USE OF PDE III INHIBITORS FOR THE REDUCTION OF HEART SIZE IN MAMMALS SUFFERING FROM HEART FAILURE

BACKGROUND OF THE INVENTION

1. TECHNICAL FIELD

The invention relates to the use of a phosphodiesterase type III (PDE III) inhibitor or a "Ca^{2+}-sensitizing agent" or a pharmaceutically acceptable derivative thereof for the preparation of a medication for the reduction of the heart size of a patient suffering from heart failure.

2. BACKGROUND INFORMATION

Intravenous positive inotropic agents play a vital role in the management of acute heart failure, and will often result in a short-term improvement in dogs with dilated cardiomyopathy (DCM). Many dogs with DCM have a very guarded prognosis (Monnet et al., 1995), with Dobermanns in particular generally experiencing only short survival times (Calvert et al., 1982; Calvert et al., 1997). There have been few studies examining the influence of treatment on survival in dogs with DCM, although a subanalysis of the dogs with DCM in the LIVE study showed an improvement in time to treatment failure in those dogs receiving enalapril compared with placebo (142.8 versus 56.5 days, respectively) (Ettinger et al., 1998). On the whole, oral positive inotropic agents have lost favour in the treatment of chronic heart failure in human patients in recent years, after a number of trials revealed adverse effects on survival despite short-term hemodynamic benefits (Packer et al., 1991; Cowley and Skene, 1994). Recently it has been suggested that calcium sensitising agents may result in positive inotropic effects without producing some of the adverse effects (including calcium overload) associated with more traditional positive inotropes such as dobutamine, amrinone and milrinone.

Pimobendan is an inodilator compound with calcium sensitising effects, as well as some phosphodiesterase type III inhibitory effects. Rather than increasing calcium entry into cardiac myocytes, calcium sensitisers achieve their positive inotropic effect by sensitising

the contractile proteins to existing cytosolic calcium, by altering the binding of calcium with troponin-C. Producing a positive inotropic effect by calcium sensitising thereby avoids some of the adverse effects of cytosolic calcium overload. Increased cytosolic calcium levels have been associated with an increased tendency for arrhythmias and sudden death. Clinical trials of long-term use of oral pimobendan in human patients with heart failure have demonstrated an improvement in exercise tolerance and quality of life without significantly adverse effects on survival (Kubo et al., 1992; Katz et al., 1992).

It is known that the progress of heart failure is associated with an increase of the size of the heart. In dilated cardiomyopathy (DCM) the ratio of left ventricular wall thickness to chamber diameter is decreased and the circumferences of the annuluses of the mitral and tricuspid valves are increased in proportion to the magnitude of chamber dilation. DCM may either be caused primarily by e.g. genetic abnormalities ar secondarily e.g. due to valvular insufficiency both resulting in cardiac volume overload. However, it involves usually cardiac remodeling that may be defined as genome expression, molecular, cellular, and interstitial changes manifested clinically as changes in size, shape, and function of the heart. Cardiac remodelling is generally an adverse sign and linked to heart failure progression. Reverse cardiac remodelling is a goal of the treatment of heart failure therapy.

Heart failure therapy has traditionally focussed largely on symptomatic relief rather than on addressing underlying disease problems.

The problem underlying the present invention was to provide a medication, which allows to remodel the size of the heart to reduce the risk of death in patients with coronary diseases. In particular, the problem underlying the present invention was to provide a medication, which allows to reduce the size of the heart to reduce the risk of death in patients suffering from heart failure.

BRIEF DESCRIPTION OF THE INVENTION

It has been found surprisingly that phosphodiesterase type III (PDE III) inhibitors and/or a Ca^{2+}-sensitizing agent or a pharmaceutically acceptable derivatives thereof can be used for the preparation of a medication for the reduction of the heart size of a patient suffering from heart failure.

According to a first aspect, there is provided the use of a phosphodiesterase type III (PDE III) inhibitor or a Ca^{2+}-sensitizing agent or a pharmaceutically acceptable derivative thereof for the preparation of a medication for the reduction of the heart size of a patient suffering from heart failure.

Moreover, the disclosure relates to a method of reduction of the heart size in a patient suffering from heart failure, which method comprises administering to said patient an effective amount of an PDE III inhibitor or a pharmaceutically acceptable derivative thereof.

Furthermore, the disclosure relates to an article of manufacture comprising packaging material contained within which is a composition effective to reduce of the heart size of a patient suffering from heart failure and the packaging material comprises a label which indicates that the composition can be used to reduce of the heart size of a patient suffering from heart failure, wherein said composition comprises at least one PDE III inhibitor or a Ca^{2+}-sensitizing agent or a pharmaceutically acceptable derivative thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the lateral thoracic radiograph of an English cocker spaniel with dilated cardiomyopathy, showing alveolar pulmonary oedema and cardiac enlargement.

Figures 2a and 2b show the thoracic radiograph of the same dog in Fig. 1, following four months treatment with furosemide, enalapril, digoxin, and pimobendan.

Figure 3 shows the Heart Insufficiency Score (ISACHC) in dogs treated with pimobendan (each left black column) or benazepril (each right grey column) on days 0, 7 and 56.

Figure 4 shows the Overall Clinical Effect in dogs treated with pimobendan (left black column) or benazepril (right grey column) on day 56.

Figure 5 shows the survival function (56-day period) in dogs treated with pimobendan (upper —O— curve) or benazepril (lower —□— curve).

Figure 6 shows the survival function in dogs treated with pimobendan (430-day period / upper —O— curve) or benazepril (228-day period / lower —□— curve).

Figure 7 shows reduction in mean heart size for pimobendan treated dogs (-0.15 v) versus benazepril treated dogs (+0.22 v).

DETAILLED DESCRIPTION OF THE INVENTION

The invention relates to the use of a phosphodiesterase type III (PDE III) inhibitor, preferably a PDE III inhibitor, a Ca^{2+}-sensitizing agent, or a PDE III inhibitor which exhibits additionally calcium sensitising effects (Ca^{2+}-sensitizing agent) , or a pharmaceutically acceptable derivative thereof for the preparation of a medication for the reduction of the heart size of a patient suffering from heart failure.

The term "PDE III inhibitor" as used hereinabove and hereinbelow relates to phosphodiesterase (PDE) III inhibitors, which prevent breakdown of cAMP to 5'AMP and thus maintain the effect of cAMP on protein kinase and other secondary messenger activation.

The effects of PDE III inhibitors are as a rule positive inotropy and vasodilatation, which reduces the afterload patients with heart failure feel better.

The term Ca^{2+}-sensitizing agent relates to a compound which increases the Ca^{2+} sensitivity of cardiac contractile proteins, i.e. increase the developed contractile force at a given concentration of Ca^{2+}.

Preferred PDE III inhibitors or Ca^{2+}-sensitizing agents are cilostazol, pimobendan, milrinone, levosimendan, amrinone, enoximone and piroximone TZC-5665 or

pharmaceutically acceptable salts, derivatives, metabolites or pro-drugs thereof. Most preferred are pimobendan and levosimendan, or pharmaceutically acceptable salts, derivatives, metabolites or pro-drugs thereof . Even more preferred is pimobendan and levosimendan. Evenmore preffered is pimobendan, pharmaceutically acceptable salts, derivatives, metabolites or pro-drugs thereof.

Pimobendan, known to the public as 4,5-dihydro-6-[2-(4-methoxyphenyl)-1H-benzimidazol-5-yl]-5-methyl-3(2H)-pyridazone, is for example disclosed in EP 008 391 B1. Levosimendan is a pyridazone-dinitrile derivative. In particular, levosimendan is known to the public as (R)-[[4-(1,4,5,6-Tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydra zono]propanedini trile and has been described earlier for example in GB 2228004, US 5,151,420 and US 5,569,657.

The term "patient" as used hereinabove and hereinbelow relates to an animal or a person suffering from heart failure. The term "patient" embraces mammal such as primates including humans.

In addition to primates, a variety of other mammals can be treated according to the method of the present invention. For instance, mammals, including but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine, equine, canine, feline, rodent or murine species can be treated. However, the method can also be practiced in other species, such as avian species.

Preferred are human patients, dogs, cats and horses. Human patients are female or male person who are suffering from heart failure. As a rule such persons are children, young adults, adults or elderly people with an age of between 6 and 80, preferably between 30 and 65 years.

The term "heart failure" as used hereinabove and hereinbelow relates to any contractile disorder or disease of the heart. Clinical manifestations are as a rule the results of changes to the heart's cellular and molecular components and to mediators that drive homeostatic

control. The heart failure is as a rule accompanied by an increase of the heart size and deterioration of cardiac functions.

Pre-dominantly, the patients suffer from heart failure, which is a chronic congestive heart failure, a heart failure due to myocardial infarction or myocardial ischemia due to cardiac arrest.

The term "reduction of the heart size" as used hereinabove and hereinbelow relates to a reduction of the size of the heart of the patient, which may be determined according to the radiograph methods suggested by James W. Buchanan et al. (Buchanan 1995) and is expressed in the relative change of the vertebral heart size. Preferably, the relative mean vertebral heart sum (VHS) of said patient is reduced by 0.05 to 0.25 within 10 to 100 days, in particular by about 0.15 within about 60 days, of treatment with the PDE III inhibitor and/or Ca^{2+}-sensitizing agent.

The term "effective amount" as used herein means an amount sufficient to achieve a reduction of the heart size when said PDE III inhibitor or Ca^{2+}-sensitizing agent is administered in a single dosage form.

Preferably, the PDE III inhibitor and/or Ca^{2+}-sensitizing agent is administered in combination with a second active therapeutic agent. Such a second active therapeutic agent is preferably selected from the group consisting of calcium channel blockers, ACE inhibitors, diuretics, platelet inhibitors, beta blockers and angiotensin II antagonists, aldosterone antagonists, digitalis glycosides, antiarrhythmic agents or diuretics in particular

- wherein the calcium channel blocker inhibitor is selected from the group consisting of diltiazem, verapamil and felodipine or a pharmaceutically acceptable derivative thereof; and/or
- wherein the ACE inhibitor is selected from the group consisting of omapatrilat, MDL100240, alacepril, benazepril, captopril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, fosinoprilat, imidapril, lisinopril, perindopril, quinapril,

ramipril, ramiprilat, saralasin acetate, temocapril, trandolapril, trandolaprilat, ceranapril, moexipril, quinaprilat and spirapril or a pharmaceutically acceptable derivative thereof; and/or

- wherein the beta blocker is selected from the group consisting of bisoprolol, carvediol, metoprolol, propranolol and timolol or a pharmaceutically acceptable derivative thereof, and/or
- wherein the angiotensin II antagonist is selected from the group consisting of saralasin acetate, candesartan, cilexetil, valsartan, candesartan, losartan potassium, eprosartan, irbesartan, tasosartan, pomisartan and telmisartan or a pharmaceutically acceptable derivative thereof and/or
- wherein the aldosterone antagonist is selected from the group consisting of spironolactone, eplerenone, canrenone, potassium canrenone or a pharmaceutically acceptable derivative thereof., and/or
- wherein the antiarrhythmic agents are selected from the group consisting of amiodarone, betrylium, disopyramide, dofetilide, flecainide, ibutilide, mexiletine, tocainide, procainamide, propafenone, quinidine, sotalol or a pharmaceutically acceptable derivative thereof., and/or
- wherein the diuretic is selected from the group consisting of furosemide, torasemide, bumetanide, etacrynic acid, azosemide, muzolimine, piretanide, tripamide, bendroflumethazide, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methychlothiazide, polythiazide, trichlormethiazide, chlorthialidone, indapamide, metolazone, quinethazone, etozolin, triamteren, amiloride, or a pharmaceutically acceptable derivative thereof., and/or
- wherein the digitalis glycosides is selected from the group consisting of digoxin, digitoxin, g-strophantin, ß-methyldigoxin, ß-acetyldigoxin or a pharmaceutically acceptable derivative thereof.

Most preferably, the PDE III inhibitor or Ca^{2+}-sensitizing agent, in particular pimobendan or levosimendan, even more preffered pimobendan is administered together with one or more medicaments selected from the group consisting of one or more ACE-inhibitors, one or more diuretics and one or more digitalis glycosides.

The compounds of this invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. A physician or veterinarian can determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the disorder.

By way of general guidance, the daily oral dosage of each active ingredient, preferably of pimobendan or levosimendan, when used for the indicated effects, will range between about 10μg/kg to10 mg/kg, preferably from 0.05 mg/kg to 5 mg/kg, in particular from 0.1 mg/kg to 2 mg/kg.

Most preferably from about 0.1 mg/kg to 1.5 mg/kg of pimobendan are administered per day.

The PDE III inhibitors and/or Ca^{2+}-sensitizing agents may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

The PDE III inhibitors and/or Ca^{2+}-sensitizing agents can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermale routes, using transdermale skin patches. When administered in the form of a transdermale delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The PDE III inhibitors and/or Ca^{2+}-sensitizing agents are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and colouring agents can also be incorporated into the mixture. Suitable binders include starch, gelatine, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The PDE III inhibitors and/or Ca^{2+}-sensitizing agents can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

The PDE III inhibitors and/or Ca^{2+}-sensitizing agents may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues.

Furthermore, the PDE III inhibitors and/or Ca^{2+}-sensitizing agents may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and cross linked or amphipathic block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit.

In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

Gelatine capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain colouring and flavouring to increase patient acceptance.

In general, water, suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl-or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Reminqton's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

Where two or more of the foregoing second therapeutic agents are administered with the PDE III inhibitor and/or Ca^{2+}-sensitizing agent, generally the amount of each component in a typical daily dosage and typical dosage form may be reduced relative to the usual dosage of the agent when administered alone, in view of the additive or synergistic effect of the therapeutic agents when administered in combination.

Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of formula 1 and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a material which effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients.

Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a low viscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

Procedures by way of example for preparing the compositions according to the invention will be described in more detail hereinafter. The Examples which follow serve solely as a detailed illustration without restricting the subject matter of the invention.

Example 1

A double-blind study has been carried out in order to evaluate the long-term efficacy and tolerance to pimobendan and its effect on long-term survival in cocker spaniels and Dobermanns with DCM.

Materials and Methods: Cocker spaniels (n=10) and Dobermanns (n=10) presenting to the Cardiopulmonary Service of the R(D)SVS with DCM were recruited for the study with owners' consent. After stabilisation on conventional therapy with digoxin, enalapril, and frusemide, dogs received in addition either pimobendan (Vetmedin®) or placebo using a double-blind study design.

Results: The mean survival time for cockers on pimobendan was 612 days (range 61-1428) compared to 589 (range 51-1127) for the placebo group. The difference was not statistically significant (Wilcoxon-Mann-Whitney-U test, $p>0.05$).

The mean survival time for Dobermanns on pimobendan was 280 days (range 42-369) compared to 72 days (range 13-196) for the placebo group. The difference was statistically significantly different (Student's t-test, $p<0.05$). The drug was well tolerated and no treatment-related adverse effects were noted in either breed.

Conclusion: Pimobendan significantly improved the survival time of the Dobermanns with DCM compared with placebo, but had no statistically significant effect on survival of the cocker spaniels. The improved survival time for the Dobermanns is an important development in the management of a disease that generally results in rapid death following diagnosis.

In both breeds the addition of pimobendan to a standard treatment regimen was associated with a significant improvement of the NYHA-class status of the patient. The benefit of pimobendan therapy was therefore additive to the beneficial effect of furosemide, enalapril and digoxin, and was even seen in the cocker spaniels which had what would be considered a favourable clinical course with conventional therapy, compared with many dogs with DCM (Monnet et al., 1995).

A striking difference in survival times was found in the Doberman pinschers treated with pimobendan. Although this breed is known to have a poor prognosis after development of congestive signs, a significant prolongation of survival time was found for pimobendan-treated animals.

Example 2

A double-blind randomised positive controlled multi-centre field trial has been carried out in order to evaluate the clinical efficacy of pimobendan treatment at a daily dose of 0.4 – 0.6 mg/kg in comparison to an angiotensin-converting-enzyme (ACE) inhibitor treatment with benazepril hydrochloride at a daily dose of approximately 0.25 - 0.5 mg/kg body

weight. Both treatments could be combined with furosemide (up to 8 mg/kg per day) or anti-arrhythmic drugs as appropriate. The study was conducted at 11 centres in Europe by experienced veterinary cardiologists under the rules of Good Clinical Practice (GCP). Mandatory minimum duration of treatment was 56 days for each patient. Dogs were examined on Day 0 prior to first treatment and on Day 7 and 56 after initiation of therapy. In order to obtain long-term survival data, the investigator had the option to continue therapy after Day 56. In the optional study period treatment code for the animal was decoded, as it was not allowed to add pimobendan to the benazepril group, in order to maintain an appropriate pimobendan control group. All other licensed concomitant therapies were allowed. For survival analysis, animals that dropped out or changed treatment due to therapy failure were also rated as dead. However, these cases were statistically evaluated as censored data.

Primary parameter for conclusion on efficacy was the clinical severity of heart failure symptoms, classified according to the recommendations of the International Small Animal Cardiac Health Council (ISACHC). Secondary parameters were exercise tolerance, demeanour, findings of the respiratory and circulatory system, overall efficacy rating, as well as, echocardiography data.

Overall 76, 41 in the pimobendan and 35 dogs in the benazepril group, were included. All dogs showed clinically overt symptoms of heart failure due to valve insufficiency. Mean duration of symptoms prior to inclusion was 4.05 months in the pimobendan and 2.77 months in the benazepril group. There were no clinically relevant differences between the groups prior to initiation of therapy in any of the parameters investigated.

The primary parameter, ISACHC heart failure classification, was improved in 84% of the pimobendan treated cases but only in 56% of the benazepril cases after the 56 day treatment period. At this time point ISACHC classification Ib (Score=2), i.e. no clinical symptoms, was reported for 76% of the pimobendan but only 48% of the benazepril cases. Differences between the groups regarding the primary parameter, were statistically significant in favour of pimobendan on Day 7 ($p=0.0280$) and Day 56 ($p=0.0201$).

Consequently, overall efficacy was rated as very good or good in 85% of the pimobendan cases but only in 41% of the benazepril cases ($p<0.0001$) . Results in other secondary parameters were in accordance with the clinical results of the heart failure classification.

In the 56-days study period, 2 dogs in the pimobendan group and 7 in the benazepril group died or were euthanised due to cardiac reasons. Survival analysis according to Kaplan-Meier revealed significant differences in favour of pimobendan ($p=0.0386$). Analysis of long-term survival data confirmed the results of the 56-day period. Median survival time for pimobendan treated dogs was 430 days versus 228 days for dogs that received no pimobendan. Again, survival analysis according to Kaplan-Meier revealed significant differences in favour of pimobendan ($p=0.0020$).

The radiographs have been made in a left to right lateral view. For the determination of cardiac size a vertebral scale system was used.

In the lateral radiographs, the long axis of the heart (L) was measured with a calliper extending from the ventral aspect of the left main stem bronchus (tracheal bifurcation hilus, carina) to the most distant contour of the left ventricular apex. The calliper was repositioned along the vertebral column beginning at the cranial edge of the 4th thoracic vertebra. The length of the heart was recorded as the number of vertebrae caudal of that point and estimated to the nearest 0.1 of a vertebra. The maximum perpendicular short axis (S) was measured in the same manner beginning at the 4th thoracic vertebra.

The length in vertebrae (v) of the long and short axes were then added to obtain a vertebral heart sum (VHS) which provided a single number representing heart size proportionate to the size of the dog. The normal range of VHS in healthy dogs is 8.5v to 10.5v (mean of 9.7v).

The mean vertebral heart sum measured on radiographs on days 0 and 56 showed improvement for dogs in the pimobendan group. With regards to the changes from baseline, the difference in the mean value indicated a reduction in mean heart size for

pimobendan treated dogs. The mean difference between the groups regarding overall clinical efficacy was statistically significant in favour of pimobendan treatment ($p < 0.0001$). See table 1. The mean scores in the control benazepril group showed deterioration with regard to changes from baseline (Fig. 7). This demonstrates that a reduction of heart size cannot routinely be achieved with standard therapy in dogs with heart failure due to valve insufficiency. The striking difference between standard therapy (ACE-inhibitor +/- diuretics) deterioration of mean heart size by 0.22 v and pimobendan treatment with an improvement of mean size of -0.15 v was unexpected and thus inventive.

Table 1: Vertebral scale system – heart sum.

Visit	Group	N	Min.	Max.	Median	Mean	SD
1	1	41	9	14.5	11.60	11.83	1.31
3	1	37	9.0	14.1	11.60	11.71	1.18
3-1	1	37	-1.9	0.8	0.00	-0.15	0.57

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CLAIMS

1. The use of a phosphodiesterase type III (PDE III) inhibitor or a Ca^{2+}-sensitizing agent or a pharmaceutically acceptable derivative thereof for the preparation of a medication for the reduction of the heart size of a patient suffering from heart failure.

2. The use according to claim 1, wherein the PDE III inhibitor exhibits additionally calcium sensitising effects.

3. The use according to claim 1 or 2, wherein the PDE III inhibitor or Ca^{2+}-sensitizing agent is selected from the group consisting of pimobendan, milrinone, levosimendan, amrinone, enoximone, and piroximone or a pharmaceutically acceptable derivative thereof.

4. The use according to any one of the preceding claims, wherein the PDE III inhibitor or Ca^{2+}-sensitizing agent is utilized in oral or parenteral form.

5. The use according to any one of the preceding claims, wherein the PDE III inhibitor or Ca^{2+}-sensitizing agent is administered in a daily dose from 10μg/kg to 10 mg/kg.

6. The use according to any one of the preceding claims, wherein the PDE III inhibitor or Ca^{2+}-sensitizing agent is administered together with a medicament selected from the group consisting of calcium channel blockers, ACE inhibitors, diuretics, aspirin, beta blockers and angiotensin 11 antagonists.

7. The use according to any one of the preceding claims, wherein the ACE inhibitor is selected from the group consisting of omapatrilat, MDL100240, alacepril,benazepril, captopril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, fosinoprilat, imidapril, lisinopril, perindopril, quinapril, ramipril, ramiprilat, saral asin

acetate, temocapril, trandolapril, trandolaprilat, ceranapril, moexipril, quinaprilat and spirapril or a pharmaceutically acceptable derivative thereof.

8. The use according to any one of the preceding claims, wherein the angiotensin II antagonist is selected from the group consisting of saralasin acetate, candesartan cilexetil, valsartan, candesartan, losartan potassium, eprosartan, irbesartan, tasosartan and telmisartan or a pharmaceutically acceptable derivative thereof.

9. The use according to any one of the preceding claims, wherein the PDE III inhibitor or Ca^{2+}-sensitizing agent is administered together with one or more medicaments selected from the group consisting of one or more ACE-inhibitors, one or more diuretics and one or more digitalis glycosides.

10. The use according to any one of the preceding claims, wherein the relative mean vertebral heart sum (VHS) of said patient is reduced by 0.05 to 0.25 within 10 to 100 days of treatment with the PDE III inhibitor or Ca^{2+}-sensitizing agent.

11. The use according to any one of the preceding claims, wherein the heart failure is chronic congestive heart failure, heart failure due to myocardial infarction or myocardial ischemia due to worsening of angina, or cardiac arrest.

12. The use according to any one of the preceding claims, wherein said patient is a mammal selected from the group consisting of primates including humans, dogs, cats and horses.