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(54) Title: ANTI-MALARIAL COMPOSITION

(57) Abstract: A pharmaceutical composition comprising artesunate and lumefantrine provided in combination in a single phar-
maceutical dosage unit. The invention also relates to a method of making the pharmaceutical composition, and to the use of the
composition in the treatment of malaria.



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ANTI-MALARIAL COMPOSITION

The present invention relates to an anti-malarial composition, a process for the manufacture of the composition, and the use of the composition as a medicament.

5 Artesunate is a water-soluble derivative of artemisinin. Artemisinin is also known as qinghaosu, artemisine, arteannuin, huanghuahaosu and qing hau sau; in some references artemisinin is called artemisinine. Artemisinin is obtained from the leaves of the shrub *Artemisia annua* and is a naturally occurring sesquiterpene lactone with an endo peroxide group. Because of the low water solubility of the natural substance artemisinin, attempts have been
10 made to convert it to a variety of synthetic derivatives in order to improve the pharmaceutical availability. Such derivatives include artemether, arteether and artesunate. Artemisinin preparations are currently the substances, which act most rapidly against malaria parasites. In particular, they show a high activity against multiresistant lines of *Plasmodium falciparum*. Also, when administered to humans, only a few side effects and no significant toxicity have
15 been observed, although neurotoxicity has occurred in animals. In the body, both artemisinin and artesunate are converted to dihydroartemisinin (DHA, artesol), which is the actual schizonticidal active substance. Artemisinin and artesunate can therefore be regarded as prodrugs for dihydroartemisinin.

Artesunate corresponds to the compound dihydroartemisinin hemisuccinate and its salts,
20 especially its sodium salt. Dihydroartemisinin has the chemical name 3.alpha.,12.alpha.-epoxy-3,4,5,5a.alpha.,6,7,8a.alpha.,9,10,12.beta.,12a-dodecahydro-10-hydroxy-3.beta.,6.alpha.,9.beta.-trimethylpyrano[4,3-j]-1,2-benzodioxepine. Dihydroartemisinin is also known by the name dihydroqinghaosu. Artesunate, or dihydroartemisinin hemisuccinate, can be prepared for example by converting dihydroartemisinin to dihydroartemisinin hemisuccinate by means of
25 acylation. Arteether, artemether and artemisin are known per se.

Several prior art documents disclose the use of anti-malarial formulations comprising artemisin and its derivatives as anti-malarial agents.

US5219865 describes a combination of artemisinin and its derivatives along with known anti-malarial drugs such as chloroquine, 10-O-methylfloxacin, quinine, mefloquine,
30 amodiaquine, pyrimethamine, sulfadoxine, primaquine and salts thereof.

EP0362 810 A describes a synergistic combination of a compound selected from the class of artemisinin, dihydroartemisinin, arteether, artemether, artesunate along with quinidine or mefloquine.

WO03/075927 discloses a dosage regimen comprising of 20-700 mg per day of artesunate and 100-900 mg per day for mefloquine. This patent also claims administering the same in a blister pack, which is divided into daily units that are preferably distinguished by different colors.

5 CH685391 describes a formulation comprising cyclodextrin complexes of artemisin in which the complex formed is said to increase the bioavailability of the active ingredient.

US6306896 claims a pharmaceutical composition in a form suitable for rectal administration active against malaria parasites and multiresistant lines of *Plasmodium falciparum*, the composition comprising a pharmaceutically effective amount of an active
10 substance selected from the group consisting of artemisinin, derivatives of artemisinin and combinations thereof, and an excipient which is inert towards the active substance, and which excipient is substantially free of compounds with an HLB value in the range of about 7 to about 9.

It is known that artemisin and its derivatives have a very short half-life. Therefore, they
15 are usually combined with one or more other anti-malarial agents in order to have longer duration of activity rendered by the combination. "Riamet Coartem" a kit combination sold by Novartis is based on combination of artemisin derivative viz artemether with lumefantrine. US6329552, describes a combination of artemisin and lumefantrine, which is now marketed as "coartem" by Novartis AG worldwide as a combination therapy for malaria. A widely
20 administered fixed dose therapy is (6-dose regimen for adults, containing 480 mg artemether and 2880 mg lumefantrine)

WO92/02217 describes a combination of artemether along with benflumetol or lumefantrine, formulated as individual dosage units in form of a kit to be administered either simultaneously or successively. However there are certain inconveniences associated with a kit
25 dosage regimen. It is more advantageous to use a single pharmaceutical dosage unit for therapy especially with the various advantages associated with the same. The first advantage is that of patient compliance which is a very important parameter in calculating success of any therapy. The second advantage is that the patient need not remember every time to simultaneously or successively take two different tablets or capsules. Therefore, chances of forgetting to take a
30 second tablet/capsule or dosage unit and therefore taking only half a therapy is completely eliminated when a single dosage unit is provided. Example 8 of WO92/02217 describes the preparation of a formulation comprising artemether and lumefantrine in a single tablet by a wet granulation process.

Claim 1 of the said published application WO92/02217 suggests the use of other compounds such as artemisinin, arteether, artesunate, dihydroartemisinin selected from the class of artemether along with lumefantrine. Therefore we carried out a trial based on example 8 of the said patent, replacing artemether with artesunate. We observed that the experiment is not feasible when artemether is replaced by artesunate in the same process. We found that artesunate is unstable in water and therefore it becomes difficult to use even part quantities of water along with artesunate. Thus, it will be clear that the prior art does not, in fact, disclose a synergistically effective single dosage form comprising artesunate and lumefantrine, since there is no enabling disclosure in the prior art which tells the skilled person how to manufacture such a single dosage form. Therefore, the present invention aims to provide a single pharmaceutical dosage unit comprising a combination of artesunate and lumefantrine.

The present invention further aims to provide a fixed dose combination of artesunate and lumefantrine, the said fixed dose ratio being therapeutically effective for treatment of malaria.

It is a further object of the present invention to provide for a single pharmaceutical dosage unit formulated either as single or layered dosage form.

It is another object of the present invention to provide a process for preparation of such single pharmaceutical dosage unit.

It is yet another object of the present invention to provide for a method for treatment of malaria by administering the formulation of the present invention in a suitable therapeutic dosage regimen.

Thus, the present invention provides for a fixed dose combination of artesunate and lumefantrine administered as a single pharmaceutical dosage unit, a process for the preparation of such single pharmaceutical dosage unit, and the use of the dosage unit as a medicament.

According to one aspect of the present invention, there is provided a pharmaceutical composition comprising artesunate and lumefantrine provided in combination in a single pharmaceutical dosage unit.

In a particularly advantageous embodiment of the invention, the artesunate and lumefantrine are each provided in the composition in a synergistically effective amount.

Preferably, the pharmaceutical composition according to the invention further includes a pharmaceutically acceptable carrier.

This combination is indicated for the treatment of most dangerous form of malaria i.e. *falciparum* malaria. Artesunate has a very short half-life (<2 hours) and therefore, it acts quickly. It is mainly active on the blood schizontocides, but is not so active on tissue

schizontocides. On the other hand, lumefantrine is effective against exo-erythrocytic schizontocides and therefore acts on the parasites present in the tissues. Lumefantrine is characterized by slow absorption and long elimination half-life (up to 5 hours). But it has a disadvantage of a slow onset of action and therefore is generally combined with drugs having a quicker onset of action so as to form a highly effective therapeutic combination. Therefore, the two drugs act in synergy such that artesunate causes rapid initial reduction of parasites biomass followed by clearance of remaining viable parasites by the intrinsically less active but more slowly eliminated lumefantrine. The combination further helps to protect against the development of resistance to either agents when used alone.

The active ingredients artesunate and lumefantrine are used in their therapeutically effective ratios of 1:5 to 5:3 more preferably in the ratio of 2: 5.

According to another aspect of the invention there is provided a method of manufacturing a pharmaceutical composition comprising:

- (i) preparing a first formulation comprising lumefantrine,
- (ii) separately preparing a second formulation comprising artesunate using a dry preparation process,
- (iii) and preparing a single dose pharmaceutical composition comprising artesunate and lumefantrine by combining the first and second formulations.

Preferably the first formulation is prepared by wet granulation of the lumefantrine. Preferably, the second formulation is prepared by dry granulation of the artesunate or direct compression of the artesunate.

A single dose pharmaceutical composition in the form of tablet may be formed by preparing the first formulation in the form of granules of lumefantrine, preparing the second formulation in the form of granules of artesunate, mixing the granules of lumefantrine and artesunate, then compressing the mixture of granules to form a tablet.

In one embodiment, a single dose pharmaceutical composition in the form of a bilayered tablet may be formed by preparing the first formulation in the form of granules of lumefantrine, preparing the second formulation in the form of granules of artesunate, separately compressing the first and second formulations to provide a first layer comprising lumefantrine and a second layer comprising artesunate, combining the two layers, then compressing the two combined layers.

In another embodiment, a single dose pharmaceutical composition in the form of a bilayered tablet may be formed by preparing the first formulation in the form of granules of lumefantrine, precompressing the first formulation to provide a first layer comprising lumefantrine, separately directly compressing artesunate to provide a second layer comprising
5 the artesunate, combining the two layers, then compressing the two combined layers.

A single dose pharmaceutical composition in the form of a capsule may be formed by preparing the first formulation in the form of granules of lumefantrine, preparing the second formulation in the form of granules of artesunate, placing the granules of artesunate and lumefantrine, in a predetermined proportion, within a capsule, then sealing the capsule.

10 The first formulation comprising lumefantrine preferably further comprises a pharmaceutically acceptable carrier. The second formulation comprising artesunate preferably further comprises a pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier may comprise one or more of diluents, binders, disintegrants, wetting agents, glidants, lubricants; various options for the carrier are described in more detail below.

15 The term 'artesunate' as used in this specification encompasses any of the individual enantiomers of artesunate; the term may refer to just a single enantiomer, or a racemic or non-racemic mixture of the enantiomers. The term "artesunate" also includes polymorphs and hydrates of artesunate. The terms "artesunate" also includes salts and esters of artesunate: the preferred salt of artesunate is the sodium salt. The term "artesunate" also includes prodrugs of
20 artesunate, and enantiomers, racemic mixtures, non-racemic mixtures, polymorphs, hydrates, salts and esters of said prodrugs.

For treatment of falciparum malaria, a total oral dose of 600 mg in divided doses for at least 3 days is preferred. Each dosage form of the present invention may preferably incorporate doses ranging from 25 mg to 200 mg for artesunate.

25 The term "lumefantrine" as mentioned in this specification includes the salts, derivatives, prodrugs, enantiomers, racemic mixtures, polymorphs and hydrates of lumefantrine. Lumefantrine is preferably given in a dose of from 93 mg to 160 mg, most preferably 120 mg.

The combination of this invention is provided as a single pharmaceutical dosage unit, i.e., not in a kit form. Administration as a single pharmaceutical dosage unit has several distinct
30 advantages. The first advantage is that of patient compliance which is a very important parameter in calculating success of any therapy. Second advantage is that the patient need not remember every time to simultaneously or successively take two different tablets or capsules.

Therefore, chances of forgetting to take a second tablet/ capsule or dosage unit and therefore taking only half a therapy is completely eliminated.

The pharmaceutical dosage units that are prepared using this combination are tablets either as a single tablet or a layered formulation using suitable pharmaceutically acceptable
5 excipients. The formulation is prepared in two parts with granules comprising lumefantrine along with excipients as part I and artesunate along with excipients as part II.

Artesunate is poorly stable in water and hence it is difficult to formulate a solid dosage form using even part quantities of water. Therefore, it would generally be directly compressed or dry granulated in order to form a solid dosage form. Lumefantrine on the other hand is not directly
10 compressible and hence would generally be granulated using a wet binder.

The granules of artesunate are preferably obtained by dry granulating artesunate along with suitable diluents and lubricants to form slugs that are then subjected to a process for size reduction such as milling. Lumefantrine granules may be prepared by commonly known wet granulation method employing diluents, binding ingredients, solvents and lubricating agents.

Both the granules are then mixed in the desired proportions. Preferably, the
15 pharmaceutical composition comprises from 1 part artesunate to 5 parts lumefantrine up to 5 parts artesunate to 3 parts lumefantrine. In a preferred embodiment there are 2 parts artesunate to 5 parts lumefantrine. In another preferred embodiment there are 5 parts artesunate to 12 parts lumefantrine. These granules can either be compressed to give a single layered tablet or the
20 granules can optionally be filled in capsules.

Optionally the formulation of the present invention can be prepared as a bi-layered formulation such that one layer comprises artesunate and the other layer comprises lumefantrine.

If desired, the single or bilayer tablets may be provided with a coating using any conventional coating material. The capsules may be prepared using any conventional capsule
25 material. Furthermore, the granules of artesunate or lumefantrine may be coated using any conventional granule coating material.

The pharmaceutical composition may include excipients such as diluents, binders, disintegrants, wetting agents, glidants, lubricants, and other excipients well known in the art. The diluents can be selected from one or more of calcium phosphate-dibasic, calcium sulfate,
30 microcrystalline cellulose, cellulose powdered, dextrans, dextrans, dextrose excipients, fructose, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners and equivalents thereof. The diluents can be added in a quantity ranging from 15 to 90 wt% of the pharmaceutical composition.

Examples of suitable binders include one or more of methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, starch, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, alginate and other cellulose derivatives and equivalents thereof. The binders can be added in a quantity ranging from 1 to 15 wt% of the pharmaceutical composition.

Examples of suitable disintegrants include one or more of hydroxypropyl cellulose, low density hydroxypropyl cellulose carboxymethylcellulose, calcium carboxymethylcellulose, sodium carboxymethylcellulose, croscarmellose sodium, starch, crystalline cellulose, sodium starch glycolate, hydroxypropyl starch, partly pregelatinized starch, crospovidone and equivalents thereof. The disintegrants can be added in a quantity ranging from 5 to 20 wt% of the pharmaceutical composition.

Wetting agents selected from tween 20, tween 60, tween 80, SLS and such other wetting agents known in the art can be used in the range of 0.5 to 10 wt% and more preferably in the range of 0.5 to 7 wt% of the pharmaceutical composition.

Examples of suitable lubricants and glidants include one or more of stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acid, microcrystalline wax, colloidal silicon dioxide and equivalents thereof. The lubricants can be added in a quantity ranging from 0.5 to 5 wt% of the pharmaceutical composition. Optionally suitable coloring agents may be added. The solvents used to prepare the lumefantrine granules can be selected from purified water, alcohol, polyols, hydroalcoholic mixtures.

The formulation of this invention is manufactured with processes commonly known in the art. Granules of lumefantrine are manufactured by wet granulation process whereas artesunate is simply mixed with excipients and a premix is formed. Lumefantrine granules and artesunate premix are mixed together and compressed to yield a tablet formulation. Alternatively lumefantrine granules can be partially compressed followed by complete compression after addition of artesunate premix resulting in a bilayered formulation. In order to formulate capsules, lumefantrine granules and artesunate premix are mixed in geometric proportion and filled in capsule shells.

In an embodiment the pharmaceutical composition comprises a core containing lumefantrine and an outer layer containing artesunate at least partially surrounding, and preferably completely surrounding, the core.

In an embodiment the pharmaceutical composition comprises a core containing artesunate and an outer layer containing lumefantrine at least partially surrounding, and preferably completely surrounding, the core.

These tablets can be made by forming the tablet core by the methods described above,
5 then compressing the core within granules of the outer layer.

The present invention further provides for a method of treatment of malaria and related infections by administering a therapeutically effective amount of the pharmaceutical composition of the present invention to a mammal in need thereof in a suitable therapeutic regimen. The formulation can be specifically used to treat the infections caused by *P.falciparum*
10 and also helps to alleviate most of its symptoms thus providing relief. The formulation is particularly effective in the treatment of humans.

It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein. Thus, it should be understood that although the present invention has been specifically disclosed by the preferred embodiments and
15 optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and such modifications and variations are considered to be falling within the scope of the invention.

The following examples are for the purpose of illustration of the invention only and are not intended in any way to limit the scope of the present invention.

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Example 1:

Ingredients	Qty (mg/ tab)
Part I	
Lumefantrine	120.0
Lactose	10.0
Microcrystalline cellulose	34.0
L-HPC	15.0
Starch	10.0
PVPK-30	5.0
Purified water	Q.S.
Tween 80	2.0
Part II	
Artesunate	50.0

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L-HPC	15.0
Talc	15.0
Magnesium stearate	7.0
Aerosil	6.0
Total	380 mg.

Process:

1. Mix Lumefantrine, Microcrystalline cellulose, L-HPC to prepare a dry mix.
2. Prepare binder solution by adding starch slurry prepared in water to aqueous slurry of PVP K-30.
3. Granulate the dry mix with the binder solution of step 2 and dry the resultant granules.
4. Mix artesunate and L-HPC to prepare Premix-I.
5. Add granules of step 3 to premix-I of step 4, along with colloidal silicon dioxide, talc and magnesium stearate.
6. Compress the mixture of step 5 to form tablets.

Example 2:

Ingredients	Qty (mg/ tab)
Lumefantrine	120.0
Lactose	10.0
Microcrystalline cellulose	34.0
L-HPC	15.0
<u>Binder solution</u>	
Starch	10.0
PVPK-30	5.0
Purified water	Q.S.
<u>Lubrication</u>	
L-HPC	15.0
Talc	15.0
Magnesium stearate	7.0
Aerosil	6.0
Part II	

10

Artesunate	50.0
Anhydrous lactose	143.0
Tabletosses 80	70.0
Croscarmellose sodium	15.0
Magnesium stearate	2.0
Total:	517.0

Process:

1. Lumefantrine, lactose, microcrystalline cellulose and L-HPC are mixed to form dry mix.
2. Binder solution is prepared by adding the aqueous starch slurry to aqueous PVP K-30
5 slurry.
3. Granules are prepared by granulating dry mix of step 1 with binder solution of step 2.
4. Granules of step 3 are lubricated with L-HPC, talc, aerosil and magnesium stearate to form lubricated granules.
5. Artesunate, Anhydrous lactose, Tabletosses 80, Croscarmellose sodium, magnesium
10 stearate are mixed together to form premix-II.
6. Lubricated granules of step 4 and premix-II are compressed to form a bilayer tablet.

CLAIMS

1. A pharmaceutical composition comprising artesunate and lumefantrine provided in combination in a single pharmaceutical dosage unit.
- 5 2. A pharmaceutical composition according to claim 1, wherein the artesunate and the lumefantrine are provided in a synergistically effective amount in the pharmaceutical dosage unit.
- 10 3. A composition according to claim 1 or 2, comprising from 1 part artesunate to 5 parts lumefantrine, to 5 parts artesunate to 3 parts lumefantrine.
4. A composition according to claim 1 2 or 3, provided in the form of a tablet containing a mixture of artesunate and lumefantrine.
- 15 5. A composition according to claim 1 2 or 3, provided in the form of a bilayer tablet, wherein one of the layers contains artesunate and substantially no lumefantrine, and the other of the layers contains lumefantrine and substantially no artesunate.
- 20 6. A composition according to claim 1 2 or 3, provided in the form of a capsule containing granules of artesunate in combination with granules of lumefantrine.
7. A pharmaceutical composition according to any preceding claim, wherein the dosage unit contains from 25 to 200 mg artesunate.
- 25 8. A pharmaceutical composition according to any preceding claim, wherein the dosage unit contain 50 mg artesunate.
9. A pharmaceutical composition according to any preceding claim, wherein the dosage unit contains 93 to 160 mg lumefantrine.
- 30 10. A pharmaceutical composition according to any preceding claim, wherein the dosage unit contains 120 mg lumefantrine.

11. A composition according to any preceding claim, further comprising a pharmaceutically acceptable carrier.
- 5 12. A composition according to claim 11, wherein the pharmaceutically acceptable carrier includes one or more of diluents, binders, disintegrants, wetting agents, glidants, lubricants.
13. A pharmaceutical composition according to any preceding claim for use as a
10 medicament.
14. A pharmaceutical composition according to any one of claims 1 to 12 for use as a medicament in the treatment of malaria.
- 15 15. A pharmaceutical composition according to any one of claims 1 to 12 for use as a medicament in the treatment of a malaria infection caused by *P.falciparum*.
16. A method of treating malaria comprising administering a therapeutically effective amount of a pharmaceutical composition according to any one of claims 1 to 12 to a
20 mammal in need thereof.
17. A method of treating a malaria caused by *P.falciparum*, comprising administering a therapeutically effective amount of a pharmaceutical composition according to any one of claims 1 to 12 to a mammal in need thereof.
25
18. A method according to claim 17, wherein the mammal is a human.
19. A method of manufacturing a pharmaceutical composition comprising:
 - (i) preparing a first formulation comprising lumefantrine,
 - 30 (ii) separately preparing a second formulation comprising artesunate using a dry preparation process,

- (iii) and preparing a single dose pharmaceutical composition comprising artesunate and lumefantrine by combining the first and second formulations.

- 5 20. A method according to claim 19, wherein the first formulation is prepared by wet granulation of the lumefantrine.
21. A method according to claim 19 or 20, wherein the second formulation is prepared by dry granulation of the artesunate or direct compression of the artesunate.
- 10 22. A method according to claim 19, 20 or 21, wherein the single dose pharmaceutical composition is in the form of tablet formed by preparing the first formulation in the form of granules of lumefantrine, preparing the second formulation in the form of granules of artesunate, mixing the granules of lumefantrine and artesunate, then compressing the mixture of granules to form a tablet.
- 15 23. A method according to claim 19, 20 or 21, wherein the single dose pharmaceutical composition is in the form of a bilayered tablet formed by preparing the first formulation in the form of granules of lumefantrine, preparing the second formulation in the form of granules of artesunate, separately pre-compressing the first and second formulations to provide a first layer comprising lumefantrine and a second layer comprising artesunate, combining the two layers, then compressing the two combined layers.
- 20 24. A method according to claim 19, 20 or 21, wherein the single dose pharmaceutical composition is in the form of a bilayered tablet formed by preparing the first formulation in the form of granules of lumefantrine, precompressing the first formulation to provide a first layer comprising lumefantrine, separately directly compressing artesunate to provide a second layer comprising the artesunate, combining the two layers, then compressing the two combined layers.
- 25 25. A method according to claim 19, 20 or 21, wherein the single dose pharmaceutical composition is in the form of a capsule is formed by preparing the first formulation in the form of granules of lumefantrine, preparing the second formulation in the form of
- 30

granules of artesunate, placing the granules of artesunate and lumefantrine, in a predetermined proportion, within a capsule, then sealing the capsule.

26. A method according to any one of claims 19 to 25, wherein the first formulation
5 comprising lumefantrine further comprises a pharmaceutically acceptable carrier.
27. A method according to any one of claims 19 to 26, wherein the second formulation comprising artesunate further comprises a pharmaceutically acceptable carrier.
- 10 28. A method according to claim 26 or 27, wherein the pharmaceutically acceptable carrier comprises one or more of diluents, binders, disintegrants, wetting agents, glidants, lubricants.