosage schedule makes preventive treatment of all types of leishmaniasis possible, in particular of leishmaniasis major and leishmaniasis infantum. According to the dosage schedule, the total daily dose for prophylactic treatment in the case of oral administration is in the range of 0.5-15 mg of miltefosine or perifosine active ingredient per kg of body weight of the animal (mg of active ingredient/kg). In a preferred embodiment, the prophylaxis is started with an initial total single dose (saturation dose) in the range of 3-15, preferably 5-10, mg of active ingredient/kg and then continued with a total daily dose (maintenance doses) in the range of 1-10, preferably 3-5, mg of active ingredient/kg. The duration of preventive use is in the range from 2 weeks to 6 months, preferably for the duration of the risk of infection.

According to a further aspect, a combination of the pharmaceutical composition with an antiemetic and/or antidiarrhoeal is provided for oral administration in the preventive treatment of leishmaniasis.

In a preferred embodiment of the invention, the pharmaceutical composition of the invention is administered in combination with an antiemetic and/or an antidiarrhoeal. The administration can take place simultaneously or successively. Antiemetic and antidiarrhoeal can be administered independently of one another. The antiemetic and/or antidiarrhoeal may be present either in the described pharmaceutical composition or in a pharmaceutical formulation independent thereof.

Examples of suitable antiemetics are 5-HT3 receptor antagonists, substituted benzamides, corticosteroids, antihistamines, neuroleptics of the phenothiatine [sic] type, neuroleptics of the butyrophenone type, benzodiazepines and cannabinoids. Preferred antiemetics are, inter alia, metoclopramide, domperidone and alizapride.

Suitable antidiarrhoeals are, inter alia, the opioids such as, for example, loperamide.

The solid oral pharmaceutical compositions are suitable preferably for the preventive treatment of leishmaniasis. Examples of other diseases caused by protozoans are malaria, trypanosomiasis, toxoplasmosis, babesiosis, amoebic dysentery and lambliasis.

Exemplary embodiments

The following examples are intended to explain the invention in more detail.

Examples of solid oral pharmaceutical formulations which can be used

Example 1: Hard gelatin capsules (content: 10 mg of miltefosine)

100 g of hexadecylphosphocholine, 808.50 g of lactose, 448.50 g of microcrystalline cellulose, 26 g of talc and 13 g of fine-particle silicon dioxide are passed through a sieve with a mesh width of 0.8 mm and then homogenized in a suitable mixer for 30 minutes. Then 4 g of magnesium stearate (0.8 mm sieve) are added, and the components are blended for a further 5 minutes. The mixture obtained in this way is packed in 140 mg portions into hard gelatin capsules with a weight of 50 mg in a known manner, using a suitable encapsulating machine for this.

Each of the capsules obtained in this way (total weight: 190 mg) contains 10 mg of hexadecylphosphocholine.

The hexadecylphosphocholine : flow-control agent/surfactant : filler ratio in the filling mixture is 1 : 0.4 : 12.4 (parts by weight).

Example 2: Hard gelatin capsules (content: 100 mg of miltefosine)

1 000 mg of hexadecylphosphocholine, 584 g of lactose, 345 g of microcrystalline cellulose, 50 g of talc, 15 g of fine-particle silicon dioxide and 6 g of magnesium stearate were blended by the process described in Example 1.

The filling mixture obtained in this way is packed in 200 mg portions into hard gelatin capsules with a weight of 76 mg in a known manner, using a suitable encapsulating machine for this.

Each of the capsules obtained in this way (total weight: 276 mg) contains 100 mg of hexadecylphosphocholine. The hexadecylphosphocholine : flow-control agent : fillers ratio in the filling mixture is 1 : 0.07 : 0.9 (parts by weight).

Example 3: Hard gelatin capsules (content: 250 mg of miltefosine)

250 mg of hexadecylphosphocholine, 80 g of lactose, 50 g of microcrystalline cellulose, 5 g of talc, 5 g of fine-particle silicon dioxide and 15 g of magnesium stearate were blended as in Example 1. The filling mixture obtained in this way is packed in 405 mg portions into hard gelatin capsules with a weight of 97 mg in a known manner, using a suitable encapsulating machine for this.

Each of the capsules obtained in this way has a total weight of 502 mg and contains 250 mg of hexadecylphosphocholine. The hexadecylphosphocholine : flow-control agent : fillers ratio in the filling mixture is 1 : 0.1 : 0.52 (parts by weight).

Example 4: Tablets (content: 250 mg of hexadecylphosphocholine)

50 g of hexadecylphosphocholine, 24.25 g of microcrystalline cellulose and 22.00 g of anhydrous dicalcium phosphate are sieved and blended. 3.75 g of magnesium stearate are sieved and added to the mixture. The mixture is then mixed once again. The mixture obtained in this way is then compressed to tablets each weighing 500 mg. The tablets each contain 250 mg of hexadecylphosphocholine.

The hexadecylphosphocholine : flow-control agent/surfactant : fillers ratio in the tablet is 1 : 0.07 : 0.925 (parts by weight).

Example 5: Tablets (content: 30 mg of hexadecylphosphocholine)

23 g of hexadecylphosphocholine, 23 g of microcrystalline cellulose and 52 g of spray-dried lactose are sieved and blended. 1 g of colloidal silicon dioxide and 1 g of magnesium stearate are added. The mixture is then mixed once again.

The mixture obtained in this way is then compressed to

tablets each weighing 130.5 mg. The tablets each contain 30 mg of hexadecylphosphocholine.
The hexadecylphosphocholine : flow-control agent/ surfactant : fillers ratio in the tablet is 1 : 0.087 : 0.31 (parts by weight).

Example 6: Effervescent tablets and effervescent blend (hexadecylphosphocholine content: 250 mg)

1 700 g of granular sodium bicarbonate are heated in an oven at 100°C for 60 min. After cooling to room temperature, the converted bicarbonate is mixed with 160 g of granular monobasic calcium phosphate, 1 030 g of granular anhydrous citric acid, 100 g of talc and 50 g of magnesium stearate. 300 g of hexadecylphosphocholine are added to the mixture obtained in this way, followed by blending for 10 min.
The effervescent blend obtained in this way is compressed to tablets each weighing 278 mg. The effervescent tablets each contain 250 mg of hexadecylphosphocholine.
The hexadecylphosphocholine : flow-control agent/ surfactant : fillers ratio in the tablet is 1 : 0.50 : 0.53 (parts by weight).

An alternative possibility is to pack 278 mg portions of the effervescent blend in a sachet, resulting in an effervescent blend.

Example 7: Effervescent tablets and effervescent blend (content: 50 mg of hexadecylphosphocholine)

1 600 g of granular sodium bicarbonate are heated in an oven at 100°C for 60 min. After cooling to room temperature, the converted bicarbonate is mixed with 150 g of granular monobasic calcium phosphate, 900 g of granular anhydrous citric acid, 80 g of talc and 30 g of magnesium stearate. 200 g of hexadecylphosphocholine are added to the mixture obtained in this way, followed

by blending for 10 min.
The mixture obtained in this way is compressed to tablets each weighing 740 mg. The effervescent tablets each contain 50 mg of hexadecylphosphocholine.
The hexadecylphosphocholine : flow-control agent/ surfactant : fillers ratio in the tablet is 1 : 0.55 : 0.75 (parts by weight).

An alternative possibility is to pack 740 mg portions of the effervescent blend in a sachet, resulting in an effervescent blend.

Example 8: Drinkable blend (sachets) (content: 50 mg of hexadecylphosphocholine)

5 g of hexadecylphosphocholine, 308 g of lactose, 280 g of microcrystalline cellulose, 5 g of saccharin and 2 g of colloidal silicon dioxide are blended. The mixture is packed into sachets. The sachets each weigh 6 g and contain 50 mg of hexadecylphosphocholine.
The hexadecylphosphocholine : flow-control agent/ surfactant : fillers ratio in the mixture is 1 : 0.4 : 117.5 (parts by weight).

Example 9: Drinkable blend (sachets) (content: 200 mg of hexadecylphosphocholine)

20 g of hexadecylphosphocholine, 306 g of lactose, 403 g of microcrystalline cellulose, 5 g of saccharin and 6 g of colloidal silicon dioxide are blended. The mixture is packed into sachets. The sachets each weigh 7.4 g and contain 200 mg of hexadecylphosphocholine.
The hexadecylphosphocholine : flow-control agent/ surfactant : fillers ratio in the mixture is 1 : 0.3 : 35.5 (parts by weight).

The examples may also contain perifosine in place of the active ingredient miltefosine.

Claims

1. Use of alkylphosphocholines for producing a medicament for the preventive treatment of protozoal diseases in humans.

2. Use according to Claim 1, in which total daily doses in the range from 10 to 250 mg of alkylphosphocholine active ingredient are administered orally over a period of from 2 weeks to 6 months, preferably for the duration of the risk of infection.

3. Use according to Claim 1 and 2, characterized in that hexadecylphosphocholine (miltefosine) or octadecyl 1,1,-dimethylpiperidinio-4-yl phosphate (perifosine) is employed for producing a medicament for the preventive treatment of, in particular, leishmaniasis in humans by oral administration, and total daily doses in the range from 10 to 250 mg of miltefosine or perifosine active ingredient are administered orally over a period of from 2 weeks to 6 months, preferably for the duration of the risk of infection.

4. Use according to Claim 1 to 3, characterized in that the total daily dose is about 20 to about 150 mg of miltefosine or perifosine active ingredient.

5. Use according to Claim 1 to 3, characterized in that the total daily dose is about 30-100 mg of miltefosine or perifosine active ingredient.

6. Use according to any of Claims 1 to 5, characterized in that the oral administration takes place once, twice or three times a day with total daily doses of 50, 100 or 150 mg of miltefosine or perifosine active ingredient.

7. Use according to any of Claims 1 to 6,

characterized in that multiple daily doses in equal portions (e.g. 100 mg of active ingredient/ day = 2 × 50 mg of active ingredient/day or 150 mg of active ingredient/day = 3 × 50 mg of active ingredient/day) are administered.

8. Use according to any of Claims 1 to 7, characterized by an initial dose, followed by maintenance doses, it being advantageous for the initial dose to comprise 100 mg of active ingredient or more and the maintenance doses to comprise 30 mg of active ingredient.

9. Use according to any of Claims 1 to 8, characterized in that the leishmaniasis is visceral, mucocutaneous and/or cutaneous leishmaniasis.

10. Use of alkylphosphocholine, in particular hexadecylphosphocholine (miltefosine), or octadecyl 1,1-dimethylpiperidinio-4-yl phosphate (perifosine) for producing a medicament for the preventive treatment of protozoal diseases, especially leishmaniasis, in mammals different from humans, by oral administration, where total daily doses in the range from 0.5 to 15 mg of miltefosine active ingredient per kg of bodyweight of the mammal (mg of active ingredient/kg) are administered.

11. Use according to Claim 10, characterized in that the initial total single dose (saturation dose) is in the range of 3-15 mg of active ingredient/kg and the subsequent total daily doses (maintenance doses) are in the range of 1-10 mg of active ingredient/kg.

12. Use according to Claim 10 or 11, characterized in that the saturation dose is in the range of 5-10 mg of active ingredient/kg.

13. Use according to Claim 10 or 11, characterized in

that the maintenance dose is in the range of 3-5 mg of active ingredient/kg.

14. Use according to any of Claims 10 to 13, characterized in that the oral administration takes place over a period of from 2 weeks to 6 months, advantageously for the duration of the risk of infection.

15. Use according to any of Claims 10 to 14, characterized in that the leishmaniasis is visceral, mucocutaneous and/or cutaneous leishmaniasis.

16. Pharmaceutical combination for the preventive treatment of protozoal diseases, especially leishmaniasis in mammals, comprising a pharmaceutical composition comprising alkylphosphocholine, in particular hexadecylphosphocholine (miltefosine), or octadecyl 1,1,-dimethylpiperidinio-4-yl phosphate (perifosine), and an antiemetic and/or an antidiarrhoeal, where the pharmaceutical composition comprising alkylphosphocholine, in particular hexadecylphosphocholine (miltefosine), or octadecyl 1,1-dimethylpiperidinio-4-yl phosphate (perifosine), and the antiemetic and/or the antidiarrhoeal can be administered either together or independently of one another.