The invention is directed to a pharmaceutical packaging product for the veterinary medical sector containing a first pharmaceutical solid formulation, preferably a pharmaceutical tablet formulation, which comprises as pharmaceutically active substances a PDE III inhibitor and an ACE inhibitor and a second pharmaceutical solid formulation, preferably a pharmaceutical tablet formulation, which comprises as pharmaceutically active substance a PDE III inhibitor as a combined preparation, particularly for separate or sequential use in the treatment of heart diseases, disorders, or complications associated therewith in mammals, preferably dogs, cats, and rodents. The packaging product, preferably in form of a blister pack, is designed particularly user-friendly in order to make the therapy of an animal more comfortable, assists to simplify the therapy and to support the animal keeper to perform a specific prescription plan to prevent and/or to treat heart diseases in animals as far as possible.
PHARMACEUTICAL PACKAGING PRODUCT FOR THE VETERINARY MEDICAL SECTOR

FIELD OF THE INVENTION

The present invention is directed to a pharmaceutical packaging product for the veterinary medical sector.

BACKGROUND OF THE INVENTION

In contrast to the therapy of humans, in the case of animals the arising problems are completely different. The animal keeper, who takes care of the animal, is always responsible for the therapy. Therefore, when the animals concerned are domestic animals, the animal keeper prefers to use an easy and time-saving therapy to treat the animals. On one hand simple and safe dosage forms are required, which, after diagnosis and indication by the veterinarian, can be given by the animal keeper himself/herself. On the other hand also a simple and safe administration sequence of different dosage forms in order to treat the disease of an animal are required in order not to overburden the animal keeper.

Therefore, there is a need to simplify a therapy of an animal and to support the animal keeper to follow a specific prescription plan to administer several different tablets as far as possible.

In prior art pharmaceutical formulations which contain an ACE inhibitor such as benazepril or a pharmaceutically acceptable salt thereof are known:

EP 1 490 037 B1 describes an animal medicine consisting of a substrate in pellet or tablet form, which is attractive to livestock and domestic animals and which consists of dry feed for animals on a vegetable and/or animal basis, in which fine-grained particles of a neutral-tasting, physiologically compatible, solid carrier material are embedded,
whereby said fine-grained particles of carrier material have an average diameter of 0.09 to 0.8 mm and are coated with benazepril, and said benazepril layer is encased with a protective layer of a physiologically compatible polymer matrix. The physiologically compatible polymer matrix is selected from the group consisting of: shellac, a polymer on a cellulose, acrylic acid or methacrylic acid, maleic acid anhydride, polyvinyl pyrrolidone and polyvinyl alcohol basis. Also the production and usage of a preparation for veterinary medicine is disclosed.

EP 1 385 489 B1 is directed to granules based on angiotensin converting enzyme inhibitor, its isomers or its pharmaceutically acceptable salts, whereby they are coated and contain ACE inhibitor monocrystals, one or several binding agents selected from the group comprising in particular cellulosic polymers, in particular ethyl cellulose, hydroxypropyl cellulose, and hydroxypropyl methyl cellulose, acrylic polymers, polyvidones, polyvinyl alcohols, and mixtures thereof, optionally a diluent selected from the group consisting in particular of cellulosic derivatives, starches, lactose and polyols, in particular mannitol, and an antistatic agent selected from the group comprising in particular colloidal silica, precipitated silica and micronized or non-micronized talcum. Benazepril is mentioned as an example of an ACE inhibitor. It is also described the method for preparing said granules and rapidly disintegrating tablets based on the coated granules, which disaggregate in the mouth on contact with salvia in less than 60 seconds.

Also pharmaceutical formulations which contain a PDE III inhibitor such as pimobendan or a pharmaceutically acceptable salt thereof are known in prior art:

WO 2005/084647 A1 discloses novel solid formulations comprising as pharmaceutically active compound pimobendan and processes for producing such solid formulations. The document furthermore relates to a method for manufacturing a medicament for the prevention and/or treatment of congestive heart failure, wherein the solid formulations are used.
However, a combined preparation containing a PDE III inhibitor as well as an ACE inhibitor at the same time is not known from prior art and also no practicable system to correlate the combined preparation with the additional administration of an PDE III inhibitor.

Taking the above items into account, it is a first object of the present invention to make the therapy of an animal more comfortable, to simplify the therapy and to support the animal keeper to perform a specific prescription plan to prevent and/or to treat heart diseases in animals as far as possible.

It is a further object of the present invention to provide an improved pharmaceutical combination formulation which may be used in the more comfortable, simplified therapy to prevent and/or to treat heart diseases in animals, wherein 2 pharmaceutically active substances known in therapy to prevent and/or to treat heart diseases in mammals are present at the same time and to provide an application form which is suitable for animal medicine, which can be used in a controlled manner without considerable effort and in a comfortable manner, such as on a daily basis, for mammals, especially domestic animals, in the case of pets such as dogs, cats, and rodents. Preferably the combination formulation of both active substances shall be bioequivalent to the respective monoproducst. The choice of the excipients and/or additives contained in the formulation shall support and improve the stability of the ACE inhibitor and/or PDE III inhibitor present. Furthermore, the formulation shall not lead to particular inacceptance problems when administered to animals. In addition, a method of manufacturing the formulation shall be provided.

**DESCRIPTION OF THE INVENTION**

Surprisingly, it has been found that a pharmaceutical packaging product for the veterinary sector may be provided which makes the therapy of an animal more comfortable, simplifies the treatment and supports the animal keeper to follow a specific prescription plan to administer several different solid formulations with regard to the prevention and/or treatment of heart diseases in animals as far as possible.
Therefore, it is provided a pharmaceutical packaging product for the veterinary medical sector containing a first pharmaceutical solid formulation, preferably a first pharmaceutical tablet formulation, comprising a first pharmaceutically active substance or substance (fixed dose) combination and a second pharmaceutical solid formulation, preferably a second pharmaceutical tablet formulation, comprising a second pharmaceutically active substance or substance combination.

Furthermore, it is provided a pharmaceutical packaging product for the veterinary medical sector containing a first pharmaceutical solid formulation, preferably a first pharmaceutical tablet formulation, comprising a first pharmaceutically active substance or substance (fixed dose) combination and a second pharmaceutical solid formulation, preferably a second pharmaceutical tablet formulation, comprising a second pharmaceutically active substance or substance combination, particularly for separate or sequential use (such as morning and evening) for the use in the prevention and/or treatment of heart diseases, disorders, or complications associated therewith in mammals. Preferably said mammal is a dog/ canine or a cat/ feline.

Furthermore, it is provided a method of preventing and/or treating heart diseases, disorders, or complications associated therewith, comprising administering a therapeutically effective amount of a first and a second pharmaceutical solid formulation, whereby said first and second pharmaceutical solid formulation are contained in a pharmaceutical packaging product for the veterinary medical sector containing a first pharmaceutical solid formulation, preferably a first pharmaceutical tablet formulation, comprising a first pharmaceutically active substance or substance (fixed dose) combination, and a second pharmaceutical solid formulation, preferably a second pharmaceutical tablet formulation, comprising a second pharmaceutically active substance or substance combination, particularly for separate or sequential use (such as morning and evening) to a (animal) patient in need thereof. Preferably said patient is a mammal, most preferably a dog/ canine or a cat/ feline.
The separate or sequential use of the first pharmaceutical solid formulation and the second pharmaceutical formulation are preferably indicated on the packaging product with 2 different colours (upper section 20 in light colour, e.g. for morning use, and the lower section 30 in dark colour, e.g. for evening use). Furthermore, preferably a sun symbol 60 is placed in the area of each cavity or pocket 20.1, 20.2, 20.3, 20.4, and 20.5 in the upper section 20 and preferably a moon symbol 50 is placed in the area of each cavity or pocket 30.1, 30.2, 30.3, 30.4, and 30.5 in the lower section 30.

Specifically, it is provided a pharmaceutical packaging product for the veterinary medical sector containing a first pharmaceutical solid formulation, preferably a first pharmaceutical tablet formulation, which comprises as pharmaceutically active substances a PDE III inhibitor and an ACE inhibitor and a second pharmaceutical solid formulation, preferably a second pharmaceutical tablet formulation, which comprises as pharmaceutically active substance a PDE III inhibitor (as a combined preparation). Said phrase "as a combined preparation" specifically relates to the pharmaceutical packaging product comprising a first and a second pharmaceutical solid formulation in combination.

Furthermore, it is provided a pharmaceutical packaging product containing a first pharmaceutical solid formulation, preferably a first pharmaceutical tablet formulation, which comprises as pharmaceutically active substances a PDE III inhibitor and an ACE inhibitor, and a second pharmaceutical solid formulation, preferably a second pharmaceutical tablet formulation, which comprises as pharmaceutically active substance a PDE III inhibitor, as a combined preparation for separate or sequential use in the prevention and/or the treatment of heart diseases, disorders, or complications associated therewith in mammals.

Said pharmaceutical solid formulation may also comprise a PDE III inhibitor, which also has an additional Ca²⁺-sensitising activity. According to another embodiment said pharmaceutical solid formulation may also comprise a Ca²⁺-sensitising agent as the pharmaceutically active ingredient in combination with a PDE III inhibitor or an ACE inhibitor.
Preferably the solid formulations according to the present invention are granules or tablets, more preferably tablets. Other solid administration forms are also possible.

The prevention and/or treatment of heart diseases in the present invention is preferably the prevention and/or the treatment of congestive heart failure originating from dilated cardiomyopathy or valvular insufficiency (mitral and/or tricuspid regurgitation), in mammals, preferably in pet animals, more preferably in dogs, cats, and rodents, most preferably in dogs.

According to the present invention the PDE III inhibitor is not limited, any known pharmaceutically active substance acting as a PDE III inhibitor may be used. PDE III inhibitors in prior art also referred to as PDE 3 inhibitors or as cGMP-inhibited phosphodiesterase are a type of phosphodiesterase inhibitors. It is a drug which inhibits the action of the phosphodiesterase enzyme PDE III. It is used for the therapy of acute heart failure and cardiogenic shock.

Exemplary PDE III inhibitors include amrinone, cilostazol, milrinone, enoximone and pimobendan. A particularly preferred PDE III inhibitor is pimobendan or a pharmaceutically acceptable salt thereof.

According to the present invention the ACE inhibitor is also not limited, any known pharmaceutically active substances acting as an ACE inhibitor may be used. Angiotensin-converting enzyme inhibitors reduce the activity of the renin-angiotensin-aldosterone system. It is a pharmaceutical drug used primarily for the treatment of hypertension (high blood pressure) and congestive heart failure.

Known ACE inhibitors can be divided into three groups based on their molecular structure: the sulfhydryl-containing agents, the dicarboxylate-containing agents, and the phosphonate-containing agents. Known sulfhydryl-containing agents are captopril (Capoten), and zofenopril. To the dicarboxylate-containing agents belong, for example, enalapril (Vasotec/Renitec), ramipril (Altace/Prilace/Ramace/Ramiwin/Triatec/Tritace), quinapril (Accupril), perindopril (Coversyl/Aceon), lisinopril (Listril/Lopril/Novatec/
Prinivil/Zestril), benazepril (Lotensin), imidapril (Tanatril), and trandolapril (Mavik/Odrik/Gopten). A phosphonate-containing agent is, for example, fosinopril (Fositen/Monopril).

In the present invention preferably used ACE inhibitors include captopril, analapril, lisinopril, ramipril and benazepril. A particularly preferred ACE inhibitor is benazepril or a pharmaceutically acceptable salt thereof, more preferably benazepril hydrochloride.

According to the present invention the first pharmaceutical solid formulation contains a combination of PDE III inhibitor and ACE inhibitor and the second pharmaceutical solid formulation contains a PDE III inhibitor alone. Any pharmaceutical solid formulation which contains a PDE III inhibitor and an ACE inhibitor at the same time may be used as first pharmaceutical solid formulation. For example a tablet having several tablet layers may be used, for example in one layer the PDE III inhibitor is present and in another layer the ACE inhibitor is present. According to the present invention the two pharmaceutical active substances are presented in one single dosage form, i.e. as combination drugs (fixed dose combination). It has been found that the fixed dose combination of both active substances of the present invention provides a synergistic combination which exceeds the activity and effectivity of the single active substances.

Any pharmaceutical solid formulation which contains a PDE III inhibitor may be used as second pharmaceutical solid formulation. For example, the solid formulation as disclosed in WO 2005/084647 A1 may be used, the disclosure thereof is herein incorporated by reference in its entirety. According to WO 2005/084647 A1 it is provided a solid formulation, comprising pimobendan or a pharmaceutically acceptable salt thereof which is homogenously dispersed in a polyvalent acid selected from the group consisting of acetic acid, tartaric acid, an anhydride thereof and mixtures thereof, and a flavor suitable for small animals. Other solid formulations are possible.

The PDE III inhibitor in the first and second solid formulation may be the same or different.
The PDE III inhibitor and the ACE inhibitor are contained in the first pharmaceutical solid formulation in an amount, respectively, suitable for exhibiting the desired pharmacological activities of each medicament, which are known and vary in accordance with the medication. In order to determine the optimum dose of each of the two active substances, respectively, various basic conditions have to be taken into consideration such as for example the age and body weight of the animal patient, the nature and stage of the disease and the potency of each compound. This is deemed to be within the capabilities of the skilled man, and the existing literature on the components can be consulted in order to arrive at the optimum dose.

The PDE III inhibitor is preferably contained in the first pharmaceutical solid formulation according to the invention, comprising 0.5 to 20 mg of PDE III inhibitor. More preferred are 1 to 10 mg of PDE III inhibitor. Even more preferred are 1.25 to 5 mg of PDE III inhibitor. Most preferred are 1.25 mg, 2.5 mg, 5 mg or 10 mg of PDE III inhibitor.

The ACE inhibitor is preferably contained in the first pharmaceutical solid formulation according to the invention, comprising 0.5 to 30 mg of ACE inhibitor. More preferred are 1 to 15 mg of ACE inhibitor. Even more preferred are 2.5 to 20 mg of ACE inhibitor. Most preferred are 2.5 mg, 5.0 mg, 10 mg and 20 mg of ACE inhibitor.

In the first pharmaceutical solid formulation any of the above dose strengths of the PDE III inhibitor may be combined with any of the dosage strengths of the ACE inhibitor. As a rough rule of thumb the following doses may be used: 1.25 mg, 2.5 mg, 5.0 mg, and 10.0 mg PDE III inhibitor; 2.5 mg, 5.0 mg, 10.0 mg, and 20.0 mg ACE inhibitor. Particularly preferred embodiments contain:

- 1.25 mg PDE III inhibitor and 2.5 mg ACE inhibitor; or
- 2.5 mg PDE III inhibitor and 5 mg ACE inhibitor; or
- 5 mg PDE III inhibitor and 10 mg ACE inhibitor; or
- 10 mg PDE III inhibitor and 20 mg ACE inhibitor.
The PDE III inhibitor is contained in the second pharmaceutical solid formulation in an amount, respectively, suitable for exhibiting the desired pharmacological activity in the medicament, which is known and vary in accordance with the medication. In order to determine the optimum dose of the active substance various basic conditions have to be taken into consideration such as for example the age and body weight of the animal patient, the nature and stage of the disease and the potency of the compound. This is deemed to be within the capabilities of the skilled man, and the existing literature on the components can be consulted in order to arrive at the optimum dose.

The PDE III inhibitor is preferably contained in the second pharmaceutical solid formulation according to the invention, comprising 0.5 to 20 mg of PDE III inhibitor. More preferred are 1 to 10 mg of PDE III inhibitor. Even more preferred are 1.25 to 5 mg of PDE III inhibitor. Most preferred are 1.25 mg, 2.5 mg, 5 mg or 10 mg of PDE III inhibitor.

According to a further aspect, the pharmaceutical packaging product according to the invention contains for example 0.5 to 20 mg, preferably 1 to 10 mg, even more preferred 1.25 to 5 mg PDE III inhibitor and 0.5 to 30 mg, preferably 1 to 15 mg, even more preferred 2.5 to 20 mg ACE inhibitor as the first pharmaceutical solid formulation, and as the second pharmaceutical tablet formulation 0.5 to 20 mg of the PDE III inhibitor, preferably 1.25 to 5 mg of the PDE III inhibitor, even more preferred 1.25 mg, 2.5 mg, 5 mg, 10 mg or 20 mg of the PDE III inhibitor; 1.25 mg PDE III inhibitor and 2.5 mg ACE inhibitor as the first pharmaceutical solid formulation, and as the second pharmaceutical tablet formulation 0.5 to 20 mg of the PDE III inhibitor, preferably 1.25 to 5 mg of the PDE III inhibitor, even more preferred 1.25 mg, 2.5 mg, 5 mg, 10 mg or 20 mg of the PDE III inhibitor; or for example 2.5 mg PDE III inhibitor and 5 mg ACE inhibitor as the first pharmaceutical solid formulation, and as the second pharmaceutical tablet formulation 0.5 to 20 mg of the PDE III inhibitor, preferably 1.25 to 5 mg of the PDE III inhibitor, even more preferred 1.25 mg, 2.5 mg, 5 mg, 10 mg or 20 mg of the PDE III inhibitor; or for example 5 mg PDE III inhibitor and 10 mg ACE inhibitor as the first pharmaceutical solid formulation, and as the second pharmaceutical tablet formulation 0.5 to 20 mg of the PDE III inhibitor, preferably 1.25 to 5 mg of the PDE
III inhibitor, even more preferred 1.25 mg, 2.5 mg, 5 mg, 10 mg or 20 mg of the PDE III inhibitor; or for example 10 mg PDE III inhibitor and 20 mg ACE inhibitor as the first pharmaceutical solid formulation, and as the second pharmaceutical tablet formulation 0.5 to 20 mg of the PDE III inhibitor, preferably 1.25 to 5 mg of the PDE III inhibitor, even more preferred 1.25 mg, 2.5 mg, 5 mg, 10 mg or 20 mg of the PDE III inhibitor.

According to an especially preferred embodiment of the present invention the first pharmaceutically active substance in the first pharmaceutical solid formulation is a pharmaceutically acceptable salt of benazepril, preferably benazepril hydrochloride, and the second pharmaceutically active substance is pimobendan. A particularly preferred embodiment of the first pharmaceutical solid formulation will be described later.

According to a preferred embodiment of the present invention the pharmaceutical packaging product is a blister pack. Other packaging articles are also possible.

Within the content of the present invention a blister pack is to be understood as a packaging for pharmaceuticals which has a cavity or pocket wherein the pharmaceuticals are present and a backing or seal which is a foil. The expressions "blister", "blister pack" and "blister card" are used interchangeably. In the present invention preferably an aluminum blister pack is used, wherein the foil is made of aluminum. The cavity or pocket may be usually made-up of a clear pre-formed plastic material such as PVC, PVC/PVDC, but in the present invention aluminum is also preferably used for the cavity or pocket. In case a clear pre-formed plastic material is used the blister should be additionally packaged in aluminum pouches. Therefore, the blister pack according to the present invention is an aluminum blister having an aluminum foil and an aluminum pocket wherein the pharmaceutical solid formulations are accommodated ("alu/alu blister").

According to the present invention the solid formulations will be packed in a blister pack preferably containing two rows of tablets. The blister pack preferably contains an equal number of the first and second pharmaceutical solid formulations, respectively. In
an examplary embodiment the blister may accomodate in total 14 solid formulations, 7 solid formulations of the first pharmaceutical solid formulation and 7 solid formulations of the second pharmaceutical solid formulation, the first pharmaceutical solid formulation containing the combination PDE III inhibitor/ACE inhibitor, the second pharmaceutical solid formulation containing the PDE III inhibitor as the only pharmaceutically active substance. In another examplary embodiment the blister may accomodate in total 10 solid formulations, 5 solid formulations of the first pharmaceutical solid formulation and 5 solid formulations of the second pharmaceutical solid formulation, the first pharmaceutical solid formulation containing the combination PDE III inhibitor/ACE inhibitor, the second pharmaceutical solid formulation containing the PDE III inhibitor as the only pharmaceutically active substance. Other arrangements are possible.

Since the 3 pharmaceutically active substances are present in one blister pack, as fixed dose combination (PDE III inhibitor/ACE inhibitor) and mono-product preparation (PDE III inhibitor), the therapy of an animal is more comfortable and simplified at the same time because the pharmaceutically active substances are not to be taken from different packaging products, for example 3 different blisters, but are all present in one packaging product at the same time. Furthermore, different dosage strengths of the fixed dose combination and/or the mono-product preparation may be combined with each other in the same blister pack. Therefore, the packaging product may be tailor-made to an individual animal patient depending from the clinical picture, the severity of the disease and the age and condition of the animal to be treated.

In order to further support the animal keeper in performing the prevention and/or treatment of the animal the blister pack is preferably divided into two halves in form of two sections, herein also referred to as "split blister", having an upper and a lower section, in the upper section the first pharmaceutical solid formulation is present and in the lower section the second pharmaceutical solid formulation is present. The purpose of such a split blister is that the packaging per se provides a differentiation between the two different pharmaceutical solid formulations provided in the blister so that the formulations are not mixed-up. In the split blister it is not necessary to adapt the shape
and size of the blister pack, but it rather represents a principle of arrangement so that the first pharmaceutical solid formulation is arranged in the upper half of the blister card (upper section) and the second pharmaceutical solid formulation is arranged in the lower half of the blister card (lower section).

A further option according to the present invention to assist the animal keeper in performing the prevention and/or treatment of the animal is that the pharmaceutical packaging product is a blister pack having a bottom foil, the outside of the bottom foil comprises one or more identification markings. The bottom foil of the blister pack which serves to cover and seal the cavities or pockets in the blister pack against the environment has a front side and a back side or outside and is preferably made of aluminum. On the front side of the bottom foil the cavities or pockets, preferably also made of aluminum, including the solid formulations are located and on the back side or outside of the bottom foil the identification markings are applied. The identification markings serve to alter the optical appearance of the blister and to clearly differentiate between the pharmaceutical solid formulations simultaneously present in the same blister pack. The markings are preferably applied in a position on the outside of the foil directly above or in the area where the cavities or pockets are located, respectively. Therefore, the markings are directly correlated with the respective solid formulation contained in the blister pack. Preferably each cavity or pocket containing a pharmaceutical solid formulation comprises on the back side thereof, i.e. on the outside of the bottom foil covering the cavity or pocket, one or more identification markings.

The identification markings may be selected from one or more colours and/or one or more legends and/or one or more symbols.

The identification markings are preferably identical for the each cavity or pocket wherein the first pharmaceutical solid formulation is present. Furthermore, the identification markings are preferably identical for each cavity or pocket wherein the second pharmaceutical solid formulation is present.
The colours used are not restricted, any colour which may be used on a bottom foil of a blister pack may be used. Any coloured marking or colour code may be used in order to differentiate between the first and second solid formulation.

According to a preferred embodiment the pharmaceutical packaging product is a blister pack divided into two sections, preferably an upper and a lower section, on the outside of the blister foil the upper section is marked with one colour, preferably the colour covers the whole surface of the upper section, and the lower section is marked with a colour different to the colour of the upper section, preferably the colour covers the whole surface of the lower section. Therefore, the first solid formulation is clearly correlated with one colour and the second solid formulation is also clearly correlated to a different colour so that the animal keeper will realize at once the different medicaments present. For safety reasons, the solid formulations for administration in the morning is preferably correlated with a bright colour code (such as yellow, orange, light red, etc), whilst the solid formulation for evening administration is preferably correlated with a dark colour (brown, dark blue, black etc.). For example, the upper section or upper half of the blister pack may be coloured in yellow colour and the lower section or lower half of the blister pack may be coloured in brown colour. Other colours or combination of colours are possible.

Additionally or instead to the colouring one or more legends may be present on the back side of the bottom foil, that is in a position directly above or in the area of the cavities or pockets wherein the first and second pharmaceutical solid formulations to be administered are contained, respectively. The one or more legends may indicate the type of solid formulation contained, the kind of pharmaceutically active substance(s) contained, the dosage strength(s) of pharmaceutically active substance(s) contained, the preferred time of administration, the kind of administration form provided, the animal to be treated and the like. The legend gives the user additional information in order to simplify the treatment of the animal.

According to a preferred embodiment of the present invention the legend may be selected from "morning", "at noon", or "evening" corresponding to the time to take the
medication. For the first pharmaceutical solid formulation the legend is preferably "morning" and for the second pharmaceutical solid formulation the legend is preferably "evening". Therefore, the animal keeper has the direct information on the blister that the solid formulation, preferably tablet contained under the identification marking such as "morning" has to be given to the animal in the morning. The information on the blister foil is directly correlated with the therapy matter that is, in the present example, the time to take the medication. Another legend is possible, for example in another language or an abreviation or another kind of legend may be used.

In order to further facilitate the administration symbols may be used for example to indicate the time to take the medication. For example a sun symbol (to be taken in the morning) or a moon symbol (to be taken in the evening) corresponding to the time to take the medication may be used. For the first pharmaceutical solid formulation, for example, a sun symbol is selected and for the second pharmaceutical solid formulation, for example, a moon symbol may be used. Such symbols would make it even easier for the user to administer the correct solid formulation.

In a further preferred embodiment according to the present invention the first pharmaceutical solid formulation and/or the second pharmaceutical solid formulation is/are present in the blister pack in the same or in different dosage strengths, the outside of the bottom foil comprises one or more identification markings so that each dosage strength is correlated with a colour and/or a labeling and/or a symbol. This concept allows to adapt the blister pack content to the specific treatment of an animal.

In order that the pharmaceutical solid formulations may be well-differentiated the physical appearance of the solid formulations may be altered in addition. For example, the first pharmaceutical solid formulation may have a colouring and the second pharmaceutical solid formulation may have a colouring different to the colouring of the first pharmaceutical solid formulation. For example the first pharmaceutical solid formulation may have a yellow colour and the second pharmaceutical solid formulation may have a brown colour. Therefore, the different colours allow to clearly distinguish between the first and second solid formulations. Other colours are possible.
In a preferred embodiment the colour of the first solid formulation is preferably similar or identical to the colour selected for the identification markings of the outside of the blister foil. In addition the colour of the second solid formulation is preferably similar or identical to the colour selected for the identification markings of the outside of the blister foil.

The expression "similar colour" shall be understood in the frame of the present invention that a colour is similar to another colour in case the key tone is the same and only the type of shade is varied. A key tone has a number of darker shades as well as lighter shades of colour, all type of shades shall be included. That is a similar colour to yellow, whereby yellow represents the key tone, is, for example, a light yellow.

In a particularly preferred embodiment the blister pack is divided in an upper and lower section, on the outside of the blister foil the upper section is marked with one colour, preferably the colour covers the whole surface of the upper section, and the lower section is marked with a colour different from the colour of the upper section, preferably the colour covers the whole surface of the lower section. Additionally the colour of the first solid formulation is preferably similar or identical to the colour selected for the upper section and the colour of the second solid formulation is preferably similar or identical to the colour selected for the lower section. For example, the foil of the upper section is completely coloured in yellow and the colour of the first pharmaceutical solid formulation is also yellow. For example, the foil of the lower section is completely coloured in brown and the colour of the second pharmaceutical solid formulation is also brown. In this regard it is sufficient that the colour tint used is similar to each other but must not absolutely identical. That is the user may identify several yellow colour tints as yellow colour so that a yellowish brown may be used or a light yellow depending from the technical realisation into practice.

The different colours may be used to simplify the plan of intake, i.e. one colour, for example yellow colour (yellow colour on the blister foil and/or yellow colour of the solid formulation), may be correlated with the intake of the solid formulation in the
morning, and another colour, for example brown colour (brown colour on the blister foil and/or brown colour of the solid formulation), may be correlated with the intake of the tablet in the evening. Thus the colours assist to facilitate further the administration of the correct solid formulation in the morning and evening.

Besides, the shape and size of the first pharmaceutical solid formulation are preferably comparable to the shape and size of the second pharmaceutical solid formulation. Furthermore, both solid formulations are preferably chewable tablets.

Since the shape and size of the pharmaceutical solid formulations has a direct impact on the form and dimensions of the pharmaceutical packaging product and due to the fact that the shape and size of the solid formulations directly depend on the composition and built-up of the pharmaceutical solid formulations selected, the pharmaceutical packaging product may be also characterised based on the pharmaceutical solid formulations contained in it.

In a preferred embodiment of the present invention, the blister pack is a child-resistant blister such as a push trough pack (PTP).

As a matter of course in addition to the first and second pharmaceutical solid formulations, contained in one blister, other pharmaceutical agents may be administered to the mammal. For example in the case of chronic treatment of heart diseases such as congestive heart failure the additional use of a diuretic agent such as furosemide is recommendable. The combined use of a PDE III inhibitor and an ACE inhibitor together with a diuretic agent serves to address the major pathogenetic mechanisms that contribute to the symptoms of congestive heart failure, particularly in dogs. The PDE III inhibitor enhances the contractile function of the heart and functions as a load reducer, resulting in an improved hemodynamic status. These effects are complemented by an ACE inhibitor, which also reduces load and antagonizes the neurohormonal imbalances caused by the underlying heart disease and the chronic administration of furosemide. Therefore, the PDE III inhibitor, for example pimobendan, and the ACE inhibitor, for example benazepril hydrochloride, in a fixed dose combination together with the PDE
III inhibitor in a mono-product preparation and optionally combined with a diuretic agent such as furosemide represent the current gold standard of such a therapeutic concept.

The present invention is also directed to a solid formulation, preferably for use as the first pharmaceutical solid formulation in the pharmaceutical packaging product as herein disclosed, which comprises as pharmaceutically active substances a PDE III inhibitor and an ACE inhibitor.

Subject of the present invention is also a pharmaceutical tablet formulation, preferably for use as the first pharmaceutical solid formulation in the pharmaceutical packaging product as herein disclosed, containing an ACE inhibitor as a first pharmaceutically active substance, and a PDE III inhibitor as a second pharmaceutically active substance, comprising granules which contain carrier core particles coated with at least one layer wherein the first pharmaceutically active substance is present, the granules being embedded in a tablet matrix wherein the second pharmaceutically active substance is present.

The present invention is also directed to the use of the pharmaceutical solid formulation, preferably a pharmaceutical tablet formulation, in the prevention and/or treatment of heart diseases, preferably congestive heart failure originating from dilated cardiomyopathy or valvular insufficiency, mitral and/or tricuspid regurgitation, in mammals.

The mammal according to the invention is preferably a mammal selected from the group consisting of dogs, cats and rodents such as rabbits, most preferably dogs.

According to the present invention the PDE III inhibitor and the ACE inhibitor as the two pharmaceutical active substances are presented in one single dosage form, i.e. as combination drugs (fixed dose combination) in the first pharmaceutical solid formulation. In the following an especially preferred embodiment of the present
invention of the first pharmaceutical solid formulation in form of a first pharmaceutical

tablet formulation will be described in detail.

According to the exemplary embodiment the first pharmaceutical tablet formulation for

the veterinary medical sector is provided, which contains an instable ACE-inhibitor or

acceptable salt thereof as well as a PDE-inhibitor or a pharmaceutically acceptable salt

thereof, which needs to be in the vicinity of acid in order to achieve bioavailability. It is

therefore provided a pharmaceutical tablet formulation for the veterinary medical sector

containing

an acid-instable ACE-inhibitor or a pharmaceutically acceptable salt thereof as a first

pharmaceutically active substance, and

pimobendan or a pharmaceutically acceptable salt thereof as a second pharmaceutically

active substance,

comprising granules, which contain carrier core particles coated with at least one layer

wherein the first pharmaceutically active substance is present,

the granules being embedded in a tablet matrix wherein the second pharmaceutically

active substance is present.

Instable ACE-inhibitors are herein defined to be ACE inhibitors, which easily undergo

degradation when in contact with for example water, acids, flavours, lubricants or any

other tableting excipient, but especially ACE-inhibitors that are degraded by for

example hydrolysis following contact with water, acids or flavour. Said ACE-inhibitors

comprise or consist of benazepril, captopril, enalapril, lisinopril, quinapril, fosinopril,

perindopril, imidapril, zofenopril, trandolapril and ramipril, preferred is benazepril.

According to a preferred embodiment of the present invention it has been found that a

pharmaceutical tablet formulation for the veterinary medical sector is provided, which

contains benazepril as instable ACE inhibitor or a pharmaceutically acceptable salt

thereof as well as pimobendan as PDE III inhibitor or a pharmaceutically acceptable salt

thereof. It is therefore provided a pharmaceutical tablet formulation for the veterinary

medical sector containing
Benazepril or a pharmaceutically acceptable salt thereof as a first pharmaceutically active substance, and
pimobendan or a pharmaceutically acceptable salt thereof as a second pharmaceutically active substance,
comprising granules, which contain carrier core particles coated with at least one layer wherein the first pharmaceutically active substance is present,
the granules being embedded in a tablet matrix wherein the second pharmaceutically active substance is present.

Benazepril is the chemical substance \([S-(R^*,R^*)]-3-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-lH-l-benzazepin-l-acetic\) acid and has the following chemical formula:

![Chemical structure of benazepril](image)

It is an ACE inhibitor (angiotensin converting enzyme inhibitor) which lowers blood pressure by inhibiting the formation of angiotensin II, thus relaxing the arteries, and consequently improves the pumping efficiency and cardiac output. ACE inhibitors are generally very difficult to formulate into dosage forms, as most ACE inhibitors on contact with some of the commonly used pharmaceutical ingredients undergo degradation at accelerated rates due to cyclization via internal nucleophilic attack to form substituted diketopiperazines or hydrolysis of the side chain ester group. It is a moisture sensitive, well water-soluble and bitter tasting substance. In case of humidity a hydrolysis of benazepril or a pharmaceutically acceptable salt thereof is to be expected. Due to the very bitter taste it is difficult to formulate conventional palatable dosage forms.
Pimobendan, a PDE III inhibitor, is the chemical substance (4,5-dihydro-6-[2-(4-methoxyphenyl)-1H-benzimidazo1-5-yl]-5-methyl-3(2H)-pyridazone) and has the following chemical formula:

![Chemical structure of Pimobendan](image)

It is a known cardiotonic vasodilator (inodilator) which derives its inotropic activity from a combination of phosphodiesterase III inhibition and sensitisation of myocardial contractile proteins to calcium (calcium sensitizer). It is a chemically stable substance having a poor and pH-dependent solubility, it is better soluble in acid. The resorption, when administered orally, is prone to considerable inter- and intra-individual fluctuations if the active substance is incorporated in conventional pharmaceutical forms for oral administration. In solid medicaments pimobendan is often mixed with citric acid in order to improve the solubility, the amount of release, and to maintain an optionally oversaturated solution as long as possible.

The preferred technical realisation of the first pharmaceutical solid formulation in form of a tablet formulation according to the present invention is based on embedding the potentially instable ACE-inhibitor or a pharmaceutically acceptable salt thereof, preferably benazepril or a pharmaceutically acceptable salt thereof, containing granules in a tablet matrix wherein pimobendan or a pharmaceutically acceptable salt thereof is present. It has been found that the fixed dose combination of both active substances of the present invention provides a synergistic combination which exceeds the activity and effectiveness of the single active substances.

The granules according to the present invention are not particularly limited. According to the frame of the present invention "granules" are associated aggregates of powder...
particles having a non-uniform surface and an inner structure. The aggregation results in a decrease of the specific surface area which leads to a reduced adhesion among the primary granule particles. Granules are in general more uniform than powders and allow a more homogeneous tablet mass and higher dosage accuracy to be achieved.

The inner structure of the granules according to the present invention is represented by the carrier core particles. The carrier core particles of the granules are preferably selected from a pharmaceutically acceptable material which upon contact with water shows a minimal or negligible swelling. Preferable materials are selected from lactose, carbohydrates, sugar alcohols, such as mannitol, sorbitol, maltitol, glucose, non-pareil-seeds, calcium phosphate, cellulose, preferably microcrystalline cellulose (MCC), and starch, and mixtures thereof, more preferably lactose, most preferably agglomerated a-lactose-monohydrate [Ph.Eur./USP-NF/JP] with a particle size \( d_{50} \) of ca. 180 \( \mu \text{m} \). Lactose such as agglomerated lactose, with the characteristics described above is particularly suitable for use in the core because of its particle size, non-hygroscopicity, and the fact that it at least partly undergoes plastic deformation upon compression so that the core will not break into pieces in the tablet press. Particularly preferred are also mixtures of agglomerated a-lactose-monohydrate together with one or more of the other materials listed above.

According to a preferred embodiment of the present invention the carrier core particles are coated with a layer containing the instable ACE-inhibitor, preferably benazepril or a pharmaceutically acceptable salt thereof as the first pharmaceutically active substance, and a coating polymer and/ or matrix forming polymer(s), optionally mixtures thereof.

Pharmaceutically acceptable salts of the instable ACE-inhibitor, preferably benazepril, include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfuric and benzenesulfonic acids. The preferred pharmaceutically acceptable salt of benazepril is the hydrochloride.
The coating polymer and/or matrix forming polymers are for example water-soluble polymers such as cellulose ethers or pH-dependently soluble, or swellable polymers such as polymethacrylates, optionally in combination with pore forming agents, or water-insoluble polymers such as polymethacrylates or cellulose ethers in combination with pore forming agents. Water-soluble cellulose ethers are for example hydroxypropyl methylcellulose (HPMC), methylcellulose, hydroxyethylcellulose. Pore forming agents are for example water soluble cellulose ethers, polyethylene glycols, sugars and sugar alcohols like saccharose, lactose.

Preferred is a polymer on methacrylic acid basis which is a polymer from the group of polymethacrylates such as methacrylic acid-ethyl acrylate copolymer (1:1). Polymethacrylates are for example synthetic neutral/uncharged, or cationic and anionic polymers of monomers comprising dimethylaminoethyl methacrylates, methacrylic acid, and methacrylic acid esters in varying ratios. A polymethacrylate polymer which is soluble under acidic conditions, but insoluble under neutral or basic conditions is even more preferred. The mentioned polymer may be used alone or in combination of two or more polymers. According to a preferred embodiment of the present invention only one polymer is used.

Particularly preferred is a cationic copolymer based on dimethylaminoethyl methacrylate copolymer (IUPAC name: poly(butyl methacrylate-co-(2-dimethylaminoethyl) methacrylate-co-methyl methacrylate) 1:2:1) (also known as Basic Butylated Methacrylate Copolymer Ph. Eur). A number of compounds are commercially available products from the company Rohm, Darmstadt, Germany, which are known as substances belonging to the Eudragit® series. For example, a polymer on methacrylic acid basis, such as poly(butyl methacrylate-co-(2-dimethylaminoethyl) methacrylate-co-methyl methacrylate) 1:2:1 is a functional polymer, which is soluble in acidic medium, for example in gastric fluid up to pH 5, swellable and permeable above pH 5.0, but insoluble under neutral and basic conditions.
A coating polymer and/or matrix forming polymer(s), preferably a polymethacrylate polymer, which is soluble under acidic conditions, but insoluble under neutral or basic conditions - a particularly preferred polymer in the present invention - has the advantage that after administration of the pharmaceutical tablet formulation the polymer is not immediately dissolved in the mouth of the animal so that the first active substance, the instable ACE-inhibitor, preferably benazepril or a pharmaceutically acceptable salt thereof, is not released. Even in case one or more acidic excipients are present in the outer tablet phase, the acidic microclimate formed would not be sufficient to contribute to the dissolution of the polymer(s) and subsequently the first pharmaceutically active substance. The intake of the tablet is so rapid that such effects will play no part. Thus there will be no contact between the active substance and water avoiding immediate dissolution of the drug in the animal's mouth or possible hydrolysis at this stage of ingestion. Furthermore, as there is no dissolution of the tablet at this stage, any flavours or tastes that are unpleasant for the patient are masked. However, as soon as the pharmaceutical tablet formulation arrives in the stomach, the polymer is dissolved and the first active substance is rapidly and completely released. Thus, the formation of a bitter taste in the mouth of the animal due to the release of the instable ACE-inhibitor, preferably benazepril or a pharmaceutically acceptable salt thereof is completely avoided.

According to a preferred embodiment of the present invention the coated carrier core particles are additionally coated with a layer containing at least a coating polymer and/or matrix forming polymer, preferably a polymer on methacrylic acid basis. The polymer on methacrylic acid basis is again a polymer which belongs to the polymethacrylates as already discussed. More preferably the polymer on methacrylic acid basis is a cationic copolymer based on dimethylaminoethyl methacrylate copolymer (IUPAC name: poly(butyl methacrylate-co-(2-dimethyl-aminoethyl) methacrylate-co-methyl methacrylate) 1:2:1, also known as Basic Butylated Methacrylate Copolymer Ph. Eur.

Therefore, the carrier core particles are coated with a layer containing the first pharmaceutically active substance and at least one coating polymer and/or matrix
forming polymer, preferably a polymer on methacrylic acid basis. This layer is also referred herein as first or inner layer.

More preferably the coated carrier core particles are additionally coated with a layer containing at least one coating polymer and/ or matrix forming polymer, preferably a polymer on methacrylic acid basis but no pharmaceutically active substance. This layer is herein referred to as second or outer layer.

The coating polymer and/ or matrix forming polymer, preferably the polymethacrylate polymer(s), in the first coating layer is the same or different from the coating polymer and/ or matrix forming polymer, preferably polymethacrylate polymer(s), used in the second coating layer. According to a particularly preferred embodiment the coating polymer and/ or matrix forming polymer, preferably polymer(s) on methacrylic acid basis, in the two layers is(are) the same. In a further preferred embodiment of the present invention only one polymer on methacrylic basis is present in the first and the second layer and the polymer is the same in both layers, while other polymers can be present in either or both layer(s).

The coating polymer and/ or matrix forming polymer, preferably a polymer on methacrylic acid basis present in the pharmaceutical tablet formulation of the present invention has several functions at the same time:

It serves to mask the bitter taste of the instable ACE-inhibitors, preferably benazepril or a pharmaceutically acceptable salt thereof because the bitter tasting first pharmaceutically active substance is embedded in the polymer. Furthermore, it provides stability to the resultant formulation. The polymer provides protection from surrounding moisture, as well as physical separation from additional excipients such as acids or flavouring agents that contribute to the instability of the ACE-inhibitor, preferably benazepril or a pharmaceutically acceptable salt thereof. In addition the release performance is optimized because the first active substance is not released immediately in the mouth of the animal as already described. Finally, the polymer binds the first pharmaceutically active substance to the carrier particles aiding homogeneous
distribution of the active ingredient in the tablet, and further enhancing mechanical
stability of the whole pharmaceutical tablet formulation. The resulting particles could
also be administered as stand-alone granules for the ACE inhibitor or any salt thereof or
be compressed with suitable excipients to a mono tablet thus underlining the flexibility
and versatility of the particles as described above. The granules containing ACE
inhibitor are well suited to be administered as granules or processed further into
capsules or tablets. It has been observed that the shape and size of the granules
according to the present invention provide an excellent mouth feeling so that animals
willingly accept the intake of such granules as medicament. The granules may also form
part of a combined preparation wherein the further dosage form comprises another
pharmacologically active substance.

As a result, the first layer is an important feature of the tablet formulation whereas the
second layer further improves the above mentioned functions. According to another
embodiment of the invention the second layer is optional.

It is a matter of course that one or more additional intermediate layers between the
carrier core particles and the first layer and/or between the first and the second layer
and/or between the second layer and the tablet matrix can optionally be present.
Therefore, in another embodiment of the present invention the first pharmaceutical
tablet formulation comprises the above described carrier core particles coated with the
first layer, the second layer and the tablet matrix and optionally one or more
intermediate layers may be disposed between. The amount/number of intermediate
layers are not limited. Any optional layer which does not interfere with the function and
effectiveness of the pharmaceutical tablet formulation may be used such as a non-
functional layer. The term "non-functional" in the present context means having no
substantial effect on release properties of the pharmaceutical tablet formulation, and the
layer in the form of a coating serves another useful purpose. For example, such a layer
can impart a distinctive appearance to the dosage form, provide protection against
attrition during packaging and transportation, improve ease of swallowing, and/or have
other benefits. A layer or coating should be applied in an amount sufficient to provide
complete coverage of the surface of the coated particles/granules.
In one embodiment according to the present invention the first pharmaceutical tablet formulation comprises or consists of the carrier core particles coated with the first layer and the second layer and the tablet matrix. In this embodiment no intermediate layer is present.

In another embodiment according to the present invention the first pharmaceutical tablet formulation comprises or consists of the carrier core particles coated with the first layer and the second layer and the tablet matrix, whereby one intermediate layer is present at one or more appropriate locations in the coated particles/ granules.

The first pharmaceutical tablet formulation according to the present invention comprises one or more excipients used according to pharmaceutical practice. Due to the different functionality the one or more polymer layer(s) on the coated particles as described above and the tablet matrix have a different composition with regard to the excipients present. As a result, the polymer layer(s) on the coated particles, for example the first and second layers, comprise one or more excipients, whereby the excipients are preferably selected from release modifying agents, binders, carriers, crystallization retarders, sweeteners, solubilizers, coloring agents, flavouring substances, pH control agents, taste masking agents, surfactants, anti-tacking agents, plasticizers, anti-static agents, and emulsifiers.

Furthermore, the tablet matrix comprises one or more excipients, whereby the excipients are preferably selected from binders, carriers, diluents, disintegrants, fillers, lubricants, acidifying agents, glidants, crystallization retarders, sweeteners, solubilizers, coloring agents, flavouring substances, pH control agents, taste masking agents, anti-tacking agents, plasticizers, surfactants, and emulsifiers.

The term "one or more" or "at least one" as used in the present invention stands for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 compounds or layers or even more and the like. Some preferred embodiments comprise 1, 2, 3, 4, or 5 such compounds or layers and the like. Some
preferred embodiments comprise 1, 2, or 3 such compounds or layers, 1 or 2 compounds or layers or one compound or layer may also be employed.

Commonly known excipients used in the first pharmaceutical tablet formulation of the present invention are listed in the following:

As binder, it is possible to use any binder usually employed in pharmaceuticals. Exemplarily mentioned are naturally occuring or partially or totally synthetic polymers selected from among acacia, agar, gum arabic, alginic acid, carbomers, carrageenan, ceratonia, chitosan, confectioner's sugar, copovidone, povidone, cottonseed oil, dextrate, dextrin, dextrose, polydextrose, maltodextrin, maltose, cellulose, and derivatives thereof such as microcrystalline cellulose, methylcelluloses, ethylcelluloses, hydroxyethyl celluloses, hydroxyethyl methylcelluloses, hydroxypropyl celluloses, carboxymethyl-celluloses, carmellose sodium, hypromelloses (cellulose hydroxypropyl methylether), cellulose acetate phthalate, starch and derivatives thereof, such as pregelatinized starch, hydroxypropylstarch, corn starch, gelatin, glycercyl behenate, guar gum, hydrogenated vegetable oils, inulin, lactose, glucose, magnesium aluminium silicate, poloxamer, polycarbophils, polyethylene oxide, polyvinyl pyrrolidone, copolymers of N-vinylpyrrolidone and vinyl acetate, polymethacrylates, alginites such as sodium alginate, stearic acid, sucrose, sunflower oil, zein as well as derivatives and mixtures thereof. Particularly preferred binders are gum arabic, hydroxypropyl celluloses, hydroxypropyl methylcelluloses, methylcelluloses, hydroxyethyl celluloses, carboxymethylcelluloses, carmellose sodium, povidone, corn starch, polyvinyl pyrrolidone, the copolymers of N-vinylpyrrolidone, and vinyl acetate, or combinations of these polymers.

Suitable carriers, diluents or fillers which are usually employed in pharmaceuticals may be selected from, for example, lactose, in particular lactose monohydrate, talc, sunflower oil, tragacanth, starches and derivatives such as pregelatinized starch or sterilizable maize, alginate such as ammonium alginate, sodium alginate, sodium chloride, calcium carbonate, dibasic calcium phosphate, calcium hydrogenophosphate, calcium sulfate, dicalcium or tricalcium phosphate, magnesium carbonate, magnesium
oxide, cellulose and derivatives, such as microcrystalline or silicified or silicified microcrystalline cellulose, cellulose acetate, starch glycolate, ethylcellulose, sugars and derivatives such as confectioner's sugar, fructose, sucrose, dextrate, dextrin, sulfobutylether β-cyclodextrin, dextrose, crospovidone, polydextrose, trehalose, maltose, maltitol, mannitol, maltodextrin, sorbitol, inulin, xylitol, erythritol, fumaric acid, glyceryl palmitostearate, tablettose, hydrogenated vegetable oils, isomalt, kaolin, lactitol, triglycerides, particularly medium-chain triglycerides, polymethacrylate, and simethicone as well as derivatives or mixtures thereof, particularly preferred are lactose, in particular lactose monohydrate, microcrystalline or silicified or silicified microcrystalline cellulose, calcium hydrogenophosphate, starch glycolate, and crospovidone.

Examples of release modifying agents are gums such as guar gum, gum acacia, xanthan gums, alginates such as sodium alginate, glycerol monooleat, and castor oil. A wide variety of other possible agents are known by the skilled person.

Exemplary disintegrants which may be preferably used are alginic acid and salts thereof including calcium, sodium, magnesium, carboxymethylcellulose calcium, carboxymethylcellulose sodium, powdered cellulose, chitosan, colloidal silicon dioxide (e.g. highly dispersed types of colloidal silicon dioxide such as Aerosil®, Cab-O-Sil®), crospovidone, croscarmellose sodium, docusate sodium, guar gum, hydroxypropyl cellulose, particularly low-substituted hydroxypropyl cellulose, hydroxypropyl starch, magnesium aluminum silicate, methylcellulose, micocrystalline cellulose, polacrilin potassium, crosslinked povidone, sodium starch glycolate, starch, undried maize starch as well as derivatives or mixtures thereof, particularly pregelatinized starch, crosslinked povidone and undried maize starch.

An anti-tacking agent, anti-sticking agent, glidant or agent to improve flowability (flow control agents) can be used to improve powder flow properties prior to and during the manufacturing process and to reduce caking. A lubricant or agglomeration inhibitor can be used to enhance release of the dosage form from the apparatus on which it is formed, for example by preventing adherence to the surface of an upper punch ("picking") or
lower punch ("sticking"). Among this group of excipients may be exemplarily mentioned boric acid, calcium silicate, cellulose, particularly powdered cellulose, anhydrous colloidal silica, DL-leucine, magnesium silicate, magnesium trisilicate, talc, silicon dioxide, starch, tribasic calcium phosphate, glyceryl behenate, magnesium oxide, mineral oil, poloxamer, polyvinyl alcohol, hydrogenated oils such as hydrogenated vegetable oils, hydrogenated castor oil, kaolin, (light) mineral oil, canola oil, triglycerides, such as medium-chain triglycerides, myristic acid, palmitic acid, polyethylene glycols (all types at different molecular weights of PEGs), benzoate such as sodium or potassium benzoate, sodium chloride, sodium lauryl sulfate, magnesium lauryl sulfate, sodium acetate, sodium benzoate, sodium fumarate, sodium oleate, sodium stearyl fumarate, talc, stearic acid, macrogol, like macrogol 400 or 6000, polyoxyl-40-stearate, waxes as well as derivatives or mixtures thereof.

Exemplarily mentioned acidifying agents or acidulants are, lactic acid, tartaric acid, fumaric acid, malic acid, and monobasic sodium phosphate as well as derivatives or mixtures thereof, preferably fumaric acid.

An example for a pharmaceutically acceptable crystallization retarder or modifier is raffinose, other excipients that can be used in this regard are for example other sugars and sugar alcohols, water soluble polymers or surfactants.

Preferable sweeteners are acesulfame potassium, alitame, aspartame, dextrose, erythritol, fructose, glycerin, inulin, isomalt, lactitol, liquid glucose, maltitol, maltose, mannitol, neospheridin dihydrochalcone, polydextrose, saccharin, saccharin sodium, sodium cyclamate, sorbitol, sucralose, sucrose, thaumatin, trehalose, and xylitol as well as derivatives or mixtures thereof.

Exemplary solubilizers are cyclodextrins, glycerin monostearate, lecithin, meglumine, poloxamers, polyethylene alkyl ethers, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene stearates, povidone, 2-pyrrolidone, sodium bicarbonate, sorbitan esters, stearic acid, and sulphobutylether as well as derivatives or mixtures thereof.
Exemplary colouring agents are preferably selected from beta-carotene, indigo carmine, iron oxides, preferably iron oxide yellow, sunset yellow, FCF, tartrazine, titanium dioxide as well as derivatives or mixtures thereof.

The taste masking agents are exemplarily selected from carbohydrates such as monosaccharides or disaccharides, ethyl lactate, ethyl maltol, ethyl vanillin, fumaric acid, leucine, malic acid, maltol, menthol, phosphoric acid, propylene glycol, sodium acetate, sodium lactate, thymol, meat flavour such as artificial beef flavour as well as derivatives or mixtures thereof, particularly preferred are dry meat flavour and vanillin.

Exemplary pH control or adjusting agents which are preferably used may be selected from glacial acetic acid, ammonia solution, diethanolamine, meglumine, sodium citrate dihydrate and also commonly known acidifying agents and buffering agents.

Exemplarily mentioned plasticizers are citrates such as acetyltributyl citrate, acetyltriethyl citrate, tributyl citrate, triethyl citrate, benzyl benzoate, castor oil, phthalates such as cellulose acetate phthalate, dibutyl phthalate, diethyl phthalate, dimethyl phthalate, hypromellose phthalate, polyvinyl acetate phthalate, dimeticon, fractionated coconut oil, chlorbutanol, dextrin, sebacate such as dibutyl sebacate, glycerine, glycerine derivatives such as glycerine monostearate, glycerine triacetate (triacetin), acetylated monoglyceride, mannitol, mineral oil, lanolin alcohols, palmitic acid, 2-pyrrolidone, sorbitol, stearic acid, triethanolamin, polyethylene glycols (all types of PEGs of different molecular weights), propylene glycol as well as derivatives and mixtures thereof. Preferred plasticizers which may be used are acetylated monoglyceride, acetyltributyl citrate, acetyltriethyl citrate, dibutyl phthalate, dibutyl sebacate, diethyl phthalate, dimethyl phthalate, tributyl citrate, triethyl citrate, polyethylene glycols (all types of PEGs of different molecular weights), and propylene glycol.

Surfactants are e.g. selected from anionic, cationic or nonionic species such as docusate sodium, emulsifying wax, self-emulsifying glyceryl monooleate, sodium lauryl sulfate,
benzethonium chloride, cetrimonide, cetylpyridinium chloride, sodium lauryl sulfate, chlorhexidine, lauric acid, paraben series, sorbic acid, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene stearates, polysorbate, sorbitan esters and triethyl citrate, as well as derivatives and mixtures thereof.

Exemplary emulsifying agents are acacia, caromers, carrageenan, propylene glycol alginate, hydroxypropyl cellulose or starch, hypromellose, palmitic acid, pectin, poloxamer, sorbitan esters, sunflower oil, tragacanth, and xanthan gum as well as derivatives and mixtures thereof.

The above listing is not intended to be of limitative character, the skilled person is familiar with further examples. As a matter of course also other pharmaceutical acceptable formulating agents in form of excipients, additives, carriers, technological adjuvants suitable in pharmaceutical formulations may be present. The term "excipients" or "additives" or "adjuvants" or the like as understood in the present invention shall mean any known suitable auxiliary compound which may be used in pharmaceuticals in order to provide one or more functionalities to the pharmaceutical tablet formulation according to the present invention. It belongs to the skill of the formulator that an excipient may have more than one function at the same time so that this excipient may form part of different categories. For example corn starch may impart several functions at the same time such as swelling polymer, filler, glidant, and the like. However, the skilled person knows the several functions and is able to select the excipient(s) according to the intended use thereof. The requirements are known by the skilled person.

The pharmaceutically acceptable excipients for the tablet formulation are in general present in order to promote manufacture, flow properties, compressibility, appearance and/or taste of the preparation. In the present invention the selection of the tablet excipients are primarily based on the main criteria to make the dissolution of pimobendan as rapid as possible and to further stabilize the instable ACE-inhibitor, preferably benazepril or a pharmaceutically acceptable salt as much as possible.
In a particularly preferred embodiment these excipients are incorporated in the tablet matrix (extra-granular phase) only, where pimobendan or a pharmaceutically acceptable salt thereof is present. A reason for this purpose is that instable ACE-inhibitors such as benazepril and its salts are more sensitive to moisture and excipients than pimobendan and its salts. Additional excipients may be present in the carrier core particles, but this is not always required. Furthermore, the first, second and any additional layer may contain one or more excipients, this is not always necessary, but keeping in mind, however, that due to the sensitive character of the ACE inhibitor such as benazepril and its pharmaceutically acceptable salt, these excipients should be carefully selected, if any.

According to the present invention it has been surprisingly found that some excipients or a combination of several excipients has/have disadvantages or advantages in the first pharmaceutical tablet formulation:

It has been found that meat flavour, for example dry meat flavour, citric acid and magnesium stearate have a negative impact on the stability of the instable ACE-inhibitor such as benazepril or the pharmaceutically acceptable salt thereof. That is, tablet mixtures using citric acid, dry meat flavour and/or magnesium stearate lead to instability and increased decomposition of benazepril or the pharmaceutically acceptable salt thereof. As a result, the selection of excipients is most preferably performed taking the following into account:

The excipients citric acid, magnesium stearate and meat flavour, for example dry meat flavour, should preferably not be present in the granules. Preferably the presence of citric acid and magnesium stearate in the first pharmaceutical tablet formulation should be avoided completely.

It is highly desirable to have one or more pharmaceutically acceptable organic acids in the tablet matrix (extra-granular phase) together with pimobendan or a pharmaceutically acceptable salt thereof because the acid possesses a good solubilising characteristic and creates an acidic microclimate. Thus, the acid improves the dissolution of pimobendan and also enhances the release of the instable ACE-inhibitor such as benazepril from the
polymer matrix present in the coating layer(s). In fact, it is common practice to circumvent the problem of pH dependent solubility by including ingestible organic acids in the formulation. By creating an acid microclimate and by utilising the tendency of pimobendan to form a supersaturated solution, the acid allows an adequate level of pimobendan solubility to be achieved. However, it has been found that citric acid clearly increases the destabilisation of instable ACE-inhibitors such as benazepril. Therefore, in case the tablet matrix comprises as acidifying agent one or more pharmaceutically acceptable organic acids, advantageously, citric acid should be excluded and preferably replaced by another pharmaceutically acceptable organic acid, such as tartaric acid, malic acid or fumaric acid, preferably fumaric acid. These acids, preferably fumaric acid are able to create an acidic microclimate and thus enhance the dissolution of pimobendan, but unlike citric acid, theses acids such as fumaric acid are less detrimental to the stability of any instable ACE-inhibitor such as benazepril or a pharmaceutically acceptable salt thereof.

Further, in case the tablet matrix comprises one or more lubricants, it is advantageous to eliminate magnesium stearate and preferably replace it by another lubricant, preferably stearic acid. It has been found that magnesium stearate should preferably be replaced by stearic acid because the stability of the ACE-inhibitor, preferably benazepril, in the presence of stearic acid is higher than in the presence of magnesium stearate.

Besides, although meat flavour has a destabilizing effect on ACE-inhibitors such as benazepril, it is undesirable to leave it out or replace it due to the use of the formulation in the veterinary medical sector. Therefore, it is most preferred to assure that the instable ACE-inhibitor, preferably benazepril, or a pharmaceutically acceptable salt thereof has no direct contact with the meat flavour. Therefore, the meat flavour is preferably not in the same layer as the active substance benazepril. From this point of view, providing a second layer between the first pharmaceutically active substance or its pharmaceutically acceptable salt and the tablet matrix containing the meat flavour has a further advantage.
According to a preferred embodiment of the present invention the first pharmaceutically active substance is a pharmaceutically acceptable salt of an instable ACE-inhibitor, preferably of benazepril, even more preferred benazepril hydrochloride, and the second pharmaceutically active substance is pimobendan.

The first and second pharmaceutically active substances are contained in an amount suitable for exhibiting the desired pharmacological activities of each medicament, respectively, which are known and vary in accordance with the medication. In order to determine the optimum dose of each of the two active substances, respectively, various basic conditions have to be taken into consideration such as for example the age and body weight of the animal patient, the nature and stage of the disease and the potency of each compound. This is deemed to be within the capabilities of the skilled man, and the existing literature on the components can be consulted in order to arrive at the optimum dose.

The first pharmaceutically active substance, preferably benazepril or a pharmaceutically acceptable salt thereof, is preferably contained in the first pharmaceutical tablet formulation according to the invention in an amount of 0.5 to 30 mg. More preferred are 1 to 15 mg. Even more preferred are 2.5 to 20 mg. Most preferred are 2.5 mg, 5.0 mg, 10 mg and 20 mg.

The second pharmaceutically active substance, preferably pimobendan or a pharmaceutically acceptable salt thereof, is preferably contained in the first pharmaceutical solid formulation according to the invention in an amount of 0.5 to 20 mg. More preferred are 1 to 10 mg. Even more preferred are 1.25 to 5 mg. Most preferred are 1.25 mg, 2.5 mg, 5 mg or 10 mg.

In the first pharmaceutical tablet formulation any of the above dose strengths of the first pharmaceutically active substances may be combined with any of the dosage strengths of the second pharmaceutically active substances.
The following doses may be preferably used: 1.25 mg, 2.5 mg, 5.0 mg, and 10.0 mg pimobendan or a pharmaceutically acceptable salt thereof; 2.5 mg, 5.0 mg, 10.0 mg, and 20.0 mg instable ACE inhibitor such as benazepril or a pharmaceutically acceptable salt thereof. Therefore, the following embodiments are particularly preferred:

curable tablets containing pimobendan and benazepril HC1 in the strengths of:
- 1.25 mg pimobendan and 2.5mg benazepril HC1; or
- 2.5 mg pimobendan and 5 mg benazepril HC1; or
- 5 mg pimobendan and 10 mg benazepril HC1; or
- 10 mg pimobendan and 20 mg benazepril HC1.

In the first pharmaceutical tablet formulation according to the present invention the ratio of the first pharmaceutically active substance to coating and/or matrix forming polymer, preferably a polymer on methacrylic acid basis, in the first layer is from about 0.5 to 2:1 to 4, preferably about 0.75 to 1.75:1.25 to 3, more preferably 0.75 to 1.25:1.25 to 2.5, even more preferred about 1:2.

Furthermore, the ratio of the first pharmaceutically active substance to coating and/or matrix forming polymer, preferably a polymer on methacrylic acid basis, in the first and second layers together is from about 0.5 to 2:4 to 16, preferably about 0.75 to 1.75:5 to 12, more preferably about 0.75 to 1.5:6 to 10, even more preferred about 1:8.

It should be noted that the ranges of values given herein expressly include all the numerical values, both whole numbers and fractions, within the ranges as specified.

According to a preferred embodiment of the present invention the first pharmaceutical tablet formulation is a chewable tablet. The tablet of the present invention can be of any suitable size and shape, for example round, oval, polygonal or pillow-shaped, and optionally bear non-functional surface markings. The tablet formulation can be divisable or not divisable, preferably the tablet is divisable into two or more pieces. As a characteristic of the new formulation the functionality and release characteristics are not affected by the division.
The solid formulation according to the present invention may also be in form of granules comprising carrier core particles coated with a layer containing an instable ACE-inhibitor or a pharmaceutically acceptable salt thereof, preferably benazepril or a pharmaceutically acceptable salt thereof, as a first pharmaceutically active substance and a coating and/ or matrix forming polymer, preferably a polymer on a methacrylic acid basis (first layer). The granules according to the invention can be administered as granules or being further processed into capsules that can be administered to the animal. The granules may form part of the first pharmaceutical solid formulation or may be administered separately or in another suitable dosage form. Therefore, the granules may be administered directly or the granules may be filled in capsules or in sachets or may be processed into tablets.

Furthermore, the granules containing the first pharmaceutically active substance, i.e. an ACE inhibitor as already disclosed, may be part of a combination preparation. Such a combination preparation may comprise a first dosage form, that is the granules according to the present invention, and a second dosage form containing one or more pharmaceutically active substances which may be combined with the ACE inhibitor contained in the granules. The combined preparation may be intended for simultaneous, separate or sequential use. The second dosage form may be any suitable dosage form known in the art such as granules, tablets, capsules or the like. The pharmaceutically active substances present in the second dosage form may be selected from a variety of possible substances, preferably the group of pharmaceutically active substances comprises PDE III inhibitors such as pimobendan, loop diuretics, potassium sparing diuretics, other diuretics than the previously mentioned, beta-blockers, calcium channel blockers, funny-channel blockers, renin antagonists, angiotensin antagonists, DPP4 inhibitors, antiarrhythmic agents, aldosterone antagonists, xanthine derivatives, arterial dilators, venodilators, positive inotropic agents, and anticoagulating agents. Other pharmaceutically active substances may be used, too.

The above explanations and disclosure, particularly with regard to the material of the carrier core particles and the polymer on methacrylic basis, apply here with regard to the granules, too.
The granules of the present invention comprise the coated carrier core particles as described above and an additional layer containing at least one coating and/or matrix forming polymer, preferably a polymer on methacrylic acid basis (second layer).

According to another embodiment of the invention the granules of the present invention may optionally comprise the coated carrier core particles additionally coated with a layer containing at least one coating and/or matrix forming polymer, preferably a polymer on methacrylic acid basis (second layer).

As already described, one or more optional intermediate layers may be present, but are not of essential character.

Typically, the granules exhibit a particle size distribution where >90% of the particles have a diameter of 125-750 µm and/or 50-80% of the particles have a diameter of 250-500 µm.

In the carrier core particles, the first and second layer of the granules may additionally comprise one or more excipients as already discussed. The carrier core particles, the first and optional additional layers of the granules may additionally comprise one or more excipients as already discussed.

Therefore, the first pharmaceutical tablet formulation comprises the granules (carrier core particles and at least one layer) and the extra-granular phase (tablet matrix), the first pharmaceutically active substance being present in the granules whereas the second pharmaceutically active substance is present in the extra-granular phase.

The granules which have been developed serve a double purpose in that they mask the bitter taste of an unstable ACE-inhibitor but also have a protective purpose for the unstable ACE-inhibitor or its salts, i.e. the granules provide an unstable ACE-inhibitor in stabilised form. Therefore, in a preferred embodiment the granules serve to better mask the bitter taste of benazepril and also have a protective purpose for benazepril or its salts.
that is the granules provide benazepril hydrochloride in a more stable form than benazepril hydrochloride alone.

The first pharmaceutical tablet formulation according to the present invention may be produced according to the following process comprising

- fluid bed coating using a coating solution, preferably an alcohol containing solution, comprising an instable ACE-inhibitor or a pharmaceutically acceptable salt thereof, preferably benazepril or a pharmaceutically acceptable salt thereof, and at least one coating and/or matrix polymer, preferably a polymer on methacrylic acid basis, using carrier core particles to obtain a coated granulate;

- a second fluid bed coating using a further coating solution, preferably an alcohol containing solution, comprising at least one coating and/or matrix polymer, preferably a polymer on methacrylic acid basis, to obtain a double coated granulate;

- mixing pimobendan or a pharmaceutically acceptable salt thereof with the excipient/s of a tablet matrix to obtain a premix;

- optionally sieving the obtained coated granulate through a screen;

- mixing the coated granulate and the premix to obtain a blend;

- mixing the blend with one or more lubricants and/or glidants to obtain a final blend, and

- compressing said final blend to a tablet.

It is a matter of course that also other formulation procedures to arrive at the first pharmaceutical tablet formulation may be used. The process according to the present
invention represents only one alternative possible, the skilled person is aware of other formulation procedures.

Subject of the present invention is also a process for preparing the granules according to the present invention comprising

- fluid bed coating using a coating solution, preferably an alcohol containing solution, comprising an instable ACE-inhibitor or a pharmaceutically acceptable salt thereof, preferably benazepril or a pharmaceutically acceptable salt thereof, and at least one coating and/or matrix polymer, preferably a polymer on methacrylic acid basis, using carrier core particles to obtain a coated granulate;

- a second fluid bed coating using a further coating solution, preferably an alcohol containing solution, comprising at least one coating and/or matrix polymer, preferably a polymer on methacrylic acid basis, to obtain a double coated granulate;

- optionally sieving the obtained coated or double coated granulate through a screen.

It is a matter of course that also other formulation procedures to arrive at the granules may be used. The process according to the present invention represents only one alternative possible, the skilled person is aware of other formulation procedures.

In the following the inventive process shall be discussed in detail. …..

At first, a fluid bed coating is performed using a coating solution (first layer). The coating solution is preferably an alcohol containing solution comprising an instable ACE-inhibitor, preferably benazepril or a pharmaceutically acceptable salt thereof, and at least one coating and/or matrix polymer, preferably a polymer on methacrylic acid basis. The coating solution used in the first coating step is produced immediately prior
to use, the instable ACE-inhibitor, preferably benazepril or a pharmaceutically acceptable salt thereof, is dissolved and subsequently the coating and/or matrix polymer is added and dissolved during optionally mixing or vice versa. Alternatively two solutions are produced separately, one solution comprising the instable ACE inhibitor, preferably benazepril or a pharmaceutically acceptable salt thereof, and the other solution comprising at least one coating and/or matrix polymer, preferably a polymer on methacrylic acid basis, and both solutions are combined prior to performing the first coating step.

The used solvent is any suitable solvents or mixtures thereof, preferably physiologically acceptable solvent or solvent mixture, e.g. a low-boiling alcohol, ester, ketones or a respective mixture with water. A number of solvents are suitable. Readily volatile solvents are preferred. Exemplarily mentioned solvents are methanol, ethanol, 1-propanol, isopropanol, butanol, iso-butanol, 2-butanol, tert-butanol, ethyl acetate, ethyl formate, acetone and the like as well as mixtures thereof with or without water.

Subsequently, a second fluid bed coating step is conducted (second layer). The second fluid bed coating step is an optional process step which is performed in case a second layer shall be present on the first layer. In the second coating step a further coating solution is used, preferably an alcohol containing solution comprising at least one coating and/or matrix polymer, preferably a polymer on methacrylic acid basis. The polymer on methacrylic acid basis is a polymer which belongs to the polymethacrylates such as methacrylic acid-ethyl acrylate copolymer (1:1) as already described. Polymethacrylate polymer(s), which is(are) soluble under acidic conditions, but insoluble under neutral or basic conditions is(are) preferred. The mentioned polymer is used alone or in combination of two or more polymers. Commercially available products are the polymers from the Eudragit® series from the company Rohm, Darmstadt, Germany. Particularly preferred are polymers on methacrylic acid basis, which belong to the polymethacrylates such as methacrylic acid-ethyl acrylate copolymer (1:1), e.g. polymers belonging to the commercially available products Eudragit® E or Eudragit® EPO.
The coating and/or matrix polymer(s) used in the first layer may be the same or different from the coating and/or matrix polymer(s) used in the second layer. According to a preferred embodiment the polymethacrylate polymer(s) used in the first layer may be the same or different from the polymethacrylate polymer(s) used in the second layer. According to a further preferred embodiment the polymer on methacrylic acid basis in the two layers is the same, while other polymers can be present in either or both layer(s). In a more preferred embodiment only one polymer on methacrylic acid basis is used and the polymer in the first and second layer is the same.

In the first coating step the first layer as already described is applied on the carrier core particles to obtain a coated granulate. In the second coating step the second layer as already described is applied on the coated carrier core particles to obtain a double coated granulate. In the second layer the coating and/or matrix polymer, preferably polymer(s) on methacrylic basis, is present but not the instable ACE-inhibitor or a pharmaceutically acceptable salt thereof. This second layer is present in order to increase the effectivity of the protecting and masking performance because the bitter tasting first pharmaceutically active substance is then no longer present on the outer or second layer.

The expression „taste masking“ according to the present invention is understood to mean the protection of the active substance against the immediate action of saliva and its constituents upon oral administration as well as against the sense of smell and taste of the animal. A masked active substance shall have a neutral taste and/or smell and/or a taste acceptable to companion animals. This is confirmed by a free-choice acceptance test.

During the formation of the coating(s) on the carrier core particles, granules are formed, the coating and/or matrix polymer(s), preferably the polymer(s) on methacrylic acid basis act(s) as a type of binder.

Any type of fluidised bed process is suitable according to the process of the present invention. The coating step(s) may be performed in a fluid bed granulator or other
suitable apparatus. A top-spray fluid bed process is preferred. The conditions and
parameters of the fluid bed coating step(s) such as the spray rate, atomization pressure,
spray nozzle diameter, inlet air temperature, product temperature and the like belong to
the skill of the expert who is readily able to determine and adjust these conditions and
parameters based on some experimentation.

It is a matter of course that the granules may further contain one or more excipients as
already described. However, due to the sensitive character of the instable ACE-inhibitor,
preferably benazepril and its pharmaceutically acceptable salt, these excipients should
be carefully selected, if any.

The further steps are omitted if the granules shall be produced. If the pharmaceutical
tablet formulation shall be produced the further steps are carried out.

In the next step pimobendan or a pharmaceutically acceptable salt thereof is mixed with
the excipient/s of a tablet matrix to obtain a premix. The one or more useful excipients
are already discussed above. The mixing may be performed in any suitable apparatus.
Additionally micronizing of the second active substance pimobendan has a positive
impact on its dissolution kinetic.

Then the coated or double coated granulate and the premix are mixed to obtain a blend.
The coated or double coated granulate are sieved through a screen prior to the addition
to the premix or the coated or double coated granulate are mixed with the premix
without any further sieving. The mesh size is preferably selected in the range of from
about 0.5 to 2 mm.

Subsequently, the blend is mixed with one or more lubricants and/or glidants to obtain
the final blend. According to a preferred embodiment the ratio of granules (carrier core
particles + first layer containing first pharmaceutically acceptable substance + optional
second layer) to extra-granular material (tablet matrix + second pharmaceutically
substance) is about 10 : 90 to about 90 : 10, preferably about 20 : 80 to about 80 : 20
(w/w), preferably 50 : 50 (w/w), in the pharmaceutical tablet formulation.
Then, the final blend is compressed to a tablet using a commonly applied tablet compressing device.

It is preferred that the coated carrier core particles meet certain characteristics in order not to affect the release performance when later processed to tablets.

For example, it is preferred that the granulate grains or granules should predominantly undergo plastic deformation upon compression. Furthermore, it is preferred that the polymer coating is sufficiently flexible so that a deformation will not cause any major rupture or brittle fracture. Finally, it is also preferred that the carrier core particles of the granulate grains or granules only show minimal/ negligible swelling.

The carrier core particles are selected from the materials as already described, whereby lactose, particularly agglomerated a-lactose-monohydrate [Ph.Eur./USP-NF/JP] with a particle size distribution as follows: \( \leq 20\% < 63 \mu \text{m}, \) \( 40-75 \% < 180 \mu \text{m}, \) \( \geq 85 \% < 400 \mu \text{m}, \) and \( \geq 97 \% < 630 \mu \text{m} \) is preferred. Lactose such as spray dried or agglomerated lactose, with the characteristics described above is particularly suitable for use in the core because of its particle size, non-hygroscopicity, and the fact that it undergoes plastic deformation upon compression so that the core will not break into pieces in the tablet press. Therefore, lactose is a carrier material to be preferably used in the carrier core particles due to the following properties:

Lactose, particularly lactose monohydrate or spray dried or agglomerated lactose, is well suited to be used as carrier material because during the later tablet forming step lactose having an amorphous proportion shows a partly ductile performance. Thus, only little brittle fracture in the inner part of the carrier core particles coated with polymethacrylate polymer(s) is occurring. This is a particular advantage because snatchings could damage the polymer film and, therefore, the dissolving properties of the tablet are altered undesirably. A significantly changed substance release could result in a modified bioavailability whereby the formulations are no longer bioequivalent or a
premature substance release in the mouth could occur and the masking of the bitter taste would be unsuccessful.

Furthermore, lactose, particularly lactose monohydrat, is particularly suitable as a non-swelling tablet excipient, because in case the granules containing polymer-ACE inhibitor-lactose come into contact with water, the polymer will interact with water and swell also in neutral pH-value so that water can penetrate by diffusion into the core of the granules. If the core of the granules would also tend to swell, the increasing swelling pressure inside the granules would result in a premature decomposition and a damage of the coating film. Thus, the active substance would be released prior to the intended time.

Since lactose does not tend to swell, this unwanted effect is eliminated. Therefore, it is particularly preferred to use lactose alone as carrier core particle material. Besides lactose also other carrier materials are suitable. Preferably the carrier core particle material consists of lactose, such as lactose monohydrat, more preferably agglomerated lactose, or another alternative carrier material.

Further alternative carrier materials to be used are carbohydrates, sugar alcohols, such as mannitol, sorbitol, maltitol, glucose, non-pareil-seeds, calcium phosphate, cellulose, particularly preferable microcrystalline cellulose (MCC), and starch.

Cellulose and starch are also ductile deformable, but these materials tend to swell resulting in the described undesirable effect that the taste masking coating would be less effective.

Another carrier material which can be used is MCC pellets, which exhibit low swelling, and uniform size and surface structure.

The above described pharmaceutical tablet formulation is preferably used as the first pharmaceutical solid formulation in the pharmaceutical packaging product of the present invention. As already described the pharmaceutical packaging product of the present invention is preferably designed particularly user-friendly in order to ease the administration of different dosages and to simplify the observation of and adherence to
the therapy. Therefore, the preferred blister, for example, contains one dosage in one row having a specific colour intended for use in the morning and another dosage in another row having another specific colour intended for use in the evening. For safety reasons there are additional different symbols on the rows meaning that the solid formulations for administration in the morning have a bright colour code (such as yellow, orange, light red, etc) and a sun symbol, whilst the rows containing the solid formulations for evening administration have a dark colour (brown, dark blue, black etc.) and a half-moon symbol printed on it.

The pharmaceutical packaging product may be accompanied by a package insert providing pertinent information such as, for example, dosage and administration information, contraindications, precautions, drug interactions, and adverse reactions.

Since the instable ACE-inhibitor, preferably benazepril and its salts are known to be highly moisture sensitive, the product stability is enhanced, for example, by reducing the initial moisture of the product before packaging and in the packed product. Therefore, the initial moisture of the product is reduced by optimizing the holding times and the storage conditions of the intermediate products, i.e. raw materials, granulate, extra-granular phase, final blend, unpacked formulations etc. The manufacturing can also be associated to a monitoring of the water content. As a precautionary measure, hygroscopic raw materials could be packed in protective packaging, and the intermediate products could be stored in protective containers with desiccant bags. Furthermore, the concentration of hygroscopic components of the formulation should be observed and reduced.

The invention described will now be illustrated by drawings. However, it is expressly pointed out that the drawings are intended solely as an illustration and should not be regarded as restricting the invention.
BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings

Fig. 1A shows an exemplary schematic illustration of the pharmaceutical packaging product according to a preferred embodiment of the present invention;

Fig. 1B shows another exemplary schematic illustration of the pharmaceutical packaging product according to a preferred embodiment of the present invention;

Fig. 2 shows an exemplary schematic illustration of the granules according to a preferred embodiment of the present invention;

Fig. 3 shows scanning electron microscope (SEM) pictures of coated granules according to the present invention; and

Fig. 4 represents a flow diagram illustrating a preferred method for the manufacturing of the first pharmaceutical solid formulation in the preferred form of a tablet formulation according to a preferred embodiment of the present invention.

Fig. 1A and Fig. 1B show an exemplary schematic illustration of the pharmaceutical packaging product according to a preferred embodiment of the present invention, namely an exemplary blister pack 10 is illustrated. The blister pack 10 as shown in Fig. 1A and Fig. 1B represents a top view of the back side or outside of the foil of the blister pack 10. The blister pack 10 accommodates in the present example in total 10 pharmaceutical solid formulations.

In the present exemplary schematic in Fig. 1B the blister pack accommodates 10 pharmaceutical solid formulations, e.g. tablets. A number of 5 pharmaceutical solid formulations are contained in a first row and 5 pharmaceutical solid formulations are contained in a second row.
The blister 10 is a split blister divided in two halves, an upper section 20 and a lower section 30. The upper section 20 contains 5 pharmaceutical solid formulations, each cavity or pocket 20.1, 20.2, 20.3, 20.4, and 20.5 contains one pharmaceutical solid formulation, respectively (only the backside of each cavity or pocket can be seen in Fig. IB). The lower section 30 contains 5 pharmaceutical solid formulations, each cavity or pocket 30.1, 30.2, 30.3, 30.4, and 30.5 contains one pharmaceutical solid formulation, respectively. The upper section 20 is coloured with a colour different to that of the lower section 30. Preferably, the upper section 20 has a light colour, e.g. yellow, symbolizing morning-time. Preferably, the lower section 30 has a dark colour, e.g. brown, symbolizing evening-time.

In the present examplary case in Fig. 1A the blister pack accommodates 10 tablets, 5 tablets of a first pharmaceutical tablet formulation in a first row and 5 tablets of a second pharmaceutical tablet formulation in a second row. The first pharmaceutical tablet formulation contains the combination PDE III inhibitor/ACE inhibitor, in the present example that is pimobendan 1.25 mg/benazepril 2.5 mg. The second pharmaceutical tablet formulation contains the PDE III inhibitor as the only pharmaceutically active substance, in the present case pimobendan 1.25 mg. These examples/combinations, however, are only to be seen as an example, as all other above described combinations of the first and second pharmaceutical tablet combinations can be packaged in the packaging product.

The blister 10 is a split blister divided in two halves, an upper section 20 and a lower section 30. The upper section 20 contains 5 tablets of the first pharmaceutical tablet formulation, each cavity or pocket 20.1, 20.2, 20.3, 20.4, and 20.5 contains one tablet, respectively (Only the backside of each cavity or pocket can be seen in Fig. 1). The lower section 30 contains 5 tablets of the second pharmaceutical tablet formulation, each cavity or pocket 30.1, 30.2, 30.3, 30.4, and 30.5 contains one tablet, respectively.

The foil is shown with several identification markings:

The upper section 20 is coloured with a colour different to that of the lower section 30.

The whole surface of the upper section 20 and the whole surface of the lower section 30 are coloured, respectively. Another kind of using colour as identification marking is possible.
Each cavity or pocket 20.1, 20.2, 20.3, 20.4, and 20.5 of the upper section 20 comprises on the outside of the covering foil a legend giving the user additional information for the treatment. The legend in the upper section 20 may be repeated identically for each cavity or pocket, wherein the first pharmaceutical solid formulation is accommodated, or several cavities or pockets, in the present example two cavities or pockets, may be combined and provided with one legend on the backing foil thereof, only. The legend comprises in the present case the pharmaceutical firm (Boehringer Ingelheim Vetmedica GmbH), the tradename and dosage strengths (Vetmedin Plus® 1.25/2.5) of the solid formulation, the pharmaceutically active substances and the amount contained (pimobendan 1.25 mg, benazepril 2.5 mg), the kind of the dosage form (chewable tablet) and the animal to be treated (for dogs).

Each cavity or pocket 30.1, 30.2, 30.3, 30.4, and 30.5 of the lower section 30 comprises on the outside of the covering foil a legend giving the user additional information for the treatment. The legend in the lower section 30 is identical for each cavity or pocket, wherein the second pharmaceutical solid formulation is accommodated or two or more cavities or pockets comprise together on the foil a legend. The legend comprises in the present case the pharmaceutical firm (Boehringer Ingelheim Vetmedica GmbH), the tradename and dosage strengths (Vetmedin Plus® 1.25/2.5) of the solid formulation, the pharmaceutically active substance and the amount contained (pimobendan 1.25 mg), the kind of the dosage form (chewable tablet) and the animal to be treated (for dogs). The legend in the lower section 30 is upside down to further distinguish the first and second solid formulation from each other. Also other types of providing a legend are possible.

Furthermore, in Fig. IA and Fig. IB, a sun symbol 60 in the upper section 20 and a moon symbol 50 in the lower section 30 are shown. In the area of each cavity or pocket 20.1, 20.2, 20.3, 20.4, and 20.5 in the upper section 20 the outside of the covering foil comprises a sun symbol 60 and in the area of each cavity or pocket 30.1, 30.2, 30.3, 30.4, and 30.5 in the lower section 30 the outside of the covering foil comprises a moon symbol 50. These symbols correspond to the time to take the medication, preferably for the first pharmaceutical solid formulation the sun symbol stands for the intake in the
morning and for the second pharmaceutical solid formulation the moon symbol stands for the intake in the evening.

Fig. 2 shows an exemplarily schematic illustration of the granules according to a preferred embodiment of the present invention. The granules 100, 110 are schematically shown. The carrier core particles 210 are enclosed by the first layer 220 which contains the instable ACE inhibitor, in the present example benazepril, or one of its salts and one or more coating and/or matrix forming polymers, e.g. one or more polymers on methacrylic acid basis. A predominantly ductile deformable carrier material is most convenient so that a brittle break of the particles does not occur and a damage of the first layer is prevented. Furthermore, a non-swelling carrier material is particularly appropriate, so that water cannot penetrate by diffusion into the core of the granules and cause swelling of the core. Thus, a premature release of the active substance is avoided. For example, lactose, particularly lactose monohydrat or spray dried lactose, more preferably agglomerated or spray dried lactose, is one of the well suited carrier materials. Other materials may be used just as well.

Furthermore, the one or more coating and/or matrix forming polymers, e.g. one or more polymers on methacrylic acid basis, in the first layer 210 are selected due to their characteristics, for example, so that the polymer coating is sufficiently flexible and a deformation can not cause any damage.

The second layer 230 comprises or consists of the one or more coating and/or matrix forming polymers, e.g. one or more polymers on methacrylic acid basis. More preferably the polymer is a cationic copolymer based on dimethylaminoethyl methacrylate copolymer (IUPAC name: poly(butyl methacrylate-co-(2-dimethylaminoethyl) methacrylate-co-methyl methacrylate) 1:2:1) such as Basic Butylated Methacrylate Copolymer Ph. Eur.

As Fig. 2 shows, the formation of the first and second layers 210 and 220 on the carrier core particles result in stabilized granules 100, 110, the polymer(s) serves as an adhesive and stabilizer between the particles meaning as a binder.
The granules 100, 110 of the present invention due to their composition and build-up, are able to mask the bitter taste of the ACE inhibitor and its salts and also have a protective purpose for the ACE inhibitor, that is the granules 100, 110 provide the ACE inhibitor in a more stable form than the ACE inhibitor per se.

As shown in Fig. 2, the granules 100, 110 can have different sizes, but typically, the granules exhibit a particle size distribution where >90% of the particles have a diameter of 125-750 μπι.

Fig. 3 shows SEM pictures of coated granules according to the present invention. There are provided 6 pictures: No. 1, No. 2 and No 3, with 2 pictures respectively. There are shown 3 different granules, the composition in detail is as follows:

Granules No. 1: Benazepril HC1 5 g; butylated methacrylate copolymer 80 g, agglomerated lactose 915g
Granules No. 2: Benazepril HC1, 5 g; butylated methacrylate copolymer 80 g, agglomerated lactose 915g
Granules No. 3: Benazepril HC1, 10 g; butylated methacrylate copolymer 80 g, agglomerated lactose 915g

The magnification of the pictures is as follows: left: 200x, right: 1000x

Fig. 4 represents a flow diagram illustrating a preferred method for the manufacturing of the first pharmaceutical tablet formulation according to a preferred embodiment of the present invention. The described method of manufacturing is not intended to limit the present invention, other processes are possible.

As derived from the flow diagram of Fig. 4, in the first step a fluid bed coating is performed using coating solution 1. The coating solution 1 is a solvent containing solution, whereby any suitable, pharmaceutically acceptable solvent containing solvent or solvent mixture, such as an alcohol-water mixture may be used. For example, the solvent may contain ethanol and water. Also the ACE inhibitor such as benazepril or a pharmaceutically acceptable salt is contained in coating solution 1. For example
benazepril hydrochloride may be employed as first active substance. It is also possible to use another ACE inhibitor or another pharmaceutically acceptable salt thereof.

Furthermore, the polymer(s) is (are) any polymer or mixture of polymers as already described. In the present exemplarily described embodiment the polymer is on methacrylic acid basis, e.g. Basic Butylated Methacrylate Copolymer Ph. Eur. Also another polymer or a mixture of more polymers can be used.

Then, the coating solution 1, containing in the present case benazepril hydrochloride dissolved together with the at least one polymer on methacrylic acid basis such as Basic Butylated Methacrylate Copolymer Ph. Eur. in one or more solvents, for example ethanol/purified water, is sprayed onto the carrier core particles in a fluid bed apparatus. In the present example the carrier core particles are any of the carrier core particles as described above. For example agglomerated lactose with a particle size \( d_{50} \) of ca. 180 \( \mu m \) is used. However, other materials are also possible. The fluid bed apparatus may be any available device known by the skilled person. Preferably a top-spray fluid bed process is used. In an exemplary embodiment a top-spray fluid bed granulator of the company Glatt may be used. In the exemplary embodiment a layer containing benazepril hydrochloride and Basic Butylated Methacrylate Copolymer Ph. Eur. on the lactose particles is produced (first or inner layer).

According to the flow chart shown in Fig. 4 the second coating step is performed using coating solution 2. Coating solution 2 is again a solvent containing solution, whereby any suitable pharmaceutically acceptable solvent containing solvent or solvent mixture, such as an alcohol containing solution may be used, which for example, contains ethanol, purified water, and Basic Butylated Methacrylate Copolymer Ph. Eur. Also another solvent or mixture of solvents and another polymer, e.g. a polymer on methacrylic acid basis or mixture of polymers may be used. The coating and/or matrix forming polymer(s) such as a polymethacrylate polymer(s) used in the first layer is the same or different from the coating and/or matrix forming polymer(s) such as a polymethacrylate polymer(s) used in the second layer. According to the exemplarily
described embodiment the polymer on methacrylic acid basis in the two layers is the same.

The coating solution 2 results in the formation of the second layer. The second layer is especially deposited in order to increase the effectivity of the masking performance because the bitter tasting active substance - in the present example benazepril hydrochloride - is then no longer present on the top surface of the particles.

After the spraying procedure, the solvent or solvent mixture may be removed carefully, e.g. by continuing to dry the granulate in the fluid bed apparatus.

The conditions and parameters of the fluid bed coating step(s) such as the spray rate, atomization pressure, spray nozzle diameter, inlet air temperature and product temperature belong to the basic knowledge of the skilled person. According to the exemplary embodiment described the coating solutions may be sprayed on the carrier core particles maintained at a product temperature range from 18°C to 25°C. Then the obtained granules may be dried and sieved through a screen. ....

The further steps are omitted if the product to be produced is the granulate. The granules containing ACE inhibitor are well suited to be administered as granules or processed further into capsules or tablets.

If the pharmaceutical tablet formulation is to be produced the further steps are carried out.

In the next step according to the flow diagram of Fig. 4 the PDE III inhibitor such as pimobendan or a pharmaceutically acceptable salt thereof is mixed with the excipient/s of a tablet matrix to obtain a premix. The tablet matrix together with pimobendan or a pharmaceutically acceptable salt thereof forms the extra-granular fraction or phase of the pharmaceutical tablet formulation according to the present invention. The excipients may be selected from one or more of the above listed excipients preferably taking the
specific particularities with regard to excipients citric acid, magnesium stearate and/or meat flavour as mentioned above into account.

The premixing may be performed in any suitable apparatus. For example a Rhonrad can be employed. Also any other mixing apparatus may be used.

Then, the coated granules and the premix are mixed to obtain a blend. The coated granules may be optionally sieved through a screen prior to the addition to the premix as already mentioned; the mesh size being preferably in the range of from about 0.5 to 2 mm.

Subsequently, the blend is mixed with one or more lubricants and/or glidants to obtain a final blend. Any lubricant and/or glidant known by the skilled person may be added but magnesium stearate should be preferably excluded. According to a preferred embodiment the ratio of granules (carrier core particles + first layer containing first pharmaceutically acceptable substance + optional second layer) to extra-granular material (tablet matrix + second pharmaceutically substance) is about 10 : 90 to about 90 : 10, preferably 20 : 80 to about 80 : 20 (w/w) in the pharmaceutical tablet formulation.

Then the final blend is compressed to a tablet in a common tablet compression apparatus.

The advantages of the present invention are manifold:

The pharmaceutical packaging product, preferably a blister pack, contains the complete medication for preferably 5 until 7 days or one week. The animal keeper needs only one blister pack to administer all solid formulations, preferably tablets to her/his animal. The blister may be used in a variable manner, i.e. the blister may be divided into two sections in order to better distinguish the 2 pharmaceutical solid formulations to be administered. Therefore, the daily intake of several formulations, preferably tablets is simplified. Furthermore, indentification markings indicated directly on the packaging
product, preferably blister, i.e. the backing of the blister foil, make the therapy of an animal more comfortable, assist to simplify the therapy and to support the animal keeper to perform a specific prescription plan to treat heart diseases in animals as far as possible.

Furthermore, all medicaments present in the pharmaceutical packaging product, preferably a blister, are packed based observing the strict pharmaceutical requirements so that the user is not obliged to gather each and every formulation required from several packagings. In addition the time of administration may be indicated on the blister, by a legend such as "morning" or by a symbol such as the sun symbol in order to provide an optimum mode of action of each pharmaceutically active substance.

With the pharmaceutical packaging product of the present invention the safety with regard to the medication is significantly improved because the medicaments are no longer portioned by hand, but the medicaments are provided ready to use in one pharmaceutical packaging product, preferably one blister, according to the high quality conditions of pharmaceutical standards (Good Manufacturing Practice, GMP).

The administration of solid formulations based on the pharmaceutical packaging product, preferably the blister pack of the present invention has the further advantage that there is a variability with regard to the combination of different formulations, having different pharmaceutically active substances, different dosage strengths and the like. That is the pharmaceutical packaging product may be arbitrarily adapted to the disease of the animal to be treated, the medication to be administered and as ordered by the veterinarian. Therefore, also complicated schemes of taking several formulations a day may be taken into account individually for the animal to be treated. The pharmaceutical care is significantly improved.

Furthermore, the first pharmaceutical solid formulation, preferably the first pharmaceutical tablet formulation, of the present invention allows to combine two pharmaceutical active substances in one single dosage form, i.e. as combination drugs. The advantage of such a formulation is that the doses are fixed in this pharmaceutical formulation, available in certain fixed doses. In such a case the pharmaceutical
formulation is called a "fixed-dose-combination". Such a type of formulation allows to further ease the treatment and administration of the medication, the treatment of the sick animal is easier to be done. The first pharmaceutical formulation according to the present invention improves the medication compliance by reducing the pill burden to the animal holder. A further improvement relies on the better observation of and adherence to the therapy by decreasing the number of formulations such as tablets to be administered. The lower number of formulations, e.g. tablets, leads to a lower treatment failure rate, minimizes dosage mistakes and avoids confusions by false dose intake and slower development of resistance.

A synergistic combination of two active substances is provided wherein the combined activity exceeds the activity of the single active substances.

Furthermore, a particularly preferred embodiment for the first pharmaceutical solid formulation in form of a first pharmaceutical tablet formulation is disclosed. In this first pharmaceutical tablet formulation a single coating (first layer) is sufficient according to the present invention but a double coating assures excellent palatability by the animal.

For this first pharmaceutical tablet formulation it has been surprisingly found that meat flavour, citric acid and magnesium stearate have an unfavourable impact on the stability of the instable ACE inhibitor or the pharmaceutically acceptable salt thereof. It has been found that citric acid should preferably be replaced by tartaric acid, malic acid or fumaric acid because the stability of instable ACE inhibitor in the presence of acids such as tartaric acid, malic acid or fumaric acid is improved compared to citric acid. Furthermore, magnesium stearate should preferably be replaced by stearic acid because the stability of instable ACE inhibitor is likewise improved. In addition it is preferred to assure that the instable ACE inhibitor or a pharmaceutical acceptable salt thereof has no direct contact with the meat flavour. As a result, the careful selection of excipients supports the increased stability of the instable ACE inhibitor or a pharmaceutically salt thereof in the dosage form. Another result or technical advantage is that this keeps the incompatible ingredients physically separate without having to resort to complex production processes such as multi-layer tablets.
The specific composition and structure of the preferred first pharmaceutical tablet formulation of the present invention provides a number of additional benefits:

The granules provided are generally more uniform than powder and allow a more homogeneous tablet mass and higher dosage accuracy to be achieved. Furthermore, the granules which have been developed in order to better mask the bitter taste of the instable ACE inhibitor or its salts also have a protective purpose for the instable ACE inhibitor or its salts, the granules provide the ACE inhibitor in a more stable form than ACE inhibitor alone.

Furthermore, the polymers present in the granules at the same time mask its bitter taste. Furthermore, the polymer(s) present in the pharmaceutical tablet formulation of the present invention is(are) employed to optimize the release performance so that the instable ACE inhibitor and the active substance pimobendan are immediately dissolved in the stomach and not in the mouth of the animal. Moreover, the polymer provides protection of the active substances from moisture. Finally the polymer(s) function as a binder to bind the active substance to the carrier material.

Also granules are provided which may be administered as stand-alone granules for the ACE inhibitor or any salt thereof or be compressed with suitable excipients to a mono tablet showing the flexibility and versatility of the particles. The granules containing ACE inhibitor are well suited to be administered as granules or processed further into capsules or tablets. Furthermore, it has been observed that the shape and size of the granules according to the present invention provide an excellent mouth feeling so that animals willingly accept the intake of such granules as medicament. According to a further preferred embodiment of the present invention the granules may be administered directly or the granules may be filled in capsules or in sachets.

Furthermore, the granules containing the first pharmaceutically active substance, i.e. an ACE inhibitor as already disclosed, may be part of a combination preparation for simultaneous, separate or sequential use. The first dosage form may be the granules and
the second dosage form may contain one or more other pharmaceutically active substances which may be combined with an ACE inhibitor. The second dosage form may be any usual dosage form known in prior art. The pharmaceutically active substance(s) present in the second dosage form may also be arbitrarily selected from a variety of possible substances, preferably the group comprises PDE III inhibitors such as pimobendan, loop diuretics, potassium sparing diuretics, other diuretics than the previously mentioned, beta-blockers, calcium channel blockers, funny-channel blockers, renin antagonists, angiotensin antagonists, DPP4 inhibitors, antiarrhythmic agents, aldosterone antagonists, xanthine derivatives, arterial dilators, venodilators, positive inotropic agents, and anticoagulating agents. Also other pharmaceutically active substances may be used.

The invention described will now be illustrated by Examples. However, it is expressly pointed out that the Examples and description are intended solely as an illustration and should not be regarded as restricting the invention.

Unless otherwise stated, percentages specified are always percent by weight.

**Examples**

I. **Process of production**

Example 1 - production of the first pharmaceutical solid formulation containing a first and a second layer

In the following a preferable general procedure to manufacture chewable tablets used as first solid formulation according to the present invention is exemplarily described. However, the process steps and components are not intended to be of limitative character:

The coating solutions were prepared by dissolving the cationic copolymer Basic Butylated Methacrylate Copolymer Ph. Eur. in an organic solvent, e.g. an ethanol 99% /
water mixture. Then, in order to produce coating solution 1 benazepril hydrochloride was dissolved in an aliquot of said coating solution. Coating solution 1 contains Basic Butylated Methacrylate Copolymer Ph. Eur., ethanol 99%, purified water, and benazepril hydrochloride. Coating solution 2 is the remaining portion which only contains Basic Butylated Methacrylate Copolymer Ph. Eur., ethanol 99%, and purified water. The coating solutions were subsequently sprayed on the carrier core particles consisting of a-lactose monohydrate, in the present case agglomerated a-lactose monohydrate, maintained at a defined product temperature range from 18°C to 25°C in a top-spray fluid bed granulator of the company Glatt GPCG30.

The spray coating parameters were as follows:

- **Spray rate:** 140 to 250 g/min
- **Spray time:** about 60 min
- **Atomization pressure:** 1.5 - 2.0 bar
- **Product temperature:** 18-25°C
- **Inlet air temperature:** 35-45°C
- **Inlet air flow rate:** 400-600 m³/h
- **Drying time:** until a product temperature of 42 °C is reached

The first spraying step corresponded to the spraying of a combined Basic Butylated Methacrylate Copolymer Ph. Eur./benazepril hydrochloride solution, whereas the second one corresponded to the deposition of pure Basic Butylated Methacrylate Copolymer Ph. Eur. solution.

The obtained granules were dried and sieved through a screen.

The desired excipients in the defined amounts and pimobendan which will form together the extra-granular fraction (tablet matrix) were premixed in a free-fall tumbler (10 min; 10 rpm) and the granules were added. The granules and the extra-granular fraction were mixed in a ratio of granules to extra-granular material of about 50 : 50 (w/w) in a free-fall tumbler (20 min, 10 rpm). Then, the lubricant micronized stearic
acid was mixed into the mixture (5 min, 10 rpm). The mixture was tabletted into tablets of 500 mg, 1000 mg, 2000 mg, or 4000 mg weight on a rotary tablet press.

The tablet formulations of four dosage strengths prepared were as follows:

- 1.25 mg/2.5 mg pimobendan/benazepril HCl for a chewable tablet of 500 mg;
- 2.5 mg/5.0 mg pimobendan/benazepril HCl for a chewable tablet of 1000 mg;
- 5.0 mg/10.0 mg pimobendan/benazepril HCl for a chewable tablet of 2000 mg;
- 10.0 mg/20.0 mg pimobendan/benazepril HCl for a chewable tablet of 4000 mg.

The detailed tablet formulation compositions are given in the following table 1. All tablet sizes are based on the same tablet mixture, the different potencies are obtained by modifying the weight of the tablet. The ACE inhibitor used is benazepril hydrochloride, and the PDE III inhibitor used is pimobendan, however, any other ACE inhibitor and any other PDE III inhibitor may be used.

Table 1:

**Tablet compositions**

<table>
<thead>
<tr>
<th>Dosage strength</th>
<th>1.25/2.50</th>
<th>2.5/5.0</th>
<th>5.0/10.0</th>
<th>10.0/20.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet weight</td>
<td>0.5 g</td>
<td>1.0 g</td>
<td>2.0 g</td>
<td>4.0 g</td>
</tr>
<tr>
<td>Ingredients</td>
<td>mg/tablet</td>
<td>mg/tablet</td>
<td>mg/tablet</td>
<td>mg/tablet</td>
</tr>
<tr>
<td>Benazepril hydrochloride</td>
<td>2.50</td>
<td>5.00</td>
<td>10.00</td>
<td>20.00</td>
</tr>
<tr>
<td>Eudragit® EPO</td>
<td>20.00</td>
<td>40.00</td>
<td>80.00</td>
<td>160.00</td>
</tr>
<tr>
<td>Monohydrate lactose Tablettose 80</td>
<td>370.25</td>
<td>740.50</td>
<td>1481.00</td>
<td>2962.00</td>
</tr>
<tr>
<td>Pimobendan</td>
<td>1.25</td>
<td>2.50</td>
<td>5.00</td>
<td>10.00</td>
</tr>
<tr>
<td>Dry Meat Flavour</td>
<td>50.00</td>
<td>100.00</td>
<td>200.00</td>
<td>400.00</td>
</tr>
<tr>
<td>Colloidal silica, anhydrous</td>
<td>2.50</td>
<td>5.00</td>
<td>10.00</td>
<td>20.00</td>
</tr>
<tr>
<td>Maize starch, undried</td>
<td>25.00</td>
<td>50.00</td>
<td>100.00</td>
<td>200.00</td>
</tr>
<tr>
<td>Fumaric acid</td>
<td>10.00</td>
<td>20.00</td>
<td>40.00</td>
<td>80.00</td>
</tr>
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Table 2: Granulate compositions

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<tr>
<th>Dosage</th>
<th>D1 (E/B 5:1)</th>
<th>D2 (E/B 5:1)</th>
<th>D3 (E/B 1.25:1)</th>
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<tr>
<td>Formula</td>
<td>ratio %</td>
<td>g/batch</td>
<td>ratio %</td>
</tr>
<tr>
<td>Benazepril</td>
<td>3%</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>Eudragit® E</td>
<td>12%</td>
<td>5</td>
<td>6%</td>
</tr>
<tr>
<td>Ethanol*</td>
<td>-</td>
<td>30 ml</td>
<td>-</td>
</tr>
<tr>
<td>Starlac</td>
<td>85%</td>
<td>34</td>
<td>91%</td>
</tr>
</tbody>
</table>

*removed during the process

Starlac = Spray-dried compound consisting of 85% alpha-lactose monohydrate and 15% maize starch dry matter

It was found during further formulation development that Starlac may be used. However, Tablettose result in additional advantages. The division of the polymer into two layers will achieve better coating efficiency at larger scales.
Example 3 - the first pharmaceutical tablet formulation containing a first layer

Following the procedure according to example 1 first pharmaceutical tablet formulations according to the present invention have been produced. The detailed compositions having only one layer (the first layer) coated on the carrier core particles are summarized in the following table 3 wherein different Eudragit® EPO : benazepril hydrochloride (E/B) ratios are used. The ACE inhibitor used is benazepril hydrochloride, and the PDE III inhibitor used is pimobendan, however, any other ACE inhibitor and any other PDE III inhibitor may be used.

Table 3:

<table>
<thead>
<tr>
<th>Dosage strength</th>
<th>1.25/2.50</th>
<th>1.25/2.50</th>
<th>1.25/2.50</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/B ratio</td>
<td>01:05</td>
<td>2.5:1</td>
<td>1.25:1</td>
</tr>
<tr>
<td>Tablet weight</td>
<td>0.5 g</td>
<td>0.5 g</td>
<td>0.5 g</td>
</tr>
<tr>
<td>Ingredients</td>
<td>mg/tablet</td>
<td>mg/tablet</td>
<td>mg/tablet</td>
</tr>
<tr>
<td>Benazepril hydrochloride</td>
<td>2.50</td>
<td>2.50</td>
<td>2.50</td>
</tr>
<tr>
<td>Eudragit® EPO</td>
<td>12.50</td>
<td>6.25</td>
<td>3.13</td>
</tr>
<tr>
<td>Monohydrate lactose / starch</td>
<td>150.00</td>
<td>156.25</td>
<td>159.37</td>
</tr>
<tr>
<td>Pimobendan</td>
<td>5.00</td>
<td>5.00</td>
<td>5.00</td>
</tr>
<tr>
<td>Dry Meat Flavour</td>
<td>50.00</td>
<td>50.00</td>
<td>50.00</td>
</tr>
<tr>
<td>Colloidal silica, anhydrous</td>
<td>2.50</td>
<td>2.50</td>
<td>2.50</td>
</tr>
<tr>
<td>Maize starch, undried</td>
<td>25.00</td>
<td>25.00</td>
<td>25.00</td>
</tr>
<tr>
<td>Fumaric acid</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
</tr>
<tr>
<td>Iron oxide yellow</td>
<td>6.00</td>
<td>6.00</td>
<td>6.00</td>
</tr>
<tr>
<td>Stearic acid, micronized</td>
<td>2.50</td>
<td>2.50</td>
<td>2.50</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>276.00</td>
<td>276.00</td>
<td>276.00</td>
</tr>
</tbody>
</table>
II. Studies
   1. Bioequivalence study

The aim of this study was to assess the bioequivalence of coated benazepril tablets with Symrise flavour (manufactured by Delpharm) as test formulation against Fortekor® Flavour Tablets as reference for both the parent and the metabolite by evaluating the pharmacokinetic parameters of benazepril and its metabolite benazeprilate after single oral dosing at a dose level of 5 mg/dog.

Fortekor® Flavour Tablets (Novartis Animal Health UK Ltd.) are available on the market and contain the active substance benazepril hydrochloride at a dose level of 5 mg. The tablets are indicated for the treatment of heart failure in dogs.

The two different tablet formulations of benazepril were given to 12 female Beagle dogs (6 per group) in 2 different periods, in a (2x2) cross-over design. A wash-out period of 7 days was applied between the consecutive periods. Animals were fasted overnight prior to dosing and fed again 4 hours post-dose. Blood samples for pharmacokinetic purposes were collected at 0 (pre-dose), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 8 and 24 hours (h) after dosing. The samples were analyzed for benazepril and benazeprilate (metabolite) plasma concentrations.

For benazepril, bioequivalence of the coated benazepril tablets with Symrise flavour compared to the Fortekor® Flavour Tablets formulation could not be statistically demonstrated for $C_{\text{max}}$ and $AUC_{\text{ast}}$. The limits of the 90% CI were outside the [80%, 125%] bioequivalence limits for $C_{\text{max}}$ and outside the upper bioequivalence limit for $AUC_{\text{ast}}$. This was probably caused by an inadequate sampling size and/or high variability in $C_{\text{max}}$ and AUC-values observed in both treatment groups. No sequence, treatment or period effect was observed based on the calculated p-values (>0.05).

For benazeprilate, bioequivalence between both formulations was demonstrated for $AUC_{\text{ast}}$. For $C_{\text{max}}$ bioequivalence could not be demonstrated because the upper value of
the 90% CI was outside the 125% bioequivalence limit. No sequence, treatment or period effect was observed based on the p-values (>0.05).

These study results were compared with bioequivalence study results from a benazepril generic formulation. The high variability observed in the bioequivalence study was not seen in the study with the benazepril generic tablets.

2. **Palatability study**

The objective of this study was to compare the palatability of Fortekor® Flavour tablets to the FDC test formulation (FDC formulation without pimobendan) in dogs. In this study the following parameters were determined:

- Amount consumed (1 = Complete consumption, 2 = Partial consumption, 3 = None)
- Acceptance score (1 = Immediate intake from bowl, 2 = Hesitant intake from bowl > 10 seconds, 3 = Immediate intake from hand, 4 = Hesitant intake from hand > 10 seconds)
- Time to consumption

The study population consisted of 12 dogs (6 dogs per group) during the test phase (Study Day 1 to 24) during which each animal received either a Fortekor® Flavour 5 mg tablet (X) or a FDC benazepril 5 mg tablet (Y). The test phase consisted of three periods of six days, where the dogs received either test article X or Y, and a 3 day wash-out phase after period 1 and 2.

The dog which received in test period 1 the test article X received in period 2 article Y and in period 3 X again. The second group received Y in the first period, then X and again Y in the third period of the study.

Results:

The acceptance in dogs of the FDC test formulation is assessed to be comparable to the Fortekor® Flavour tablets in this study. One dog rejected the FDC formulation especially in phase 3 of the study.
Claims

1. Pharmaceutical packaging product for the veterinary medical sector containing a first pharmaceutical solid formulation, preferably a first pharmaceutical tablet formulation, which comprises as pharmaceutically active substances a PDE III inhibitor and an ACE inhibitor, and a second pharmaceutical solid formulation, preferably a second pharmaceutical tablet formulation, which comprises as pharmaceutically active substance a PDE III inhibitor.

2. Pharmaceutical packaging product according to claim 1 containing a first pharmaceutical solid formulation, preferably a first pharmaceutical tablet formulation, which comprises as pharmaceutically active substances a PDE III inhibitor and an ACE inhibitor, and a second pharmaceutical solid formulation, preferably a second pharmaceutical tablet formulation, which comprises as pharmaceutically active substance a PDE III inhibitor, as a combined preparation for separate or sequential use in the prevention and/or the treatment of heart diseases, disorders, or complications associated therewith in mammals.

3. Pharmaceutical packaging product according to claim 1 or 2, characterised in that the pharmaceutical packaging product is a blister pack.

4. Pharmaceutical packaging product according to any one of claims 1 to 3, characterised in that the pharmaceutical packaging product is an aluminum blister pack having an aluminum foil and aluminum pockets wherein the pharmaceutical solid formulations are accommodated.

5. Pharmaceutical packaging product according to any of the preceding claims, characterised in that the pharmaceutical packaging product is a blister pack divided into two halves in form of two sections as a split blister having an upper and a lower section, in the upper section the first pharmaceutical solid formulation is present and in the lower section the second pharmaceutical solid formulation is present.
6. Pharmaceutical packaging product according to any of the preceding claims, characterised in that the pharmaceutical packaging product is a blister pack having a bottom foil, the outside of the bottom foil comprises one or more identification markings selected from one or more colours and/or one or more legends and/or one or more symbols, respectively correlated with the first or second pharmaceutical solid formulations with respect to the type of solid formulation contained, the kind of pharmaceutically active substance(s) contained, the dosage strength(s) of pharmaceutically active substance(s) contained, the preferred time of administration, the kind of administration form provided, and/or the animal to be treated and the like.

7. Pharmaceutical packaging product according to any of the preceding claims, characterised in that the pharmaceutical packaging product is a blister pack divided into two sections, preferably an upper and a lower section, on the outside of the blister foil the upper section is marked with one colour, preferably the colour covers the whole surface of the upper section, and the lower section is marked with a colour different to the colour of the upper section, preferably the colour covers the whole surface of the lower section.

8. Pharmaceutical packaging product according to any of the preceding claims, characterised in that the first pharmaceutical solid formulation and/or the second pharmaceutical solid formulation is/are present in the blister pack in the same or in different dosage strengths, the outside of the bottom foil comprises one or more identification markings so that each dosage strength is correlated with a colour and/or a labeling and/or a symbol.

9. Pharmaceutical packaging product according to any of the preceding claims, characterised in that the first pharmaceutical solid formulation has a colouring and the second pharmaceutical solid formulation has a colouring different to the colouring of the first pharmaceutical solid formulation, preferably the colouring being similar or identical to the colours selected for the identification markings of the outside of the blister foil.
10. Pharmaceutical packaging product according to any of the preceding claims, characterised in that the pharmaceutical packaging product is a blister pack divided into two sections, preferably an upper and a lower section, on the outside of the blister foil one colour covers the whole surface of the upper section, and a colour different to the upper section covers the whole surface of the lower section, the colour of the upper section is similar or identical to the colouring of the first pharmaceutical solid formulation and the colour of the lower section is similar or identical to the colouring of the second pharmaceutical solid formulation.

11. Pharmaceutical packaging product according to any of the preceding claims 5 to 9, characterised in that the legend is selected from "morning", "at noon", or "evening" corresponding to the time to take the medication, preferably for the first pharmaceutical solid formulation the legend is "morning" and preferably for the second pharmaceutical solid formulation the legend is "evening".

12. Pharmaceutical packaging product according to any of the preceding claims 5 to 10, characterised in that the symbol is selected from a sun symbol or a moon symbol corresponding to the time to take the medication, preferably for the first pharmaceutical solid formulation a sun symbol is selected and for the second pharmaceutical solid formulation a moon symbol is selected.

13. Pharmaceutical packaging product according to any of the preceding claims, characterised in that the blister pack is a child-resistant blister pack such as a push trough pack (PTP).

14. Pharmaceutical packaging product according to any of the preceding claims, characterised in that the first pharmaceutical solid formulation is a tablet formulation which comprises an ACE inhibitor as a first pharmaceutically active substance, and a PDE III inhibitor as a second pharmaceutically active substance, comprising granules which contain carrier core particles coated with at least one layer wherein the first pharmaceutically active substance is present,
the granules being embedded in a tablet matrix wherein the second pharmaceutically active substance is present.

15. Pharmaceutical packaging product according to any of the preceding claims, characterised in that the first pharmaceutical solid formulation is a tablet formulation which comprises 0.5 to 30 mg of the ACE inhibitor as a first pharmaceutically active substance, and 0.5 to 20 mg of the PDE III inhibitor as a second pharmaceutically active substance, comprising granules which contain carrier core particles coated with at least one layer wherein the first pharmaceutically active substance is present, the granules being embedded in a tablet matrix wherein the second pharmaceutically active substance is present.

16. Pharmaceutical packaging product according to any of the preceding claims, characterised in that the second pharmaceutical solid formulation is a tablet formulation which comprises 0.5 to 20 mg of the PDE III inhibitor.

17. Pharmaceutical packaging product according to any of the preceding claims, characterised in that it comprises
i) a first pharmaceutical solid formulation comprising 0.5 to 30 mg of the ACE inhibitor as a first pharmaceutically active substance, and 0.5 to 20 mg of the PDE III inhibitor as a second pharmaceutically active substance, and
ii) a second pharmaceutical solid formulation comprising 0.5 to 20 mg of the PDE III inhibitor.

18. Pharmaceutical packaging product according to any of the preceding claims, characterised in that it comprises
i) a first pharmaceutical solid formulation comprising 0.5 to 30 mg of the ACE inhibitor as a first pharmaceutically active substance, and 0.5 to 20 mg of the PDE III inhibitor as a second pharmaceutically active substance for administration in the morning, and
ii) a second pharmaceutical solid formulation comprising 0.5 to 20 mg of the PDE III inhibitor for administration in the evening.
Fig. 4
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K9/16 A61K9/20 A61K9/50 A61K31/00
A61J1/00

ADD.
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)
A61K A61J

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 practicable, search terms used)
EPO-Internal , CHEM ABS Data, EMBASE, WPI Data, BIOSIS, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of Box C.  [X] See patent family annex.

* Special categories of cited documents:
A* document defining the general state of the art which is not considered to be of particular relevance
E* earlier application or patent but published on or after the international filing date
L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
O* document referring to an oral disclosure, use, exhibition or other means
P* document published prior to the international filing date but later than the priority date claimed
T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
A* document member of the same patent family

Date of the actual completion of the international search
2 April 2013

Date of mailing of the international search report
09/04/2013

Name and mailing address of the ISA:
European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax. (+31-70) 340-3016

SchLil e, Stefani e

Authorized officer

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