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(54) Title: PHARMACEUTICAL COMPOSITIONS

(57) Abstract

A pharmaceutical composition in the form of a solid dispersion comprising a macrolide, e.g. a rapamycin or an ascomycin, and a carrier medium.

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Pharmaceutical compositions

This invention relates to oral pharmaceutical compositions comprising a macrolide, e.g. a rapamycin or an ascomycin, in a solid dispersion.

Rapamycin is an immunosuppressive lactam macrolide produceable, for example by Streptomyces hygroscopicus. The structure of rapamycin is given in Kesseler, H., et al.; 1993; Helv. Chim. Acta; 76: 117. Rapamycin is an extremely potent immunosuppressant and has also been shown to have antitumor and antifungal activity. Its utility as a pharmaceutical, however, is restricted by its very low and variable bioavailability. Moreover, rapamycin is highly insoluble in aqueous media, e.g. water, making it difficult to formulate stable galenic compositions. Numerous derivatives of rapamycin are known. Certain 16-O-substituted rapamycins are disclosed in WO 94/02136, the contents of which are incorporated herein by reference. 40-O-substituted rapamycins are described in, e.g., in US 5 258 389 and WO 94/09010 (O-aryl and O-alkyl rapamycins); WO 92/05179 (carboxylic acid esters), US 5 118 677 (amide esters), US 5 118 678 (carbamates), US 5 100 883 (fluorinated esters), US 5 151 413 (acetals), US 5 120 842 (silyl ethers), WO 93/11130 (methylene rapamycin and derivatives), WO 94/02136 (methoxy derivatives), WO 94/02385 and WO 95/14023 (alkenyl derivatives) all of which are incorporated herein by reference. 32-O-dihydro or substituted rapamycin are described, e.g., in US 5 256 790, incorporated herein by reference.

Further rapamycin derivatives are described in PCT application number EP96/02441, for example 32-deoxorapamycin as described in Example 1, and 16-pent-2-ynyloxy-32(S)-dihydrorapamycin as described in Examples 2 and 3. The contents of PCT application number EP96/02441 are incorporated herein by reference.

Rapamycin and its structurally similar analogues and derivatives are termed collectively herein as "rapamycins".

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On oral administration to humans, solid rapamycins, e.g. rapamycin, may not be absorbed to any significant extent into the bloodstream. Simple mixtures are known for rapamycins, e.g. rapamycin, with conventional pharmaceutical excipients; however, disadvantages encountered with these compositions include unpredictable dissolution rates, irregular bioavailability profiles, and instability. To date there is no conveniently administrable oral solid formulation available for rapamycin or a derivative thereof.

Accordingly, in one aspect, this invention provides a pharmaceutical composition in the form of a solid dispersion comprising a rapamycin and a carrier medium.

The compositions of this invention provide a high bioavailability of drug substance, are convenient to administer, and are stable.

The rapamycin used in the compositions of this invention may be any rapamycin or derivative thereof, for example as disclosed above or in the above-mentioned patent applications.

Thus the rapamycin used in the solid dispersion compositions of this invention may be rapamycin or an O-substituted derivative in which the hydroxyl group on the cyclohexyl ring of rapamycin is replaced by $-OR_1$ in which R_1 is hydroxyalkyl, hydroxyalkoxyalkyl, acylaminoalkyl and aminoalkyl; e.g. as described in WO94/09010, for example 40-O-(2-hydroxy)ethyl-rapamycin, 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin and 40-O-(2-acetaminoethyl)-rapamycin. The rapamycin derivative may be a 26- or 28-substituted derivative.

Preferred rapamycins for use in the solid dispersion compositions of this invention include rapamycin, 40-0-(2-hydroxy)ethyl rapamycin, 32-deoxorapamycin and 16-pent-2-ynyloxy-32(S)-dihydrorapamycin. A more preferred rapamycin is 40-0-(2-hydroxy)ethyl rapamycin (hereinafter referred to as compound X).

Numbering of rapamycin derivatives as used herein refers to the structure disclosed as

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Formula A at page 4 of published PCT application WO 96/13273, the contents of which are incorporated herein by reference.

The term solid dispersion as used herein is understood to mean a co-precipitate of the rapamycin, e.g. 40-0-(2-hydroxy)ethyl rapamycin or rapamycin, with the carrier medium. In the solid dispersion, the rapamycin is in amorphous or substantially amorphous form and is physically bound to the carrier medium.

Compositions of this invention may be administered in any convenient form, for example tablet, capsule, granule or powder form, e.g. in a sachet.

The rapamycin may be present in the composition in an amount of about 0.01 to about 30-weight-% based on the weight of the composition (% w/w), and preferably in an amount of 1 to 20 % w/w based on the total weight of the composition.

The carrier medium is present in an amount of up to 99.99% by weight, for example 10 to 95 wt-%, based on the total weight of the composition.

In one embodiment the carrier medium comprises a water-soluble polymer, preferably a cellulose derivative such as hydroxypropylmethylcellulose (HPMC), hydroxypropylmethylcellulose phthalate, or polyvinylpyrrolidone (PVP). Good results may be obtained using HPMC with a low apparent dynamic viscosity, e.g. below 100 cps as measured at 20°C for a 2 % by weight aqueous solution, e.g below 50 cps, preferably below 20 cps, for example HPMC 3 cps. HPMC is well-known and described, for example, in the Handbook of Pharmaceutical Excipients, Second Edition, pub. Pharmaceutical Society of Great Britain and American Pharmaceutical Association, 1994, p.229 to 232, the contents of which are incorporated herein by reference. HPMC, including HPMC 3cps, is available commercially under the trade name Pharmacoat 603 from the Shinetsu company.

PVP is available, for example, under the name Povidone (Handbook of Pharmaceutical

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