

Pharmaceutical preparation containing an antivirally active dihydroquinazoline derivative

The present invention relates to a pharmaceutical composition, containing {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazoline-4-yl} acetic acid or a salt, a solvate or a solvate of a salt thereof.

The invention further relates to methods for the production and use of the composition in methods of treatment and/or prevention of virus infections, as well as its use for the production of medicinal drugs for use in treating and/or preventing virus infections, in particular for use in treating infections with the human cytomegalovirus (HCMV) or another representative of the Herpes viridae group.

{8-fluoro-2-[4-(3-methoxyphenyl)piperazine-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazoline-4-yl} acetic acid is known, for example, from WO 2004/096778, full disclosure of which is included herein by reference; it was developed by Applicant as a promising candidate for an antivirally active substance, in particular for combating infections caused by the human cytomegalovirus. However, in the course of development it was discovered that problems occurred with the solubility of the substance, and in particular it proved complicated to produce stable formulations for intravenous administration or solid easily soluble compositions for producing solutions used for intravenous administration.

Summary

It is thus an object of the ~~invention~~ present disclosure to describe a pharmaceutical composition that is used in particular for intravenous administration, that contains {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazoline-4-yl} acetic acid, that has long-term stability and can be stored, and that in addition has a substantially physiological pH.

A further object of the ~~invention~~ present disclosure is to describe a pharmaceutical composition with which it is possible, in a simple and reliable manner, to produce pharmaceutical compositions for intravenous administration which contain

{8-fluoro-2-[4-(3-methoxyphenyl)piperazine-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazoline-4-yl}acetic acid and which also remain stable for an adequate period of time, e.g. more than 24 hours.

5 In a first aspect, there is provided a pharmaceutical composition, particularly for intravenous administration, comprising the following, namely: a) {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazoline-4-yl}acetic acid or a salt, a solvate or a solvate of a salt thereof, b) at least one excipient selected from the cyclodextrins, lysine and arginine, and c) water.

10 In a second aspect, there is provided a solid pharmaceutical composition produced by lyophilizing a pharmaceutical preparation as disclosed herein.

In a third aspect, there is provided a method for producing a pharmaceutical composition as disclosed herein using the following steps, namely: A) Dissolving the at least one excipient in the water, B) Adding {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-1-yl]-3-[2-methoxy-5-(tri-fluoromethyl)phenyl]-3,4-dihydroquinazoline-4-yl}acetic acid or a salt, a solvate or a solvate of a salt thereof to the solution obtained in step A), C) If necessary, add at least one sugar and/or at least one buffer, D) Adjust the pH to the desired value in order to obtain a pharmaceutical composition, and E) Sterile-filter the solution obtained in step D) and fill into suitable containers. F) If necessary, perform a final sterilization of the solution obtained in step E) under heat.

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In a fourth aspect, there is provided a method for producing a pharmaceutical composition as disclosed herein using the following steps, namely: I.) Dissolving the at least one excipient in a part of the water, II.) Adding {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-1-yl]-3-[2-methoxy-5-(tri-fluoromethyl)phenyl]-3,4-dihydroquinazoline-4-yl}acetic acid or a salt, a solvate or a solvate of a salt thereof to the solution obtained in step I.), III.) If necessary, adjusting the pH of the solution obtained in step II.) to the desired value to obtain a first solution, IV.) Dissolving at least one sugar and/or a buffer in a part of the water, V.) If necessary, adjust the pH of the solution obtained in step IV.) to the desired value to obtain a second solution, VI.) Mixing the first and second solution to obtain a

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pharmaceutical composition, and VII.) Sterile filtration of the solution obtained in step VI.) and filling into suitable containers. VIII.) If necessary, perform a final sterilization of the solution obtained in step VII.) under heat.

5 In a fifth aspect, there is provided a method for producing a pharmaceutical composition as disclosed herein using the following steps, namely: a.) Adding {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-1-yl]-3-[2-methoxy-5-(tri-fluoromethyl)phenyl]-3,4-
dihydroquinazoline-4-yl}acetic acid or a salt, a solvate or a solvate of a salt to an aqueous
NaOH solution, preferably an aqueous 0.1M NaOH solution to produce a solution or
10 suspension, b.) Adding water to the solution or suspension obtained in step a.), c.) Adding cyclodextrin and NaCl to the solution or suspension obtained in step b.), d.) Sterile
filtration of the solution obtained in step c.) and fill into suitable containers. e.) If
necessary, perform a final sterilization of the solution obtained in step d.) under heat.

15 In a sixth aspect, there is provided a method for producing a solid pharmaceutical composition as disclosed above comprising the production of a pharmaceutical composition corresponding to a method as disclosed above followed by lyophilization of the pharmaceutical composition obtained in order to obtain a solid pharmaceutical composition.

20 In a seventh aspect, there is provided the pharmaceutical composition as disclosed herein for use in a method of treatment and/or prophylaxis of diseases, in particular of virus infections, preferably human cytomegalovirus (HCMV) infections or infections with another member of the herpes viridae group.

25 In an eighth aspect, there is provided the use of a pharmaceutical composition as disclosed herein for producing a medicament for the treatment and/or prophylaxis of diseases, in particular of virus infections, preferably human cytomegalovirus (HCMV) infections or infections with another member of the herpes viridae group.

Detailed Description

30 Within the scope of the invention the term "stability" is understood to mean not only the chemical stability of the constituents of the pharmaceutical composition, but also the

stability of the solution itself. In particular, the composition according to the invention must be stable against precipitation of the constituents.

In this context, the term "stability" means that at 2 °C to 8 °C, or at 25 °C or at 40 °C the pharmaceutical compositions according to the invention contain a minimum proportion of >90% and preferably >95% {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazoline-4-yl}acetic acid for a storage period of at least two, preferably at least three, and most preferred at least six weeks, when said liquid pharmaceutical compositions are measured using one of the HPLC methods 1-3. Said stability of the liquid pharmaceutical compositions is regarded as adequate within the scope of the invention.

Furthermore, the term "stability" means that, after they have been diluted or reconstituted to a final concentration of 0.8-10 mg/ml for infusion at 2 °C to 8 °C, the compositions according to the invention contain a minimum proportion of 90%, preferably at least 95%, of {8-fluoro-2-[4-(3-methoxyphenyl)piperazine-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazoline-4-yl}acetic acid for a period of at least four hours, preferably at least six hours, and most preferred at least 24 hours in storage when, after dilution or reconstitution, said liquid pharmaceutical compositions are measured using one of the HPLC methods 1-3. Said stability of the pharmaceutical compositions after dilution or reconstitution is regarded as adequate within the scope of the invention.

It has surprisingly been discovered that pharmaceutical compositions, in particular those used for intravenous administration, that contain

16. The pharmaceutical composition according to any one of claims 1 to 11 for use in a method of treatment and/or prophylaxis of diseases, in particular of virus infections, preferably human cytomegalovirus (HCMV) infections or infections with another member of the herpes viridae group.

~~17. The use of a pharmaceutical composition according to any one of claims 1 to 11 in a method of treatment and/or prophylaxis of diseases, in particular of virus infections, preferably human cytomegalovirus (HCMV) infections or infections with another member of the herpes viridae group.~~

~~18.~~ 17. The use of a pharmaceutical composition according to any one of claims 1 to 11 for producing a medicament for the treatment and/or prophylaxis of diseases, in particular of virus infections, preferably human cytomegalovirus (HCMV) infections or infections with another member of the herpes viridae group.

~~19. A method for combating virus infections, preferably human cytomegalovirus (HCMV) infections or infections with another member of the herpes viridae group, in humans and animals by administering a pharmaceutical composition according to any one of claims 1 to 11 or a pharmaceutical composition produced according to any one of claims 12 to 15 to a human or an animal who or which requires such a treatment.~~