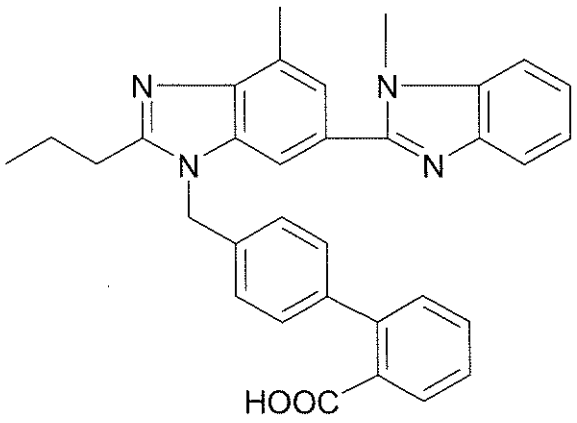
105630 PCT

Oral suspension comprising telmisartan

The present invention relates to a pharmaceutical solution, preferably a drinkable pharmaceutical solution with a pH of 10 or more containing an angiotensin-II-receptor antagonist, preferably the active substance telmisartan, as well as one or more sugar alcohols added in order to improve flavour and shelf life, wherein the content of reducing sugars before the addition of the sugar alcohol or alcohols to the solution does not exceed 1000 ppm.

Background to the invention

Telmisartan, the INN name of the compound 4'-((2-n-propyl-4-methyl-6-(1-methylbenz-imidazol-2-yl)-benzimidazol-1-yl)methyl)biphenyl-2-carboxylic acid (IUPAC) having the following formula



is an angiotensin-II-receptor antagonist, which is licensed for the treatment of hypertension and is available in tablet form in different dosage strengths. For use in children, particularly children under 6 years old, and in older or sick people with difficulty swallowing, it is often not possible to use tablets as a medical formulation. In domestic pets such as dogs and cats it would theoretically be possible to administer tablets, but often the tablets are held in the animal's cheek pouches and spat out again later, thus seriously impairing the dosage reliability. In addition, it is only possible to adapt dosage to weight to a limited extent, owing to the given fixed dosage steps of the tablets.

More suitable, and preferable from a physiological point of view, is a drinkable solution, free from organic cosolvents, which may be administered in controlled amounts using suitable

calibrated dosing aids such as dosage sprays, pipettes, spoons or cups. There is also the possibility of making the formulation more acceptable to children and even pets by the addition of flavour improvers, which is advantageous particularly for long-term administration for treating hypertension.

Description of the invention

The aim of the present invention is to provide a pharmaceutical solution, preferably a drinkable pharmaceutical solution containing an angiotensin-II-receptor antagonist. Preferred angiotensin II receptor antagonists are the substances known by the following INN names: candesartan, eprosartan, irbesartan, losartan, olmesartan, tasosartan, telmisartan and valsartan, and the pharmaceutically acceptable salts, hydrates or polymorphs thereof. The concentration of the angiotensin-II-receptor antagonist, preferably telmisartan, needed in the solution in order to achieve therapeutic doses should be between 1 mg/ml and 10 mg/ml. Moreover, because of the strongly pH-dependent solubility profile of telmisartan an aqueous formulation should have a pH that is either less than 2 or more than 10, in order to ensure a physically stable solution.

Based on these requirements, attempts were made first of all to provide a formulation in the acid pH range, as significantly more preservatives are available for this pH range, if needed (the use of multi-dose containers for this intended application is clearly preferable).

The following main ingredients of the formulation were used:

a) pH-active components for ensuring solubility in the desired concentration range;
b) flavour-correcting components (sugars, sugar alcohols, sugar substitutes, flavour additives) to mask the bitter, rasping taste of telmisartan;
c) texture enhancers, usually viscosity-increasing adjuvants such as for example cellulose derivatives, PVP, glycerol;
d) preservatives for ensuring microbiological quality in the multi-dose container
e) optionally antioxidants such as for example BHA, BHT, EDTA or propylgallate for stabilising the formulation.

During this development work it was surprisingly found that for concentrations of active substance greater than 1 mg/ml a pH of less than 1.5 is needed, which requires the use of strong organic acids such as for example methanesulphonic acid or phosphoric acid. The very powerfully astringent effect of such acidic solutions makes acidic formulations of this

kind totally unsuitable for long-term use particularly in children but also in domestic pets such as dogs and cats.

Further development work therefore had to be unexpectedly shifted to the pH range ≥10. The base components used for this were first of all sodium hydroxide solution, meglumine or a combination of sodium hydroxide solution and meglumine, in order to produce a physically and chemically stable solution. The use of alkali metal or alkaline earth metal carbonates/-hydrogen carbonates does not produce a sufficiently high pH in the present instance. The use of ethanolamines was also ruled out in view of the administration route and target group.

For masking or improving the bitter, rasping taste of telmisartan in solution, besides conventional quantities of synthetic sugar substitutes (saccharine, saccharine-Na, Na-cyclamate, acesulfame, aspartame, sucralose etc.), which have a risk of intolerance or in some cases are not internationally permitted (Na-cyclamate), sugar alcohols such as for example xylitol, maltitol, sorbitol, or mannitol were investigated for their suitability. They are not cariogenic (converted slowly into the acid) and have a low calorific value, which is a major advantage for long-term use particularly in children but also in pets. Although they are suitable in principle, the use of the normal sugars (glucose, glucose syrup, fructose, saccharose, maltose, lactose etc.) is avoided because of the disadvantages mentioned above (cause of tooth decay, calorie loading).

Against the background of the target groups and long-term administration the addition of flavourings was largely avoided because of the potential for allergies, although it is theoretically possible to add a substance without affecting the properties of the telmisartan solution according to the invention. Examples of such flavourings are cherry, strawberry, raspberry, tutti-frutti, currant, caramel, chocolate and mint flavourings, as well as meat and fish flavourings for animals.

In order to improve the subjective overall impression of the telmisartan solution according to the invention (fullness/ consistency/ viscosity/ texture) it is also possible to use glycerol as well as cellulose derivatives such as hydroxyethylcellulose, hydroxypropylcellulose, methylcellulose or hydroxypropylmethylcellulose; or soluble PVP in small concentrations. Their use is not necessary but is useful for prolonging the contact times before the taste receptors are reached, and thereby further masking the bitter flavour.

There are only a very few preservatives available in suitable concentrations for the pH range of 10 and above: thus, apart from the phenol derivatives such as e.g. the cresols, which are used predominantly parenterally in the field of insulin formulations, only the quaternary ammonium compounds are available. Their toxicity must be viewed critically with regard to the target groups and long-term administration. Thus, basically, the only sufficiently acceptable option available is benzalkonium chloride, but its orally unpleasant bitter flavour represents an additional problem. Therefore investigations were carried out first of all to determine the degree to which the concentration of the sugar alcohols used was able to meet the requirements of the Pharmacopoeia regarding the Preservation Loading Test (PLT) summarised in the following Table.

	Required reduction in number of microbes in log PFU per test microbe Preservation loading test according to USP or Ph.Eur.			
	after 14 days' incubation		after 28 days' incubation	
	USP	Ph.Eur.	USP	Ph.Eur.
Bacteria *	1	3	no increase	no increase
Fungi**	no increase	1	no increase	no increase

* E.coli, S.aureus, P.aeruginosa ** C.albicans, A.niger

Because of their sweetening power and taste similarity to glucose in terms of sweet sensation the sugar alcohols xylitol, maltitol, sorbitol and mannitol are particularly preferred. Maltitol is particularly preferred. However, identical results in terms of preserving effect can also be obtained with the other sugar alcohols. Surprisingly it has been found that above a sugar alcohol concentration of at least 60% (percent by weight/volume) in a drinkable aqueous telmisartan solution the requirements of the USP Pharmacopoeia in a preservative load are met, but the enhanced requirements of the European Pharmacopoeia are not. The criteria of the USP Preservation Loading Test are met less reliably as the concentration of active substance increases, but can be demonstrated up to an active concentration of 4 mg/ml.

Surprisingly it has now been found that reliably meeting the criteria of the USP Preservation Loading Test and also the concentration of telmisartan and the sugar alcohol concentration are dependent on the quality of the sugar alcohol or alcohols used. Of particular importance

is the quantity of reducing sugars present. A content of up to 0.2% is permitted according to the Pharmacopoeia monograph. Within the scope of our investigations it has become apparent that to ensure that the USP Preservation Loading Test is safely complied with the content of reducing sugar (primarily maltose and glucose) in the sugar alcohol, i.e. the quantity of reducing sugars in the sugar alcohol should not exceed 1000 ppm, best of all should not exceed 300 ppm, before the addition.

The threshold value of less than 300 ppm of reducing sugar in the maltitol corresponds to less than 300 mg of reducing sugar per kg of maltitol, or less than 0.3 mg of reducing sugar per g of maltitol.

A 60% sugar alcohol solution (i.e. 60 g sugar alcohol per 100 ml of solution) thus should contain at most 18 mg of reducing sugar per 100 ml or 0.18 mg reducing sugar per ml of drinkable solution.

The threshold value represents, for example, for a

- 40% sugar alcohol solution less than 0.12 mg reducing sugar per ml of drinkable solution;
- 50% sugar alcohol solution less than 0.15 mg reducing sugar per ml of drinkable solution;
- 60% sugar alcohol solution less than 0.18 mg reducing sugar per ml of drinkable solution;

or for a

- 70% sugar alcohol solution less than 0.21 mg reducing sugar per ml of drinkable solution

Based on the amount of active substance of the angiotensin II receptor antagonist, preferably telmisartan, the content of reducing sugars should be less than 20 percent by weight, preferably less than 10 percent by weight and particularly preferably less than 5 percent by weight .

Surprisingly it has thus been shown that the stability of a drinkable telmisartan solution is dependent on the amount of reducing sugar contained in the sugar alcohol. Thus, the stability of a drinkable telmisartan solution deteriorates as the content of reducing sugars increases. Acidic breakdown products are formed resulting in a drop in the pH within the solution, which finally leads to the precipitation of the telmisartan as soon as the pH falls below 9.5/9.0. However, to obtain a telmisartan solution which is stable on storage, it is essential to add sugar alcohols such as e.g. xylitol, sorbitol or maltitol, provided that the amount of reducing sugars in the sugar alcohol of an aqueous drinkable telmisartan solution with a pH of $\geq$ 10 or higher is limited to below the content of sugar alcohols specified

according to the Pharmacopoeia. A threshold value of 300 ppm or less is preferred. A correspondingly prepared aqueous drinkable telmisartan solution is stable for long periods. It thus has a storage stability of at least 12 months at 25°C/60% RH and 30°C/70% RH, preferably at least 36 months at 25°C/60% RH and 30°C/70% RH. However it has also been found that a quantity of reducing sugars of at least 250 ppm has a positive effect on the stability of the active substance. Consequently, a content of between 1000 ppm, preferably 300 ppm and 250 ppm, of reducing sugars in the pharmaceutical solution is to be regarded as being preferred.

A drinkable telmisartan solution prepared using a sugar alcohol with a content of reducing sugar of 300 ppm or less does not require any antioxidants or stabilisers, and their addition is thus optional.

As the exclusive use of one or more sugar alcohols meets only the USP requirement for adequate preservation, the addition of benzalkonium chloride as a preservative was investigated by way of example for international licensing. The target was to add the smallest possible amount to meet the criteria, in accordance with the requirements laid down by the Pharmacopoeias. It was demonstrated that aqueous drinkable telmisartan solutions in a range of concentrations from 1-10 mg/ml, preferably 1-5 mg/ml, with a pH value of ≥ 10 or higher, a content of sugar alcohol of 40 percent by weight/volume (% W/V) or more as well as other optional formulation adjuvants above a benzalkonium chloride concentration of 0.005% W/V or higher reliably meet the requirements of the Ph.Eur. as well, while reliably masking the bitter taste of the benzalkonium chloride. Thus on the one hand it is ensured that the requirements of the Ph.Eur. are met and on the other hand the physiological loading is reduced to a minimum.

Preparation process

The present invention also describes a process for preparing the drinkable telmisartan solution according to the invention containing 1-10 mg/ml telmisartan, preferably 1-5 mg/ ml telmisartan. As far as possible this process also uses methods known from the literature for aqueous solutions to be taken orally.

The process is characterised in that a suitable amount of active substance, optionally in the form of a salt or hydrate, is combined with a molar excess of a physiologically acceptable base dissolved in water, in order to obtain a solution with a pH of ≥ 10. Further formulation adjuvants are optionally added, and the solution is made up with purified water to obtain a concentration range of 1-10 mg of active substance per millilitre of solution. It should be noted that the solution corresponds to the properties already mentioned, particularly that of the pH value of ≥ 10.

In one particular embodiment a consistency-providing component such as for example a cellulose derivative or PVP is pre-swollen in a given amount of purified water at ambient temperature, then heated to a temperature of 70-80°C until fully dissolved and then adjusted to a pH of 10 by the addition of the physiologically acceptable base, while the temperature is maintained at 70-80°C. The active substance is then added, with stirring, until a concentration of 1-10 mg/ml is obtained, and the sugar alcohol containing an amount of less than 1000 ppm, preferably less than 300 ppm of reducing sugar is added and dissolved. After the addition and dissolving of the sugar alcohol the solution is cooled to room temperature. Other formulation adjuvants such as synthetic sugar substitutes, flavourings or preservatives are added at RT with stirring. Finally, the pH is restored to 10 using the physiologically acceptable base, before purified water is added to top up to the required weight/volume. Lastly, the solution can be filtered to eliminate particulate impurities, before being transferred into suitable glass or plastic bottles.
The drinkable telmisartan solution according to the invention exhibits high stability on storage, which is not limited either by physical instability or by breakdown reactions of the active substance, and in terms of the selected pH it is sufficiently well tolerated physiologically.

The drinkable telmisartan solution according to the invention will now be explained by means of the following Examples. The Examples serve only as an illustration and are not to be regarded as restrictive.

EXAMPLES

Example 1

telmisartan	0.2 g
NaOH 1N	0.68 ml
maltitol*	60.0 g
hydroxyethylcellulose	0.1 g
purified water	ad 100 ml
pH	10
stability 25°C/ 60% RH 30°C/ 70% RH	 > 12 (18?) months > 12 (18?) months
Complies with PLT** according to USP/ Ph.Eur.	USP

* ≤ 300 ppm red. sugar, ** PLT = preservation loading test

Example 2

telmisartan	0.1 g
meglumine	0.6 g
maltitol*	50.0 g
saccharine-Na	0.6 g
hydroxyethylcellulose	0.1 g
purified water	ad 100 ml
pH	10
stability 25°C/ 60% RH 30°C/ 70% RH	 > 12 months > 12 months
Complies with PLT** according to USP/ Ph.Eur.	---

* ≤ 300 ppm red. sugar, ** PLT = preservation loading test

Example 3

telmisartan	4 mg/ ml
NaOH 1N	0.8 ml
maltitol*	60.0 g
hydroxyethylcellulose	0.1 g
benzalkonium chloride	0.005 %
purified water	ad 100 ml
pH	10
stability 25°C/ 60% RH 30°C/ 70% RH	 > 24 months > 24 months
Complies with PLT** according to USP/ Ph.Eur.	USP and Ph.Eur.

* ≤ 300 ppm red. sugar, ** PLT = preservation loading test

Example 4

telmisartan	0.40 kg/ 100 L
NaOH 1N	0.8 kg/ 100 L
maltitol*	60.0 kg/ 100 L
hydroxyethylcellulose	0.10 kg/ 100 L
benzalkonium chloride	0.01 kg/ 100 L%
purified water	ad 100 L
pH	10
stability 25°C/ 60% RH 30°C/ 70% RH	 > 24 months > 24 months
Complies with PLT** according to USP/ Ph.Eur.	USP and Ph.Eur.

* ≤ 300 ppm red. sugar, ** PLT = preservation loading test

Example 5

telmisartan	0.1 g
meglumine	q.s. ad pH 10
maltitol*	70.0 g
collidone K 25	0.2 g
purified water	ad 100 ml
pH	10
stability 25°C/ 60% RH 30°C/ 70% RH	 > 18 (12?) months > 18 (12?) months
Complies with PLT** according to USP/ Ph.Eur.	USP

* ≤ 300 ppm red. sugar, ** PLT = preservation loading test

Example 6

telmisartan	4 mg/ml
NaOH 1N	0.8 ml
xylitol*	60.0 g
hypromellose	0.1 g
purified water	ad 100 ml
pH	10
stability 25°C/ 60% RH 30°C/ 70% RH	 > 12 (18?) months > 12 (18?) months
Complies with PLT** according to USP/ Ph.Eur.	USP

* ≤ 300 ppm red. sugar, ** PLT = preservation loading test

Example 7

telmisartan	2 mg/ml
NaOH 1N	0.68 ml
sorbitol	60.0 g
hypromellose	0.1 g
purified water	ad 100 ml
pH	10
stability 25°C/ 60% RH 30°C/ 70% RH	 > 18 months > 18 months
Complies with PLT** according to USP/ Ph.Eur.	USP

* ≤ 300 ppm red. sugar, ** PLT = preservation loading test

Example 8

telmisartan (5 mg/ml)	0.5000 g
NaOH	1.9000 g
maltitol*	60.000 g
hydroxyethylcellulose	0.1000 g
purified water	59.1600 g
pH	10
stability 25°C/ 60% RH 30°C/ 70% RH	 > 24 months > 24 months
Complies with PLT** according to USP/ Ph.Eur.	USP

* ≤ 300 ppm red. sugar, ** PLT = preservation loading test

Patent Claims

1. Pharmaceutical solution with a pH value of 10 or higher, containing an angiotensin II receptor antagonist, characterised in that one or more sugar alcohols are present up to a total concentration of 40 wt.% to 70 wt.%, preferably 60 wt.% to 70 wt.%, wherein the sugar alcohol or alcohols have a maximum content of 1000 ppm of reducing sugar before they are added to the solution.

2. The pharmaceutical solution according to claim 1, characterised in that the solution is a drinkable solution.

3. The pharmaceutical solution according to claim 1 or 2, characterised in that the angiotensin II receptor antagonist is telmisartan.

4. The pharmaceutical solution according to one of claims 1 to 3, characterised in that the pharmaceutical solution has a maximum content of 1000 ppm of reducing sugars.

5. The pharmaceutical solution according to one of claims 1 to 4, characterised in that the pharmaceutical solution has a minimum content of 250 ppm of reducing sugars.

6. The pharmaceutical solution according to one of claims 1 to 5, characterised in that the pH is obtained by the presence of meglumine, sodium hydroxide, potassium hydroxide or a basic amino acid such as arginine or glutamine.

7. The pharmaceutical solution according to one of claims 1 to 6, characterised in that the angiotensin II receptor antagonist, preferably telmisartan, is present in a concentration of 1 to 10 mg/ml, preferably 1 to 5 mg/ml.

8. The pharmaceutical solution according to one of claims 1 to 7, characterised in that the the proportion of reducing sugars in the solution based on the quantity of active substance of the angiotensin II receptor antagonist is less than 20 % by weight.

9. The pharmaceutical solution according to one of claims 1 to 8, characterised in that the sugar alcohol or alcohols are selected from among xylitol, maltitol, sorbitol, mannitol, erythritol and isomaltol.

10. The pharmaceutical solution according to one of claims 1 to 9, characterised in that it optionally contains other formulation adjuvants.

11. The pharmaceutical solution according to one of claims 1 to 10, characterised in that o-cresol, m-cresol, p-cresol or benzalkonium chloride are added as preservatives, optionally alone or in combination.

12. The pharmaceutical solution according to one of claims 1 to 11, characterised in that it is substantially free, preferably free from antioxidants or stabilisers.

13. The pharmaceutical solution according to one of claims 1 to 12 for treating hypertension or kidney disease in people, particularly children, old people or people having difficulty swallowing; or in animals, particularly dogs or cats.

14. Method of preparing a pharmaceutical solution according to one of claims 1 to 12, characterised by
    a) dissolving the angiotensin-II-receptor antagonist, preferably telmisartan, and a sugar alcohol having a content of reducing sugars of less than 1000 ppm, preferably less than 300 ppm, in an excess of a pharmaceutically acceptable base until a pH of at least 10 or higher is obtained; and
    b) adjusting the concentration of the angiotensin-II-receptor antagonist, preferably telmisartan, to 1 to 10 mg/ml.

15. Method according to claim 14 comprising the steps of:
    a) swelling a consistency-producing agent with purified water;
    b) dissolving the swollen consistency-producing agent at a temperature of ≥ 50°C;
    c) adding a pharmaceutically acceptable base at a temperature of ≥ 50°C until a pH of ≥ 10.0 is obtained;
    d) adding and dissolving the angiotensin-II-receptor antagonist, preferably telmisartan, and the sugar alcohol at a temperature of ≥ 50°C;
    e) cooling the solution to ambient temperature; and
    f) topping up the aqueous solution with purified water to give the desired concentration of the angiotensin-II-receptor antagonist, preferably telmisartan.

16. Method according to claim 15, wherein steps b) to d) are carried out at a temperature of between 70°C and 80°C.

17. Method according to one of claims 15 or 16, wherein the process comprises the following additional step:

g) adding one or more synthetic sugar substitutes, flavourings and/or preservatives with stirring at ambient temperature.

18. Method according to claim 17, wherein the additional step g) is carried out between steps e) and f).

19. Method according to claim 14, characterised in that the pharmaceutical solution is designed to treat hypertension or kidney disease in humans or animals.

20. Glass or plastics container with or without dosing aid containing the drinkable solution according to one of claims 1 to 13.