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(71) Applicant *(for GB only)*: PFIZER LIMITED [GB/GB]; Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(71) Applicant *(for all designated States except GB US)*: PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: HARDING, Valerie, Denise [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(74) Agents: HAYLES, James, Richard et al.; Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

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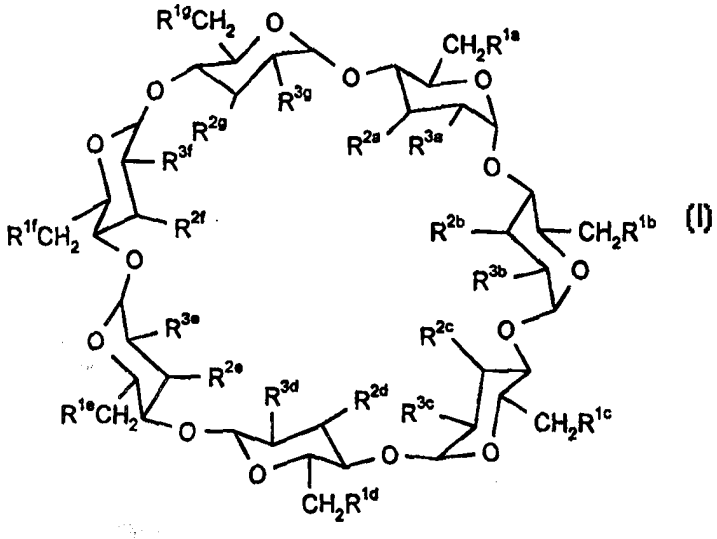
(54) Title: PHARMACEUTICAL FORMULATIONS CONTAINING VORICONAZOLE

(57) Abstract

The invention provides a pharmaceutical formulation comprising voriconazole, or a pharmaceutically acceptable derivative thereof, and a cyclodextrin derivative of formula (I), wherein R^{1a-g}, R^{2a-g} and R^{3a-g} independently represent OH or $O(CH_2)_4SO_3H$; or a pharmaceutically acceptable salt thereof.



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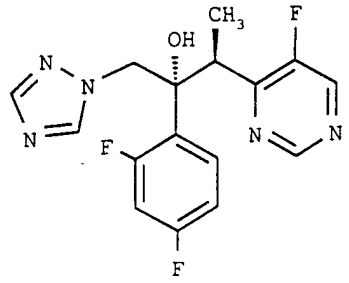
Pharmaceutical formulations containing voriconazole

This invention relates to a new pharmaceutical formulation of voriconazole with a sulphobutylether β-cyclodextrin.

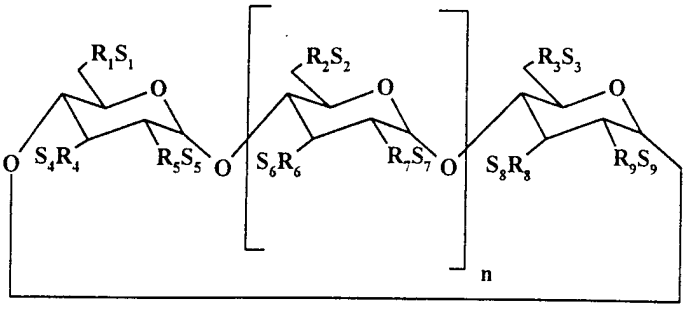
Voriconazole is disclosed in European Patent Application 0440372 (see Example 7). It has the following structure:



and is useful in the treatment of fungal infections. Voriconazole has a low aqueous solubility (0.2mg/ml @ pH 3), and is not stable in water (an inactive enantiomer is formed from recombination of the retro-aldol products of hydrolysis). Thus, development of an aqueous intravenous formulation with a sufficient shelf life is difficult. These problems are magnified by the semi-polar nature of the compound (log D = 1.8) which means that it is not generally solubilised by conventional means such as oils, surfactants or water miscible co-solvents.

European Patent Application 0440372 mentions that the compounds disclosed therein may be formulated with cyclodextrin: however, it is now suspected that underivatised or unmetabolised cyclodextrin has toxic effects on the body and so is unsuitable as a pharmaceutical excipient, particularly when administered parenterally.

International Patent Application WO 91/11172 discloses sulphoalkylether cyclodextrin derivatives of formula A,



(A)

wherein

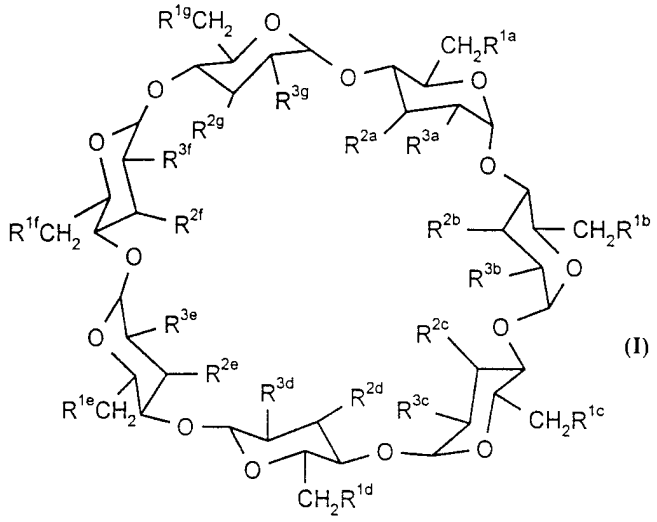
n is 4, 5 or 6;

R_{1-9} independently represent O^- or O-(C_{2-6} alkylene)-SO^-, provided that at least one of R_1 and R_2 is O-(C_{2-6} alkylene)-SO^-; and

S_{1-9} independently represent a pharmaceutically acceptable cation (such as H^+ or Na^+).

It has now been found that the solubility of voriconazole in water can be increased by molecular encapsulation with sulphoalkylether cyclodextrin derivatives of the type disclosed in International Patent Application WO 91/11172, particularly when n is 5 (a β-cyclodextrin derivative) and the cyclodextrin ring is substituted by sulphobutyl groups.

Thus, according to the present invention, there is provided a pharmaceutical formulation comprising voriconazole, or a pharmaceutically acceptable derivative thereof, and a cyclodextrin derivative of formula I,



(I)

wherein

R^{1a-g}, R^{2a-g} and R^{3a-g} independently represent OH or $O(CH_2)_4SO_3H$;

provided that at least one of R^{1a-g} represents $O(CH_2)_4SO_3H$;

or a pharmaceutically acceptable salt thereof.

Pharmaceutically acceptable salts of particular interest are salts of the $O(CH_2)_4SO_3H$ groups, for example alkali metal salts, such as sodium salts.

Preferably, the average number of $O(CH_2)_4SO_3H$ groups per molecule of formula I is in the range 6.1-6.9, for example 6.5. This enhances molecular encapsulation resulting in enhanced voriconazole solubility. This effect would not be anticipated because increasing the degree of substitution increases steric hindrance around the cavity of the cyclodextrin and would be expected to reduce complexation efficiency.

It is preferred that each $O(CH_2)_4SO_3H$ present is in the form of an alkali metal salt (such as the sodium salt). This enhances the affinity of the molecule for voriconazole, which is unexpected because voriconazole is not charged.

Preferably, the formulation is for parenteral administration, for example, i.v. administration.

The aqueous stability of the voriconazole-cyclodextrin derivative complex is further enhanced by lyophilisation (freeze-drying). The cyclodextrin derivatives used in formulations according to the invention enable the finished lyophilised product to accommodate high levels of moisture (up to 3.0%) without a detrimental effect on stability. Furthermore, the use of such cyclodextrin derivatives controls and minimises the formation of the inactive enantiomer of voriconazole.

Generally, in aqueous intravenous and intramuscular formulations according to the invention, the voriconazole will be present at a concentration of from 5 mg/ml to 50 mg/ml, for example 10 mg/ml to 30 mg/ml. The cyclodextrin derivative of formula I will be present in a molar ratio of voriconazole:cyclodextrin derivative of from 1:1 to 1:10, for example 1:2 to 1:7, in particular 1:2 to 1:3. The formulations may be lyophilised (freeze dried) for storage prior to use, and made up with water when required.

In the following example, the sulphobutylether β-cyclodextrin has an average sulphobutylether substitution of 6.5 per cyclodextrin molecule, and each sulphobutylether unit is present as its sodium salt.

Example 1

i.v. formulation of voriconazole

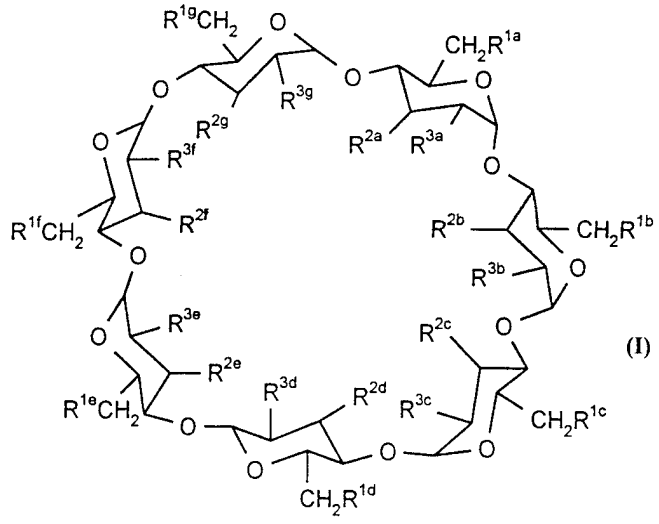
Ingredient	Specification	mg/ml
Voriconazole	Pfizer	10.000
Sulphobutylether β-cyclodextrin	Pfizer	160.000
Water for injections	Ph. Eur.	to 1.000 ml
	Total	1.000 ml

Method:

1. With constant stirring, add the sulphobutylether β cyclodextrin (SBECD) to 80% of the final volume of water for injections, and continue to stir until all the SBECD has dissolved.
2. Add the voriconazole and dissolve with stirring.
3. Make the solution up to volume with water for injections.
4. Filter the resulting solution through a sterile 0.2 mm nylon filter into a sterile container.
5. Fill 20 ml volumes into sterile freeze drying vials and stopper. Lyophilise.

Claims:

1. A pharmaceutical formulation comprising voriconazole, or a pharmaceutically acceptable derivative thereof, and a cyclodextrin derivative of formula I,



(I)

wherein

R^{1a-g}, R^{2a-g} and R^{3a-g} independently represent OH or $O(CH_2)_4SO_3H$;

provided that at least one of R^{1a-g} represents $O(CH_2)_4SO_3H$;

or a pharmaceutically acceptable salt thereof.

2. A formulation as claimed in claim 1, wherein the average number of $O(CH_2)_4SO_3H$ groups per molecule of formula I is in the range 6.1-6.9.

3. A formulation as claimed in claim 1 or claim 2, wherein each $O(CH_2)_4SO_3H$ present is in the form of an alkali metal salt.

4. A formulation as claimed in any one of the preceding claims, which is adapted for parenteral administration.

5. A formulation as claimed in any one of the preceding claims, wherein the cyclodextrin derivative of formula I is present in a molar ratio of voriconazole:cyclodextrin derivative of from 1:1 to 1:10.

6. A formulation as claimed in any one of the preceding claims, which is a solution in water.

7. A formulation as claimed in any one of claims 1-5, which has been lyophilised.

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/EP 98/03477

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K47/40

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 440 372 A (PFIZER INC.) 7 August 1991 cited in the application see claims; example 7	1-7
A	EP 0 357 241 A (PFIZER LIMITED) 7 March 1990 see claims	1-7
A	WO 94 02518 A (THE UNIVERSITY OF KANSAS) 3 February 1994 see claims	1-7
A	WO 91 11172 A (THE UNIVERSITY OF KANSAS) 8 August 1991 cited in the application see claims	1-7

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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