LIQUID PREPARATION COMPRISING A COMPLEX OF PIMOBENDAN AND CYCLODEXTRIN

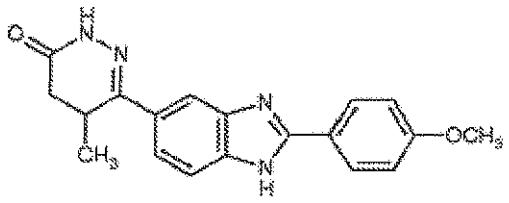
FIELD OF INVENTION

The invention relates to the field of medicine. In particular, the invention relates to novel liquid preparation comprising a substituted benzimidazol, preferably pimobendan as pharmaceutically active compound.

BACKGROUND OF THE INVENTION

Pimobendan is a well-known compound for the treatment of congestive heart failure (CHF) originating for example from dilated cardiomyopathy (DCM) or decompensated endocardiosis (DCE) in animals, especially dogs (WO 2005/092343). Pimobendan is also approved as a drug product for cardiovascular treatment of humans.

Pimobendan (4,5-dihydro-6-[2-(4-methoxyphenyl)-1H-benzimidazol-5-yl]-5-methyl-3(2H)-pyridazinone) is disclosed in EP B-008 391, herein incorporated by reference in its entirety, and having the formula:



As already was described in EP A-439 030 and WO 2005/08467, pimobendan drug substance is insoluble in water, 1 g substance is soluble in more than 10000 ml. At pH 7 the solubility of pimobendan is about 0.1 mg per 100 ml.

The substance is administered by the oral route twice daily. Yet no liquid preparation comprising pimobendan is available. In order to achieve an immediate onset of action for all the innovative indications mentioned above, an injectable solution for parenteral administration by the i.v. and/or s.c. route is obligatory. An aqueous formulation is required to administer a drug product by the i.v. / s.c. route to either humans or animals, formulations with a non-aqueous solvent are neither acceptable nor state of the art due to the risk of severe tolerance problems.

Solubility in aqueous solutions is depending on the pH. The solubility of pimobendan is significantly higher at pH 1 to 3, however, the chemical stability in solution is reduced so that a stable solution with a reasonable shelf-life cannot be achieved. In addition, the local tolerance of such a formulation is very poor. This is due to the fact that the target dose would require a drug concentration in solution which can only be achieved by a pH of about pH3 and lower. The required concentration in solution exceeds the solubility of pimobendan in water by a factor of about 250, a factor of 1 to 1000 might be the maximum required increase.

Certain etherified beta-cyclodextrin derivatives are known to improve solubility of sparingly soluble drugs (WO85/02767). However, in WO85/02767 only the use of etherified beta-cyclodextrin derivatives up to a concentration of 10 % is described. A molar ratio of drug to etherified beta-cyclodextrin derivative of 1:6 to 4:1 was thought. The solubility of flubendazol within the above given ratio was only increased by a factor 30. However, those formulations are not suitable for the preparation of liquid preparations comprising pimobendan, or any other substituted benzimidazol in therapeutically effective amounts of up to 5 mg/ml, preferably of 0.5 to 3 mg/ml, even more preferably of 0.5 to 1.5 mg/ml. As mentioned above, at least pimobendan formulation comprising up to 1.5 mg/ml needs an increase in solubility at pH 7 by a factor of about 1000 to 1500.

The objective underlying the present invention was to provide liquid preparations comprising a substituted benzimidazol, preferably pimobendan as pharmaceutically active compound.

The objective underlying the present invention was to provide a pharmaceutically acceptable solution comprising a substituted benzimidazol, preferably pimobendan as pharmaceutically active compound.

Another objective underlying the present invention was to provide injectable solutions comprising a substituted benzimidazol, preferably pimobendan as pharmaceutically active compound.

SUMMARY

In a first aspect, there is provided a liquid preparation comprising an etherified cyclodextrin derivative and a pimobendan or a pharmaceutically acceptable salt thereof, wherein the etherified cyclodextrin derivative is selected from the group consisting of: alpha-, beta, and gamma-cyclodextrin ether and wherein the liquid preparation has a pH of 5.5 to 7.5.

In a second aspect, there is provided a process for producing a liquid preparation as defined above, comprising the steps:

a) dissolving the etherified cyclodextrin derivative in a solvent,
b) adding pimobendan or a pharmaceutically acceptable salt thereof to the solution obtained in step (a) and
a) admixing the mixture obtained in step (b) to obtain the liquid preparation in the form of an aqueous solution at a pH of 5.5 to 7.5.

In a third aspect, there is provided a liquid preparation as defined above for use as a medicament.

In a fourth aspect, there is provided the use of a liquid preparation as defined above for preparing a pharmaceutical composition for the treatment or prevention of diseases in a subject in need of such treatment, selected from among the indications: congestive heart failure (CHF), acute CHF, decompensated endocardiosis (DCE), dilated cardiomyopathy (DCM), asymptomatic (occult) CHF, asymptomatic DCM, maintenance of cardiovascular function and/or renal perfusion during anaesthesia, shock, gastric dilation, volvulus, myocardial and renal ischemia.

In a fifth aspect, there is provided a kit of parts that comprises:

d) liquid preparation as defined above; and
e) a package leaflet including the information that the liquid preparation is to be used for the prevention and/or treatment of congestive heart failure in a subject in need of such prevention or treatment.

DESCRIPTION OF THE INVENTION

Description of the Figures

Figures 1 and 2 show the saturated solubility of pimobendan, a substituted benzimidazol in an aqueous solution comprising various concentrations of the etherified cyclodextrin derivative hydroxypropyl-beta-cyclodextrin (HPβCD) at pH 3, 5, and 7.

Figure 3 shows the saturated solubility of pimobendan, a substituted benzimidazol in an aqueous solution comprising various 20 to 25 % (w/v) of the etherified cyclodextrin-derivative hydroxypropyl-beta-cyclodextrin (HPβCD) dissolved in 10 mM phosphate buffer at pH 7.

Figure 4 shows the saturated solubility of pimobendan, a substituted benzimidazol in an aqueous solution comprising 24 % (w/v) of the etherified cyclodextrin-derivative hydroxypropyl-beta-cyclodextrin (HPβCD) dissolved in 10 mM phosphate buffer and sodium chloride at pH 7.

Figure 5 shows the effect of autoclaving on the soluble formulation of pimobendan, a substituted benzimidazol.

Detailed Description of the Invention

Before the embodiments of the present invention it shall be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to "a preparation" includes a plurality of such preparations, reference to the "carrier" is a reference to one or more carriers and equivalents thereof known to those skilled in the art, and so forth. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. All given ranges and values may vary by 1 to 5 % unless indicated otherwise or known otherwise by the person skilled in the art, therefore, the term "about" was omitted from the description. Although any methods and materials similar or equivalent to those described herein can be used in

the practice or testing of the present invention, the preferred methods, devices, and materials are now described. All publications mentioned herein are incorporated herein by reference for the purpose of describing and disclosing the substances, excipients, carriers, and methodologies as reported in the publications which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

The solution to the above technical problem is achieved by the description and the embodiments characterized in the claims.

The present invention is based on the unexpected observation that a non-linear relationship exists between the rise in concentration of hydroxypropyl-beta-cyclodextrin (HPβCD), an etherified cyclodextrin derivative, and the increase in solubility of pimobendan a structurally member of a substituted benzimidazol at a pH of about 5 or 7. Solutions containing a target concentration for pimobendan of about 0.5 to 1.5 mg/ml could be obtained by the use of HPβCD concentration of more than 15 %, preferably of about 20% (w/v) to up to 70% (w/v) of the final formulation. Figure 1 teaches, that based on such a non-linear relationship, a HPβCD concentration of more than 20 (w/v) caused in a significant increased solubility of pimobendan, which is used in an exemplarily manner for a substituted benzimidazol. In general, by "(w/v)" as used herein is meant weight of substance per volume of the final preparation/formulation.

In addition, it was an unexpected observation that the solubility enhancement achieved by HPβCD did not decrease at an increasing pH. Solubility of pimobendan at low pH values was in principle higher than at higher pH values. This effect was already known from WO 2005/08467. This also was found for solutions comprising the etherified cyclodextrin derivative HPβCD (See Figure 1). However, this effect surprisingly is reversed at pH 7.0. The solubility of pimobendan at pH 5 in the presence of HPβCD was significantly reduced as compared to pH 3. Contrary, at pH 7 the solubility of pimobendan in the presence of HPβCD is significantly higher than

that pH 5. The relationship between increasing HPβCD concentrations (by mass) and increase in saturated solubility of pimobendan was linear at pH 3, but non-linear at pH 7 (see Figure 1). The higher the concentration of HPβCD the higher the solubility of pimobendan. This non-linear effects allows an increase of solubility of more than factor 1000, which is needed for the preparation of liquid preparation of pimobendan, or any other substituted benzimidazol comprising therapeutically effective amounts of those active ingredients.

Thus according to one aspect, the present invention relates to a liquid preparation comprising an etherified cyclodextrin derivative and a substituted benzimidazol, wherein the etherified cyclodextrin derivative is selected from the group consisting of: alpha-, beta, and gamma-cyclodextrin ether.

The term "liquid preparation" as used herein, simply means that the majority of the preparation is present in liquid form. The term "liquid preparation" as used herein, includes any form of an aqueous solution as well as any kind of suspension. If the liquid preparation is obtained in the form of a suspension, it is a dispersed system. By a "dispersed system" is meant, in general terms, a systems consisting of two or more phases in which one type of form (dispersed phase) is finely divided in the other type of form (dispersion agent). By a "suspension" is meant, according to the invention, a mixture of solid particles in a liquid. Preferably, the liquid preparation according to the invention is an aqueous solution, more preferably a non-alcoholic aqueous solution. Even more preferably, those liquid preparations are aqueous solutions that are suitable as injectable solutions for i.v. and / or s.c. application in animals. The term "aqueous solution" as used herein, simply means that the majority of the preparation is present in a dissolved form. The term non-alcoholic aqueous solutions as used herein means that preparation is present in a dissolved form but do not include alcoholic or other organic solvents.

Thus according to a further aspect, the present invention relates an aqueous solutions comprising an etherified cyclodextrin derivative and a substituted benzimidazol, wherein the etherified cyclodextrin derivative is selected from the group consisting of: alpha-, beta, and gamma-cyclodextrin ether. Preferably, those

aqueous solutions are injectable solutions for i.v. and / or s.c. application in animals, or can be can be used for the preparation of injectable solutions for i.v. and / or s.c. application in animals.

The term etherified cyclodextrin derivatives as used herein includes but is not limited to alpha-, beta- or gamma-cyclodextrins. Preferably the etherified cyclodextrin derivatives as used herein means etherified beta-cyclodextrins, more preferably of the formula:

(beta-CD)-OR (formula I),

in which the residues R are hydroxyalkyl groups and part of the residues R may optionally be alkyl groups. A partially etherified beta-cyclodextrin of formula I is preferably used in which the residues R are hydroxyethyl, hydroxypropyl or dihydroxypropyl groups, Optionally part of the residues R may for instance be methyl or –ethyl groups; the use of partially - methylated beta-cyclodextrin ethers with 7 to 14 methyl groups in the beta-cyclodextrin molecule as they are known from German Offenlegungsschrift 31 18 218 do not come under the present invention. Partial ethers of beta-cyclodextrin comprising only alkyl groups (methyl, ethyl) may be suitable in accordance with the invention if they have a low degree of substitution (as defined below) of 0.05 to 0.2.

Even more preferably, the etherified cyclodextrin derivative as used herein is hydroxyethyl-beta-cyclodextrin, hydroxypropyl-beta-cyclodextrin, dihydroxypropyl-beta-cyclodextrin.. Most preferably, the etherified cyclodextrin derivative as used herein is hydroxypropyl-beta-cyclodextrin (HPβCD), for example as described in the European Pharmacopoeia (5th Edition 2005, European Directorate for the Quality of Medicines (EDQM), European Pharmacopoeia, 226 avenue de Colmar, F-67029 Strasbourg, France, http://www.pheur.org). Hydroxypropyl-beta-cyclodextrin (HPβCD) of pharmaceutical grade is marketed for example under the Trademark Kleptose® HP and can be ordered from Roquette, France.

Beta-cyclodextrin is a compound with ring structure consisting of 7 anhydro glucose units; it is also referred to as cycloheptaamylose. Each of the 7 glucose rings contains in 2-,3-, and 6-position three hydroxy groups which may be etherified. In the partially etherified β-cyclodextrin derivatives used according to the invention only part of these hydroxy groups is etherified with hydroxyalkyl groups and optionally further with alkyl groups. When etherifying with hydroxy alkyl groups which can be carried out by reaction with the corresponding alkylene oxides, the degree of substitution is stated as molar substitution (MS), viz. in mole alkylene oxide per anhydroglucose unit, compare U.S. Patent 3,459,731, column 4. In the hydroxyalkyl ethers of beta-cyclodextrin used in accordance with the invention the molar substitution is between 0.05 and 10, preferably between 0.2 and 2. Particularly preferred is a molar substitution of about 0.40 to about 1.50. The etherification with alkyl groups may be stated directly as degree of-substitution (DS) per glucose unit which as stated above - is 3 for complete substitution. Partially etherified beta-cyclodextrins are used within the invention which comprise besides hydroxyalkyl groups also alkyl groups, especially a methyl or ethyl groups, up to a degree of substitution of 0.05 to 2.0, preferably 0.2 to 1.5. Most preferably the degree of substitution with alkylgroups is between about 0.5 and about 1.2.

Thus, according to a further aspect, the present invention relates to liquid preparations as described above, comprising an etherified cyclodextrin derivative and a substituted benzimidazol, wherein the etherified cyclodextrin derivative is etherified beta-cyclodextrin. Preferably, that etherified beta-cyclodextrin is hydroxyethyl-beta-cyclodextrin, hydroxypropyl-beta-cyclodextrin, or dihydroxypropyl-beta-cyclodextrin. Even more preferably, that etherified beta-cyclodextrin is hydroxypropyl-beta-cyclodextrin (HPβCD), for example as described in the European Pharmacopoeia (5th Edition 2005, European Directorate for the Quality of Medicines (EDQM), European Pharmacopoeia, 226 avenue de Colmar, F-67029 Strasbourg, France, http://www.pheur.org). Most preferably, that etherified beta-cyclodextrin is Kleptose® HP (Roquette, France).

The term "substituted benzamidazol" as used herein means, but is not limited to thiabendazol, fuberidazol, oxibendazol, parbendazol, cambendazol, mebendazol,

fenbendazol, flubendazol, albendazol, oxfendazol, nocodazol, astemisol and pimobendan, pharmaceutical acceptable salts, derivatives, metabolites or pro-drugs thereof. Preferably, the term substituted benzimidazol as used herein means pimobendan, or any pharmaceutical acceptable salts, derivatives, metabolites or pro-drugs thereof. Pimobendan as such is described *supra*.

Thus, according to a further aspect, the present invention relates to liquid preparations as described above, comprising an etherified cyclodextrin derivative and a substituted benzimidazol, wherein:

a) the etherified cyclodextrin derivative is etherified beta-cyclodextrin, preferably, hydroxyethyl-beta-cyclodextrin, hydroxypropyl-beta-cyclodextrin, or dihydroxypropyl-beta-cyclodextrin, even more preferably hydroxypropyl-beta-cyclodextrin (HPβCD), and most preferably, Kleptose® HP (Roquette, France); and

b) the substituted benzamidazol is thiabendazol, fuberidazol, oxibendazol, parbendazol, cambendazol, mebendazol, fenbendazol, flubendazol, albendazol, oxfendazol, nocodazol, astemisol or pimobendan, pharmaceutical acceptable salts, derivatives, metabolites or pro-drugs thereof, preferably pimobendan as described *supra* or any pharmaceutical acceptable salt, derivative, metabolite or pro-drug thereof.

The amount of etherified cyclodextrin that is needed for the liquid preparation depends on the pH of the final liquid preparation, the substituted benzimidazol and the portion that is used. However, it was surprisingly found, that the use of about 15 – 70% (w/v) of etherified cyclodextrin derivative, preferably HPβCD in the final preparation is appropriate to dissolve an therapeutically effective amount of any of the substituted benzimidazol described above. In particular, it is shown, that the use of about 15 – 70% (w/v) of etherified cyclodextrin derivatives as described above, preferably of HPβCD in the final preparation is appropriate to dissolve an therapeutically effective amount pimobendan. Thus, according to a further aspect, any of the final liquid preparation as described herein, comprises about 15 to 70% (w/v) etherified cyclodextrin derivative, preferably HPβCD. Preferably the portion of

etherified cyclodextrin derivative, preferably of HPβCD; of the final liquid preparation is 20 – 50% (w/v), even preferably 20 – 40%, even more preferably 20 – 30% (w/v), even more preferably 22 – 28%, even more preferably 23 – 27% (w/v), even more preferably 24 – 26% (w/v), for example the portion of the final preparation is 15, 16, 17, 18, 19, 20, 21, 22, 23 ,24, 25, 26, 27, 28, 29, 30, 20, 21, 22, 23 ,24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70 % (w/v) or any fraction thereof.

The portion of the substituted benzimidazol of the liquid preparation as described herein is as a rule between 0.005 and 0.15 % (w/v), preferably between 0.01 and 0.15% (w/w), further preferred between 0.05 and 0.15 % (w/w), and even further preferred between 0.075 and 0.10 % (w/w). Consequently, the portion is, for example, 0.001, 0.002, 0.003 ... 0.008, 0.009, etc.; 0.01, 0.02, 0.03, 0.04, 0.05, ... 0.08 0.09 etc.; 0.10, 0.11, 0.12 ...0.14, 0.15% (w/v). Preferably, the substituted benzimidazol is anyone of those described herein, preferably pimobendan.

Thus according to further aspect, the present invention relates to a liquid preparation comprising an etherified cyclodextrin derivative, and a substituted benzimidazol as described above, preferably HPβCD and pimobendan, wherein that liquid preparation comprises:

a) about 15 to 70% (w/v), preferably 20 – 50% (w/v), even preferably 20 – 40%, even more preferably 20 – 30% (w/v), even more preferably 22 – 28%, even more preferably 23 – 27% (w/v), most preferably 24 – 26% (w/v) of such etherified cyclodextrin derivative, preferably of HPβCD; and

b) between 0.005 and 0.15 % (w/v), preferably between 0.01 and 0.15% (w/w), further preferred between 0.05 and 0.15 % (w/w), and even further preferred between 0.075 and 0.1 % (w/w) of a substituted benzimidazol as described herein, preferably of pimobendan.

The general therapeutic effective target dose, in particular for the treatment of acute CHF, but also for any other therapeutic use as described herein is about 0.05 to 0.5

mg pimobendan per kg body weight of the animal, preferably about 0.1 to 0.3 mg pimobendan per kg body weight of the animal, even more preferably about 0.15 mg pimobendan per kg body weight of the animal. The target concentration of pimobendan in the drug product should be set to 0.75 mg / ml allowing the administration of safe and even injection volumes. E.g. a dog with a weight of 10 kg would receive exactly a dose of 2 ml containing 1.5 mg of pimobendan. Thus according to a further aspect, the present invention relates to a liquid preparation, preferably an aqueous solutions for injection, comprising an etherified cyclodextrin derivative as described above, preferably HPβCD and 0.75 mg/ml (0.075 % (w/v)) pimobendan. More preferably, the portion of etherified cyclodextrin derivative in that liquid preparation comprises about 15 to 70% (w/v), preferably 20 – 50% (w/v), even preferably 20 – 40% (w/v), even more preferably 20 – 30% (w/v), even more preferably 22 – 28% (w/v), even more preferably 23 – 27% (w/v), most preferably 24 – 26% (w/v) of such etherified cyclodextrin derivative. Most preferred is a liquid preparation, preferably an aqueous solutions for injection, that comprises 0.75 mg/ml (0.075 % (w/v)) pimobendan and about 15 to 70% (w/v), preferably 20 – 50% (w/v), even preferably 20 – 40% (w/v), even more preferably 20 – 30% (w/v), even more preferably 22 – 28% (w/v), even more preferably 23 – 27% (w/v), most preferably 24 – 26% (w/v) HPβCD of the final formulation.

The liquid preparations are tolerable to the addition of buffers, antioxidants such as sodium edetate, isotonic agents such as sodium chloride, and are suitable as single-use injectable solutions for i.v. and / or s.c. application in animals, especially dogs. Preservatives can be added, too. Thus, according to a further aspect, the present invention relates to any of the above mentioned liquid preparations, preferably to aqueous solutions for injection, that comprise an etherified cyclodextrin derivative as described herein, preferably HPβCD, and a substituted benzimidazol as described herein, preferably pimobendan, wherein such preparation further comprises pharmaceutical acceptable excipients, and/or salts.

Purely by way of example, the excipients in a standard liquid preparation, in particular in a solution for injection according to the present invention might be meglumin, macrogol, poloxamer 188, parabens and glycin. The formulations

according to the invention may contain complexing agents as other ingredients. By complexing agents are meant within the scope of the present invention molecules which are capable of entering into complex bonds. Preferably, these compounds should have the effect of complexing cations, most preferably metal cations. The formulations according to the invention preferably contain edetic acid (EDTA) or one of the known salts thereof, e.g. sodium EDTA or disodium EDTA dihydrate (sodium edetate), as complexing agent. Preferably, sodium edetate is used, optionally in the form of its hydrates, more preferably in the form of its dihydrate. If complexing agents are used within the formulations according to the invention, their content is preferably in the range from 1 to 20 mg per 10 ml, more preferably in the range from 2 to 10 mg per 10 ml of the formulation according to the invention. Preferably, the formulations according to the invention contain a complexing agent in an amount of about 5 mg per 10 ml of the formulation according to the invention. Of course, other excipients known to the skilled man may also be used.

Thus, according to a further aspect, the present invention relates to any of the above mentioned liquid preparations, preferably to aqueous solutions for injection, that comprise an etherified cyclodextrin derivative as described herein, preferably HPβCD, and a substituted benzimidazol as described herein, preferably pimobendan, wherein such preparation further contains one or more suitable preservative(s), preferably selected from the group consisting of meglumin, macrogol, parabens and EDTA.

In the case of the salts these are, for example, inorganic salts such as chloride, sulfate, phosphate, diphosphate, bromide and / or nitrate salts. Furthermore, the powders according to the invention may also contain organic salts such as malate, maleate, fumarate, tartrate, succinate, ethylsuccinate, citrate, acetate, lactate, methansulfonate, benzoate, ascorbate, para-toluensulfonate, palmoate, salicylate, stearate, estolate, gluceptate or lactobionate salts, for example. At the same time, corresponding salts may contain pharmaceutically acceptable cations such as sodium, potassium, calcium, aluminum, ammonium, for example.

However, it is shown by the present invention, that the salt might reduce the solubility of pimobendan in the presence of fix amount of HPβCD. There are two ways to overcome this problem. The first option is to further increase the concentration of HPβCD. The other way is to keep restrict the amount of salts. It was shown, that after addition of phosphates resulting in an osmolality of about 300 mOsm/Kg the solubility of pimobendan in an exemplarily manner was not affected. Thus, according to a further aspect, the present invention relates to any of the above mentioned liquid preparations, preferably to aqueous solutions for injection, that comprise an etherified cyclodextrin derivative as described herein, preferably HPβCD, and a substituted benzimidazol as described herein, preferably pimobendan, wherein such liquid preparation contains an osmolality of about 250 to 350 mOsm/Kg, preferably of about 270 to 320 mOsm/Kg, even more preferably of about 280 to 300 mOsm/Kg. A person skilled in the art is able to adjust the osmolality of any of such liquid preparations to the above mentioned ranges by means well known in the art. For example, a liquid preparation that comprises about 24 % (w/v) HPβCD and 0.75 mg/ml pimobendan may contain 10 mM of an alkali phosphate, preferably of sodium phosphate to adjust the osmolality of the final liquid preparation to about 290 to 300 mOsm/kg.

The pH of the liquid preparation according to the invention is preferably between 5.5 and 8.5. In particular, in case of an injectable solution, the pH is preferably between 6.5 and 7.5. Preferred buffer systems that can be used to adjust the pH to 6.5 to 7.5 are, for example, phosphate, acetate and citrate buffer systems. Preparations of any of those buffer systems are described for example in the European Pharmacopoeia (5^{th} Edition 2005, European Directorate for the Quality of Medicines (EDQM), European Pharmacopoeia, 226 avenue de Colmar, F-67029 Strasbourg, France, http://www.pheur.org). Thus, according to a further aspect, the present invention relates to any of the above mentioned liquid preparations, preferably to aqueous solutions for injection, that comprise an etherified cyclodextrin derivative as described herein, preferably HPβCD, and a substituted benzimidazol as described herein, preferably pimobendan, wherein such liquid preparation is adjusted to pH 5.5 to 8.5, preferably to pH 6.5 to 7.5 in case of an injectable solution.

As described above, a preferred embodiment of the present invention relates to an injectable solution adjusted to pH 6 to 7.5, that comprise an etherified cyclodextrin derivative as described herein, preferably HPβCD, and a substituted benzimidazol as described herein, preferably pimobendan. In such case, the preparation of an isotonic solution would further be preferred.

In order to achieve an immediate onset of action of the substituted benzimidazol, preferably of pimobendan for all suitable indications, an injectable solution for parenteral administration by the i.v. and/or s.c. route is obligatory. An aqueous formulation is required to administer a drug product by the i.v. / s.c. route to either humans or animals, formulations with a non-aqueous solvent are neither acceptable nor state of the art due to the risk of severe tolerance problems.

Thus according to a further aspect, the current invention relates to an injectable solution, i.e. for parenteral administration by the i.v. and/or s.c. route, comprising any of the liquid preparation as described above. It might be useful to administer the drug continuously over a defined period of time and not in a one-shot application. In such case, administration of an aqueous solution comprising the substituted benimidazol, preferably pimobendan by infusion is advantageous. Thus according to a further aspect, the current invention relates to an injectable solution for infusion, comprising any of the liquid preparation as described above.

A solution is absolutely necessary for i.v. administration, suspended particles bear a high risk of emboli and have to be excluded. Ready-to-use solutions are preferred compared to lyophilised products which have to be reconstituted by adding a diluent / solvent before administration. The reconstitution of a drug product to be administered will add several minutes to the treatment which has to be avoided in a life-threatening situation as this. In addition local tolerance will depend on the isotonicity and pH range of the formulation. A pH in the neutral range of about pH 7 is usually preferred, the higher the actual pH deviates from this target the more likely the risk of not acceptable local tolerance.

Thus, according to a further aspect, the invention relates to any of the liquid preparations described herein and comprising an etherified cyclodextrin derivative as described herein, preferably HPβCD and a substituted benzimidazol as described herein, preferably pimobendan, wherein the liquid solution is a Ready-to use solution. The Ready-to-use solution is in general adjusted to a pH of about 6.5 to 7.5, preferably of about 6.8 to 7.2, even more preferred of about 7.0. Moreover, that Ready-to-use solution is also adjusted to an osmolality of about 250 to 350 mOsm/Kg, preferably of about 270 to 320 mOsm/Kg, even more preferably of about 280 to 300 mOsm/Kg. It was surprisingly found, that the addition of some salts resulting in about 300 mOsm/Kg significantly reduce the solubility of the substituted benzimidazol, in particular of pimobendan. However, it is in the knowledge of a person skilled in the art to slightly increase the osmolality of that Read-to-use solution to about 300 mOsm/Kg, e.g. to about 305 to 310 mOsm/Kg, that an appropriate solubility of the substituted benzimidazol, in particular of pimobendan is ensured.

According to a further aspect, the present invention relates to a liquid preparation as described supra, wherein the preparation comprises about i) 20 to 30% (w/w) of a HPβCD; ii) 0.005 to 0.15 % (w/w) pimobendan, a pharmaceutical acceptable salt, derivative, metabolite or pro-drug thereof; and optional iii) 0.025 to 0.075% (w/w) of stabilizer preferably EDTA; and wherein the pH of the liquid preparation is adjusted to about 6.5 to 7.5 and the osmolality is about 280 to 300 mOsm/Kg.

According to a further aspect, the present invention also relates to a manufacturing process for the production of any of the liquid preparation as described herein. In the knowledge of the specific formulation of any of the above described liquid formulation, those formulations can be prepared according to stand procedures known to a person skilled in the art. That process comprises the steps:

a) Dissolving the etherified cyclodextrin derivative in a solvent;
b) Adding the substituted benzimidazol to the solution obtained in step (a); and
c) Admixing the mixture obtained in step (b) to obtain the liquid preparation in the form of an aqueous solution.

Preferably, that etherified cyclodextrin derivative is HPβCD. Moreover, the solvent preferably is water for injection.

According to more preferred embodiment that manufacturing process comprises the steps:

a) Weight the etherified cyclodextrin, preferably HPβCD into the manufacturing container;
b) Add water to approximately 40 to 80% of the final volume;
c) Mix until the etherified cyclodextrin dissolves using magnetic stirred or paddle stirrer;
d) Add any buffer component(s) , transfer with water and mix until dissolved;
e) Check pH to ensure that it is close to the set-point. Adjust with sodium hydroxide or hydrochloric acid if required;
f) Add the substituted benzimidazol, preferably pimobendan, transfer with water and mix until dissolved;
g) Make to volume with water;

According to a even more preferred aspect, the manufacturing process comprises the steps:

h) Filter the liquid preparation of step g) and dispense into vials;
i) Autoclave the vials, preferably for 30 min at 121 °C.

According to a further aspect, the present invention relates to the use of any of the liquid preparation as described herein as a medicament. Preferably that medicament is a veterinary medicament. Even more preferred, that medicament is a solution for injection. That solution for injection is, according to a further aspect an infusion solution.

As described *supra*, there is an unmet need in the field of medicine regarding the treatment of acute congestive heart failure (acute CHF) in animals and humans, and especially in dogs. Thus, the liquid preparation as provided herewith can be used in human and veterinary medicine, preferably in veterinary medicine. No product is

licensed in veterinary medicine for this indication so far. So the treatment of acute CHF in a life-threatening situation would be an important innovation allowing to save the animal's life in an acute crisis situation. Due to an immediate onset of action, the rapid visual change of the animal's status would allow both the veterinarian and the animal owner to evaluate the success of the measures taken to overcome the situation. Additionally, this way of treatment would be a therapy option in cases where oral treatment is not possible. Peri-operative administration to maintain cardiovascular function and/or renal perfusion during anaesthesia as well as treatment of shock and/or gastric dilation volvulus situations are other potential indications for a pimobendan formulation with an immediate onset.

Thus, according to a further embodiment, the present invention also relates the use of any of the liquid preparation comprising pimobendan described herein for preparing a pharmaceutical composition for the treatment or prevention of diseases in a subject in need of such treatment, selected from among the indications: congestive heart failure (CHF), acute CHF, decompensated endocardiosis (DCE), dilated cardiomyopathy (DCM), asymptomatic (occult) CHF, asymptomatic DCM, maintenance of cardiovascular function and/or renal perfusion during anaesthesia, shock, gastric dilation, volvulus, myocardial and renal ischemia. As described *supra*, the general therapeutically effective amount of pimobendan is about 0.05 to 0.5 mg pimobendan per kg body weight of the animal and application, preferably about 0.1 to 0.3 mg pimobendan per kg body weight of the animal and application, even more preferably about 0.15 mg pimobendan per kg body weight of the animal. Preferably, one dose is to be administered per day.

According to a further aspect, the present invention also relates to method of treatment and/or prevention of diseases, wherein cardiotonic, hypotensive, anti-inflammatory and anti-thrombotic substances have a therapeutic benefit comprising the step: administering to such subject in need of such treatment a therapeutically effective amount of any of the liquid preparations as described herein. Preferably, the liquid preparation is administered to a therapeutically effective amount of about 0.05 to 0.5 mg pimobendan per kg body weight of the animal and application, preferably about 0.1 to 0.3 mg pimobendan per kg body weight of the animal and

application, even more preferably about 0.15 mg pimobendan per kg body weight of the animal. Preferably, one dose is to be administered per day.

As mentioned above, pimobendan is a well established medicament in the treatment of congestive heart failure (CHF), decompensated endocardiosis (DCE), dilated cardiomyopathy (DCM), asymptomatic (occult) CHF, asymptomatic DCM, among others. Thus according to a further aspect, the present invention directly relates to a method of treatment and/or prevention a subject suffering on or having a congestive heart failure (CHF), decompensated endocardiosis (DCE), dilated cardiomyopathy (DCM), asymptomatic (occult) CHF, asymptomatic DCM, myocardial and renal ischemia, shock, comprising the step: administering to said subject in need thereof any of the liquid preparations described herein and comprising a therapeutically effective amount of pimobendan. In particular, the therapeutically effective amount for the treatment of CHF is about 0.05 to 0.5 mg pimobendan per kg body weight of the animal and application, preferably about 0.1 to 0.3 mg pimobendan per kg body weight of the animal and application, even more preferably about 0.15 mg pimobendan per kg body weight of the animal and application. Preferably, one dose is to be administered per day. Such a treatment is also advantageous in the case of maintenance of cardiovascular function and/or renal perfusion during anaesthesia, shock, gastric dilation or volvulus, for examples caused by surgery, especially gastrointestinal surgery as well as trauma.

The subject in need of any such treatment mentioned above is a mammal, preferably a human or an animal. The term animal as used herein includes but is not limited to companion animals such as dogs, cats, guinea pigs, hamsters, horses, cattle, goats, sheeps or the like. Preferably, the subject in need of such treatment is a dog, horse or cat, most preferably a dog. However, such animal in need of such treatment also includes zoo animals such as monkies, elephants, giraffes and other ungulates, bears, mice and other small mammals.

The present invention furthermore relates to a kit of parts, that comprises

a) a container with a liquid preparation, preferably an injectable solution, according to the present invention as described herein,

b) and a package leaflet including the information that the liquid preparation, preferably the injectable solution, according to the present invention is to be used, preferably via injection (s.c. or i.v.), for the prevention and/or treatment of congestive heart failure in a subject in need of such prevention or treatment, preferably in a mammal as defined above.

In case of the treatment of an animal, that package leaflet preferably includes the information that the pimobendan is to be used at a dose as described *supra*, preferably of about 0.15 mg per kg body weight and application. Preferably, one dose is to be administered per day. More preferably, the package-leaflet includes the specific indication as described above.

According to a further aspect, the container comprises 2 ml, 5 ml, 10 ml, 50 ml, or 250 ml of the liquid preparation. Preferably the container comprises 3.75, 7.5 or 37.5 mg pimobendan.

EXAMPLES

The following examples serve to further illustrate the present invention; but the same should not be construed as a limitation of the scope of the invention disclosed herein.

Example: 1

Solubility of pimobendan in the presence of hydroxypropyl-beta-cyclodextrin (HPβCD) at different pH values

The solubility of pimobendan, a substituted benzimidazol, was tested at various concentrations of hydroxypropyl-beta-cyclodextrin (HPβCD) and at pH 3, 5 and 7. Kleptose® HP (Roquette, France) was used as HPβCD of pharmaceutical grade. Saturated solubility of pimobendan was investigated at 10 to 40% (w/v) of HPβCD at pH 3, 5, and 7. The solutions were buffered with a sodium phosphate solution. The sample solutions were prepared using the following method:

a) Approximately 3 ml of the solution under test was placed in a 7 ml glass vial with a magnetic stirring bar.

b) The pH was adjusted with hydrochloric acid

c) An excess of pimobendan was added. The sample was placed in an ultrasonic bath and sonicated for 5 min. to ensure an excess of pimobendan was present and more added if required;

d) The samples were placed in a water bath at 25°C and stirred for at least 16 hours.

e) The samples were filtered using 0.2 µm PVDF syringe filter.

f) The samples were assayed by HPLC.

The results are shown in Figure 1 and 2. It was surprisingly found that due to a non-linear relationship between the rise in concentration of HPβCD and the increase in solubility of pimobendan both at a pH of about 5 or 7, solutions containing the target concentration for pimobendan could be obtained by the use of (HPβCD) concentration of more than 15 % (see Figure 1). In addition, it was an unexpected observation that the solubility enhancement achieved by HPβCD did not increase with decreasing pH, but that at pH 7 the solubility at a certain HPβCD concentration was lower at pH 7 than at pH 3, but higher than at pH 5. The relationship between increase of HPβCD concentration (by mass) and increase in saturated solubility of pimobendan was linear at pH 3, but non-linear at pH 5 and pH 7 (see Figure 2).

Example: 2

Formulation Development

1. Level of hydroxypropyl-beta-cyclodextrin (HPβCD)

Saturated solubility of pimobendan was investigated at 20 to 25% (w/v) of HPβCD in 10 mM phosphate buffer pH 7.0. The study was carried out on three different batches of HPβCD and each solution tested in duplicate (see Figure 3). The solutions were prepared using the following method:

a) Approximately 3 ml of the solution under test was placed in a 7 ml glass vial with a magnetic stirring bar.

b) An excess of pimobendan was added. The sample was placed in an ultrasonic bath and sonicated for 5 min. to ensure an excess of pimobendan was present and more added if required.

c) The samples were placed in a water bath at 25°C and stirred for at least 16 hours.

d) The samples were filtered using 0.2 µm PVDF syringe filter.

e) The samples were assayed by HPLC.

A level of 22 to 24% (w/v) HPβCD was chosen for the formulations comprising 0.5, 0.75 and 1.0 mg/ml pimobendan.

2. Osmolality:

An isotonic solution was required for the formulation. The formulation with 24% (w/v) HPβCD and 10 mM phosphate buffer had an osmolality of 287 mOsm/Kg. Sodium chloride was added to increase the osmolality to 303 mOsm/Kg. Saturated solubility of pimobendan 0.75 mg/ml at 24% (w/v) HPβCD were investigated and results were compared with those formulations that were not supplemented with sodium chloride. Results are shown in Figure 4. The amount of soluble pimobendan dramatically decrease from about 1.23 mg/ml to about 0.71 mg/ml.

3. Physical Stability:

A sample of the final formulation comprising 24% (w/v) HPβCD, 0.75 mg/ml pimobendan, 10 mM phosphate buffer, pH 7.0 was filtered through a 0.2 µm syringe PVDF filter into two screw cap class vials. One vial was stored at room temperature and the other at 5°C. Samples were assessed initially, after one and after two weeks for changes in appearance and sign of precipitation. No changes in appearance and no sign of precipitation were observed.

3. Filter studies and Autoclaving studies:

A) A sample of the final formulation comprising 24% (w/v) HPβCD, 0.75 mg/ml pimobendan, 10 mM phosphate buffer, pH 7.0 was filtered through three different filters (Fluorodyne® 0.2 µm (Pall); Durapore®, 0.22 µm (Millipore) and Supor® 0.2 µm (Pall)). For each experiment, 30 ml of the test solution was placed in a 50 ml

syringe and then forced through an in-line holder housing a 47 mm membrane of each type. Filtrate samples were collected at sampling points 1, 2, 3, 4, 5, 10, 15 and 25 ml and analyzed to its pimobendan content. No change in the pimobendan content was measured for each filter system.

B) A sample of the final formulation comprising 24% (w/v) HPβCD, 0.75 mg/ml pimobendan, 10 mM phosphate buffer, pH 7.0 was filtered through a 0,2 µm syringe PVDF filter and the filtrate was autoclaved at 121 °C for 30 min. The results are shown in Figure 5. Only a small amount of degradation was observed when the formulation was autoclaved. The level was very low and indicates that the formulation can be autoclaved.

Example: 3

Manufacturing process

The manufacturing process for the preparation of final formulation comprising HPβCD and pimobendan, is:

a) Weight the HPβCD into the manufacturing container;
b) Add water to approximately 60% of the final volume;
c) Mix until HPβCD dissolves using magnetic stirred or paddle stirrer;
d) Add the buffer components, transfer with water and mix until dissolved;
e) Check pH to ensure that it is close to pH 7.0. Adjust with sodium hydroxide or hydrochloric acid if required;
f) Add pimobendan, transfer with water and mix until dissolved;.
g) Make to volume with water;
h) Filter the solution and dispense into vials;
i) Autoclave the vials for 30 min at 121 °C.

Example: 4

Liquid preparations

A)

	mg / 10 ml

Material	Formulation # 1	Formulation # 2
Pimobendan	10	7.5
Kleptose HP (HPβCD)	3000.0	3000.0
Citric acid monohydrate	200.0	200.0
NaOH 0.1N	q.s. ad pH 6.0	q.s. ad pH 6.0
Disodium edetate	5.0	5.0
Water for injection	q.s. to 10 ml	q.s. to 10 ml

B)

	mg / 10 ml	
Material	**Formulation # 1**	**Formulation # 2**
Pimobendan	10	7.5
Kleptose HP (HPβCD)	2600.0	2400.0
Disodium hydrogen phosphate dodecahydrate	0.1343	0.1343
Sodium dihydrogen phosphate dihydrate	0.0975	0.0975
Water for injection	q.s. to 10 ml	q.s. to 10 ml

c)

	mg / 10 ml	
Material	**Formulation # 1**	**Formulation # 2**
Pimobendan	10	7.5
Kleptose HP (HPβCD)	2600.0	2400.0
Disodium hydrogen phosphate dodecahydrate	0.1343	0.1343
Sodium dihydrogen phosphate dihydrate	0.0975	0.0975
Disodium edetate	5.0	5.0
Water for injection	q.s. to 10 ml	q.s. to 10 ml

D)

	mg / 10 ml	
Material	**Formulation # 1**	**Formulation # 2**
Pimobendan	10.0	7.5
Kleptose HP (HPβCD)	3300.0	3000.0
Disodium hydrogen phosphate dodecahydrate	17.6	17.6
Sodium dihydrogen phosphate dihydrate	8.0	8.0
Methyl paraben	20.0	10.0
Propyl paraben	5.0	5.0
Disodium edetate	5.0	5.0
Water for injection	q.s. to 10 ml	q.s. to 10 ml

E)

	mg / 10 ml	
Material	**Formulation # 1**	**Formulation # 2**
Pimobendan	10	7.5
Kleptose HP (HPβCD)	2500.0	2300.0
Disodium hydrogen phosphate dodecahydrate	17.6	17.6
Sodium dihydrogen phosphate dehydrate	8.0	8.0
Disodium edetate	5.0	5.0
Water for injection	q.s. to 10 ml	q.s. to 10 ml

5

CLAIMS:

1. A liquid preparation comprising an etherified cyclodextrin derivative and a pimobendan or a pharmaceutically acceptable salt thereof, wherein the etherified cyclodextrin derivative is selected from the group consisting of: alpha-, beta, and gamma-cyclodextrin ether and wherein the liquid preparation has a pH of 5.5 to 7.5.

2. The liquid preparation according to claim 1, wherein the etherified cyclodextrin derivative is hydroxypropyl-beta-cyclodextrin.

3. The liquid preparation according to claim 1 or claim 2, wherein the portion of the etherified cyclodextrin derivative contains about 15 to 70% (w/v).

4. The liquid preparation according to claim 3, wherein the portion of the etherified cyclodextrin derivative contains about 20 to 30% (w/v).

5. The liquid preparation according to anyone of claims 1 to 4, wherein the portion of substituted benzimidazol contains about 0.005 to 0.15 % (w/v).

6. The liquid preparation according to anyone of claims 1 to 5, wherein the preparation further comprises pharmaceutical acceptable carriers, excipients, and/or salts.

7. The liquid preparation according to anyone of claims 1 to 6, wherein the preparation is isotonic.

8. The liquid preparation according to anyone of claims 1 to 7, wherein the preparation has pH value of about 6.5 to 7.5 and an osmolality of about 280 to 300 mOsm/Kg.

9. The liquid preparation according to anyone of 1 to 8, wherein the preparation contains one or more suitable preservative/s.

10. The liquid preparation according to anyone of claims 1 to 9, wherein the preparation comprises about:
    a) 20 to 30% (w/w) of a hydroxypropyl-beta-cyclodextrin;
    b) 0.005 to 0.15 % (w/w) pimobendan, a pharmaceutical acceptable salt, derivative, metabolite or pro-drug thereof;

    and wherein the pH of the liquid is adjusted to about 6.5 to 7.5 and the osmolality is about 280 to 300 mOsm/Kg.

11. The liquid preparation according to claim 10, wherein the liquid preparation further comprises 0.025 to 0.075 % (w/v) of one or more stabilizers.

12. A process for producing a liquid preparation according to anyone of claims 1 to 11, comprising the steps:
    a) dissolving the etherified cyclodextrin derivative in a solvent,
    b) adding pimobendan or a pharmaceutically acceptable salt thereof to the solution obtained in step (a) and
    c) admixing the mixture obtained in step (b) to obtain the liquid preparation in the form of an aqueous solution at a pH of 5.5 to 7.5.

13. The process according to claim 12, wherein the solvent is water.

14. A liquid preparation according to anyone of claims 1 to 11 for use as a medicament.

15. The liquid preparation according to claim 14, wherein said medicament is a veterinary medicine.

16. Use of a liquid preparation according to one of claims 1 to 11 for preparing a pharmaceutical composition for the treatment or prevention of diseases in a subject in need of such treatment, selected from among the indications: congestive heart failure (CHF), acute CHF, decompensated endocardiosis (DCE), dilated cardiomyopathy (DCM), asymptomatic (occult) CHF, asymptomatic DCM, maintenance of cardiovascular function and/or renal perfusion during anaesthesia, shock, gastric dilation, volvulus, myocardial and renal ischemia.

17. The use according to claim 16, wherein the subject in need of such treatment is a horse, dog or cat.

18. Use of a liquid preparation according to claim 16 or claim 17 wherein the pharmaceutical composition is to be administered by injection or infusion.

19. A kit of parts that comprises:

d) liquid preparation according to anyone of claims 1 to 11; and

e) a package leaflet including the information that the liquid preparation is to be used for the prevention and/or treatment of congestive heart failure in a subject in need of such prevention or treatment.