Pharmaceutical composition comprising pimobendan

1. BACKGROUND OF THE INVENTION

TECHNICAL FIELD

The invention relates to the field of animal health. In particular, the invention relates to novel oral pharmaceutical compositions comprising as pharmaceutically active compounds pimobendan.

BACKGROUND INFORMATION

Pimobendan (4,5-dihydro-6-[2-(4-methoxyphenyl)-1H-benzimidazol-5-yl]-5-methyl-3(2H)-pyridazone) is disclosed in EP 008 391 B1, herein incorporated by reference in its entirety. Pimobendan is a cardiotonic, hypotensive and anti-thrombotic. Said substance is the standard in the indication congestive heart failure.

Pimobendan only hardly dissolves in water. The resorption of pimobendan when administered orally is prone to considerable inter- and intra-individual fluctuations if the active substance is incorporated in known or conventional pharmaceutical forms for oral administration. The reason for this is that pimobendan is characterized by a low solubility in aqueous media and a very highly pH-dependent solubility. To overcome this, hard gelatine capsules were used containing pimobendan formulated with citric acid, in particular at a weight ratio of pimobendan to citric acid of between 1:10 and 1:20 (EP 439 030 B1, herein incorporated by reference in its entirety). However, the high quantity of citric acid and the acidic taste of citric acid is not voluntarily accepted by most animals - thus, such capsules have to be force-fed to the animals or mixed with food prior to application.

The problem underlying the present invention was to provide a pimobendan solid formulation voluntarily acceptable by mammalian subjects, especially small animals.

2. BRIEF SUMMARY

The disclosure relates to novel solid formulations comprising as pharmaceutically active compound pimobendan or a pharmaceutically acceptable salt thereof which is homogenously dispersed in a polyvalent acid and a flavor acceptable to small animals.

In a first aspect, there 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 of citric acid, tartaric acid or its anhydride, and a flavor for small animals.

Preferably, such solid formulations are granules or tablets. Most preferred is a tablet characterized in that the tablet comprises, preferably consists of 1.25 mg, 2.5 mg, 5 mg or 10 mg pimobendan, and further consists of lactose, corn starch, croscarmellose-sodium, citric acid, preferably at an amount of 50 mg / g of the solid formulation, artificial beef flavor, polyvidone, colloidal anhydrous silica and magnesium stearate.

The disclosure further relates to fluid-bed granulation processes for production of the solid formulations comprising or consisting of the steps:

a) an aqueous solution of pimobendan and a binder as defined above is sprayed onto a solid carrier bed comprising one or several carriers and/or excipients, flavor and citric acid anhydride and
b) the mixture of a) is dried and
c) the mixture of b) is sieved and de-agglomerated and
d) a flow regulator is added to the mixture of c) and
e) a lubricant is added to the mixture of d) and
f) the mixture of e) is blended for uniformity of granules to obtain final granules and/or

g) the final granules of f) are compressed to solid formulations.

Step g) is omitted if the solid formulation is a granule. If the solid formulation is a tablet, step g) is carried out.

Hence, in a second aspect, there is provided a fluid-bed granulation process comprising the steps:

a) an aqueous solution of pimobendan and a binder is sprayed onto a solid support comprising one or several carriers and/or excipients, flavor and citric acid anhydride and
b) the mixture of a) is dried and
c) the mixture of b) is sieved and de-agglomerated and
d) a flow regulator is added to the mixture of c) and
e) a lubricant is added to the mixture of d) and
f) the mixture of e) is blended for uniformity of granules to obtain final granules and/or
g) the final granules of f) are tabletted.

Furthermore, the disclosure relates to a method of prevention and/or treatment of diseases wherein cardiotonic, hypotensive and anti-thrombotic substances have a therapeutic benefit, comprising administering to a mammal in need of such

treatment a therapeutically effective amount of a solid formulation as disclosed above.

Preferred is a method of prevention and/or treatment of congestive heart failure, comprising administering to a mammal in need of such treatment a therapeutically effective amount of a solid formulation as disclosed above. Most preferably, the method comprises administering a tablet as defined above.

Furthermore, the disclosure relates to a method for manufacturing a medicament for the prevention and/or treatment of congestive heart failure, characterised in that a solid formulation according to the disclosure is used. Preferably, the disclosure relates to a method for manufacturing a medicament for the prevention and/or treatment of congestive heart failure, characterised in that a tablet comprising, preferably consisting of 1.25 mg, 2.5 mg, 5 mg or 10 mg pimobendan and further consisting of lactose, corn starch, croscarmellose-sodium, 50 mg / g citric acid, artificial beef flavor, polyvidone, colloidal anhydrous silica and magnesium stearate is used.

In a third aspect, there is provided a solid formulation as defined above for treating congestive heart failure.

3. BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: Illustration of the basic top spray fluid bed process Reference signs: 1 Exhaust air ventilator; 2 Filter; 3 Pump; 4 Stirrer; 5 Aqueous Suspension of micronised pimobendan and binder solution (PVP, HPMC, starch, gelatine); 6 Heating device for inlet air; 7 Sieve; 8 Nozzle, aqueous suspension is sprayed onto powder bed (citric acid, lactose, starch, flavour); 9 Powder bed

Figure 2: Flow Chart of Manufacturing Process

Figure 3: Dissolution Profiles, Pimobendan 1.25 mg tablets, showing 95% confidence intervals of the mean; USP apparatus 2 (Paddle), Rotation Speed 75

rpm, Buffer pH 4.0. Comparison of dissolution profiles of tablets which were stored 1 and 6 months at 40°C/75 % in HDPE bottles; batch no. PB020049

Figure 4: Dissolution Profiles, Pimobendan 1.25 mg tablets, showing 95% confidence intervals of the mean; USP apparatus 2 (Paddle), Rotation Speed 75 rpm, Buffer pH 4.0. Comparison of dissolution profiles of tablets which were stored 12 days at 25°C/60 % in open glass bottles; batch no. PB010080

Figure 5: Dissolution Profiles, Pimobendan 2.5 mg tablets, showing 95% confidence intervals of the mean; USP apparatus 2 (Paddle), Rotation Speed 75 rpm, Buffer pH 4.0. Comparison of dissolution profiles of tablets which were stored 3 and 6 months at 40°C/75 % in Alu-Alu Blister; batch no. PB010076

Figure 6: Dissolution Profiles, Pimobendan 5.0 mg tablets, showing 95% confidence intervals of the mean; USP apparatus 2 (Paddle), Rotation Speed 75 rpm, Buffer pH 4.0. Comparison of dissolution profiles of tablets which were stored 6 months at 40°C/75 % in HDPE bottles; batch no. PB020059

Figure 7: Dissolution Profiles, Pimobendan 5.0 mg tablets, showing 95% confidence intervals of the mean; USP apparatus 2 (Paddle), Rotation Speed 75 rpm, Buffer pH 4.0. Manufacturing variable: Different compression forces; batch no. PB020205

4. DETAILED DESCRIPTION OF THE INVENTION

Before the embodiments of the present invention it must be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to "a tablet" includes a plurality of such tablets, reference to the "carrier" is a reference to one or more carriers and equivalents thereof known to those skilled in the art, and so forth. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of

ordinary skill in the art to which this invention belongs. All given ranges and values may vary by 1 to 5% unless indicated otherwise or known otherwise by the person skilled in the art, therefore, the term "about" was omitted from the description. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are now described. All publications mentioned herein are incorporated herein by reference for the purpose of describing and disclosing the substances, excipients, carriers, and methodologies as reported in the publications which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

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

To overcome the difficulties in the art, a process was invented. Only the invention of this novel fluid-bed granulation process allowed the formulation of voluntarily acceptable solid formulations according to the invention. With the process according to the invention, it was possible to formulate a voluntarily accepted, long-term stable, large scale producable, homogenously dispersed, fast-releasing solid formulation. Despite the large size, pimobendan was homogenously dispersed. Such solid formulations comprising a flavor suitable for small animals, which surprisingly still allows a formulation comprising a polyvalent acid and yet have a palatibility rate of more than 70%- in many cases more than 90%. Thus, the solid formulations according to the invention are a major step forward in therapeutic application as they do not have to be force-fed to the animal.

In a first important embodiment, the invention relates to a solid formulation, comprising pimobendan or a pharmaceutically acceptable salt thereof, see e.g. EP 008 391 B1 or EP 439 030 B1 (both herein incorporated by reference in its entirety), which is homogenously dispersed in a polyvalent acid selected from the

group of citric acid, acetic acid, maleic acid, tartaric acid or the anhydride of any of said polyvalent acids, and a flavor acceptable to small animals. Such flavors according to the invention preferably are selected from artificial beef flavours, artificical chicken flavours, pork liver extract, artificial meat flavour, honey flavour and the like. Said flavors not only disguise the taste of the polyvalent acid, but also of pimobendan.

Preferably, the solid formulation according to the invention is a tablet or granule formulation. The granule formulation according to the invention is explained in more detail below. More preferably, the solid formulation is chewable.

The invention preferably also relates to a solid formulation according to the invention, further comprising one or several pharmaceutically acceptable excipients. Excipients according to the invention are preferably selected from the group consisting of diluents, disintegrants, carriers, binders, flow regulators, lubricants and solvents. Any other excipients known to the skilled person and found suitable for the solid formulation according to the invention may also be comprised in the solid formulation according to the invention. See also Remington, J.P. The science and Practice of Pharmacy (2000). 20th ed. Lippincott Williams & Wilkins Publishers, Philiadelphia, US. More preferably, said excipients are carriers / disintegrants selected from the group lactose, starch, cellulose, microcrystalline cellulose and cellulose derivatives, e.g. methylcellulose, and the like. Any other carrier known to the skilled person and found suitable for the solid formulation according to the invention may also be comprised in the solid formulation according to the invention. See also Remington, J.P. The science and Practice of Pharmacy (2000). 20th ed. Lippincott Williams & Wilkins Publishers, Philiadelphia, US.

One or several binders according to the invention are preferably selected from the group consisting of polyvidone (used synonymously for povidone), methylcellulose, hydroxypropylmethylcellulose (HPMC), hydroxymethylcellulose,

starch, gelatine, and the like. Any other binder known to the skilled person and found suitable for the solid formulation according to the invention may also be comprised in the solid formulation according to the invention. See also Remington, J.P. The science and Practice of Pharmacy (*loc. cit.*).

The solid formulation according to the invention may also comprise one or several flow regulators selected from the group consisting of silica, preferably colloidal anhydrous silica, calcium silicate, magnesium silicate, talc, and the like. Any other flow regulator known to the skilled person and found suitable for the solid formulation according to the invention may also be comprised in the solid formulation according to the invention. See also Remington, J.P. The science and Practice of Pharmacy (*loc. cit.*).

The solid formulation according to the invention may also comprise one or several disintegrants selected from the group consisting of croscarmellose sodium, sodium starch glycolate, pregelatinised starch, cross-linked polyvinylpyrrolidone and the like. Any other disintegrant known to the skilled person and found suitable for the solid formulation according to the invention may also be comprised in the solid formulation according to the invention. See also Remington, J.P. The science and Practice of Pharmacy (*loc. cit.*).

The solid formulation according to the invention may also comprise one or several lubricants selected from the group consisting of magnesium stearate, calcium stearate, glyceryl behenate, polyethylene glycol, stearic acid, talc and the like. Any other lubricant known to the skilled person and found suitable for the solid formulation according to the invention may also be comprised in the solid formulation according to the invention. See also Remington, J.P. The science and Practice of Pharmacy (*loc. cit.*).

The invention preferably also relates to a solid formulation according to the invention, characterized in that the carriers are starch and lactose. The invention preferably also relates to a solid formulation according to the invention,

characterized in that the lactose consists of coarse particles greater than 200 μm in size. The person skilled in the art knows other types of lactose which are suitable as well as carrier according to the invention , e.g. fine lactose equal or smaller than 200 μm in size or spray-dried lactose. Preferred is lactose consisting of coarse particles greater than 200 μm in size.

The invention preferably also relates to a solid formulation according to the invention, characterized in that the starch or various starches are selected from the group consisting of native starch, gelatinized starch, partly gelatinized starch, starch powder, starch granules, chemically modified starch and swellable physically modified starch.

The invention preferably also relates to a solid formulation according to the invention, characterized in that the starch is corn starch.

The invention preferably also relates to a solid formulation according to the invention, comprising 0,5 to 20 mg of pimobendan. The more preferred solid formulation contains 1 to 10 mg of pimobendan. The even more preferred solid formulation contains 1.25 to 5 mg of pimobendan. Most preferred solid formulations contain 1.25 mg, 2.5 mg, 5 mg or 10 mg of pimobendan.

The invention preferably also relates to a solid formulation according to the invention, comprising a content of 1:10 – 1:40 of pimobendan in relation to citric acid anhydride, preferably 1:20.

The invention preferably also relates to a solid formulation according to the invention, characterized in that the weight of the whole solid formulation is in the range of 250 to 3000 mg, with a more preferred weight range of 500 mg to 2000 mg, and most preferred weight of 500 mg, 1000 mg or 2000 mg.

The invention preferably also relates to a solid formulation according to the invention, characterized in that the solid formulation is produced by a fluid-bed granulation process comprising or consisting of the steps:

a) an aqueous solution of pimobendan and a binder as defined above is sprayed onto a solid carrier bed comprising one or several carriers and/or excipients as defined above, flavor and citric acid anhydride and
b) the mixture of a) is dried and
c) the mixture of b) is sieved and de-agglomerated and
d) a flow regulator is added to the mixture of c) and
e) a lubricant is added to the mixture of d) and
f) the mixture of e) is blended for uniformity of granules to obtain fina granules and/or
g) the final granules of f) are compressed to solid formulations.

Step g) is omitted if the solid formulation is a granule. If the solid formulation is a tablet, step g) is carried out.

The invention preferably also relates to a solid formulation according to the invention, characterized in that the solid formulation is produced by a fluid-bed granulation process comprising or consisting of the steps:

a) an aqueous solution of pimobendan and povidone is sprayed onto a solid carrier bed comprising lactose, starch, flavor and citric acid anhydride and
b) the mixture of a) is dried and
c) the mixture of b) is sieved and de-agglomerated and
d) a flow regulator is added to the mixture of c) and
e) a lubricant is added to the mixture of d) and
f) the mixture of e) is blended for uniformity of granules to obtain fina granules and/or
g) the final granules of f) are compressed to solid formulations.

Step g) is omitted if the solid formulation is a granule. If the solid formulation is a tablet, step g) is carried out.

The invention preferably relates to a granule formulation as obtained by the process above that can either be administered in the granular form or as tablets after compressing the final granules to tablets. Therefore, the solid formulation according to the invention preferably is a granule (or a plurality of such granules) or a tablet. The administration of the granules can take place by mixing with food or by offering the granules directly to the animal, e.g. in a bowl. The application of the granular form will allow an individual dosing of pimobendan according to the body weight of the animal.

The tablets according to the invention have surprising advantages. The dissolution profile is ensuring immediate release of pimobendan. Surprisingly, it could be demonstrated that while compressing the final granules as mentioned above, a decrease in the dissolution characteristics is not observed. By ensuring an immediate release profile of pimobendan, the amount of drug to be administered can be kept as low as possible, thereby improving the safety profile especially for long-term treatment.

Furthermore, the dosing accuracy of the tablet is excellent. This is due to the fact that in accordance with the manufacturing process according to this invention, an excellent uniformity of pimobendan content is achieved. Furthermore, the tablets can be broken into two halves so that half the dose per tablet can be administered. Compared with the existing gelatine capsule, the dosing accuracy and compliance of both the animal and the animal owner are assured. This is even more important since the drug is administered for a life-long treatment.

Also, the palatability of the tablet is excellent. More than 90 % of the dogs to whom the tablet according to this invention is given, accept the tablet voluntarily with only the tablet offered in a bowl. Compared with the existing gelatine capsule, the

compliance of both the animal and the animal owner are significantly improved. This is even more important since the drug is administered for a life-long treatment.

The invention preferably also relates to a tablet according to the invention, characterized in that the tablet is stable for at least 18 months at 25°C and 60% relative humidity. In the examples, testing parameter assays are disclosed for degradation of pimobendan, dissolution, loss on drying, hardness and disintegration of the tablet. The tablets according to the invention are within the specification limits regarding degradation of pimobendan, dissolution, loss on drying, hardness and disintegration.

Suitable packaging materials for tablets according to the invention are selected from, but not limited to: aluminum/aluminum blisters, PVC/PVDC blisters, and HDPE (high density polyethylene bottles).

The invention preferably also relates to a tablet according to the invention, characterized in that the tablet is oblong in shape. For such a tablet, characteristics like crushing strength, disintegration, uniformity of weight and content uniformity fulfill the requirements of the European Pharmacopoeia (ISBN/ISSN 92-871-5106-7 of 4th Edition 2004, Vol. 4.8, European Directorate for the Quality of Medicines (EDQM), European Pharmacopoeia, 226 avenue de Colmar, F-67029 Strasbourg, France, http://www.pheur.org) and the United States Pharmacopoeia (http://www.usp.org; in print: USP-NF, catalog No. 2270001).

The invention preferably relates to a solid formulation, and most preferred a tablet according to the invention, characterized in that the solid formulation or tablet comprising 0,5 – 20 mg pimobendan, preferably of 1.25 mg, 2.5 mg, 5 mg or 10 mg pimobendan, and further comprises, preferably consists of lactose (35 - 50 % by weight relative to the dry mass of the solid formulation/tablet = (w/w)), corn starch (25 - 50 % w/w), croscarmellose-sodium (1 – 5 %), citric acid (2,5 - 10 %

w/w), artificial beef flavor (5 – 30 % w/w), polyvidone (1 – 5 % w/w), colloidal anhydrous silica (0.1 – 1, preferably 0.1 - 0.5 % w/w) and magnesium stearate (0,25 – 1,5 % w/w), wherein the percentage by weight of pimobendan contains preferably about 0,25% (w/w) and the sum of the percentages by weight of all ingredients of the solid formulation including pimobendan is 100 % (w/w). A skilled man is in a position to prepare such solid formulations, preferably a tablet. Thus, the skilled man knows that he can add to 0,25 % (w/w) pimobendan at most 32,625 % (w/w) corn starch, 4 % (w/w) croscarmellose-sodium 5 % (w/w) citric acid, 20 % (w/w) artificial beef flavor, 4% (w/w) polyvidone, colloidal, 0,5 % (w/w) anhydrous silica, 1 % (w/w) magnesium stearate if the amount of lactose to be 32,625 % (w/w). Moreover, the skilled man also knows, that if he decided to reduce the amount of the artificial beef flavor, for example, to the minimum of 5 % (w/w), he can increase the amount of lactose, for example, to 47,625 % (w/w). The invention also relates to a solid formulation, preferably a tablet, comprising about 0,25% (w/w) pimobendan and any of the above other ingredients of the solid formulation, preferably the tablet, in the range given above so that the sum of the amounts by weight of the individual formulation ingredients is 100%.

The present invention is also directed to a solid formulation, preferably to a tablet, which comprises, preferably consists of 1 mg pimobendan, 100 – 200 mg lactose, 100 - 200 mg corn starch, 4 – 20 mg croscarmellose-sodium, 10 – 40 mg citric acid anhydrous, 20 – 120 mg artificial beef flavor, 4 – 20 mg polyvidone, 0.4 – 4 mg colloidal anhydrous silica, and 1 – 6 mg magnesium stearate for each 400 mg of total weight of the solid formulation, preferably a tablet. According to a further embodiment of the present invention, the solid formulation, preferably the tablet, comprises, preferably consists of 1 mg pimobendan, 120 – 180 mg lactose, 120 - 180 mg corn starch, 8 – 18 mg croscarmellose-sodium, 15 – 30 mg citric acid anhydrous, 40 – 100 mg artificial beef flavor, 8 – 18 mg polyvidone, 0.5 – 2 mg colloidal anhydrous silica, and 2 – 5 mg magnesium stearate for each 400 mg of total weight of the solid formulation / tablet. For example, the present invention relates to a solid formulation comprising for each 400 mg of total weight: 1 mg

pimobendan, 20 mg citric acid anhydrous, 130,5 mg lactose, 130,5 mg corn starch, 16 mg polyvidone, 16 mg croscarmellose-sodium, 80 mg artificial beef flavor, 4 mg magnesium stearate, and 2 mg colloidal anhydrous silica. A skilled man is in a position to prepare such solid formulation/tablet. The skilled man also knows that he can varied the amount of each ingredient of the solid formulation / tablet within the ranges given above in that the total weight of the solid formulation / tablet for each 1 mg pimobendan is 400 mg. For example, the amount of lactose may be 100, 101, 102, ... 108, 109, 110 etc.; 111, 112, ... 118, 119, 120 etc; 121, 122, ... 128, 129, 120 etc; 131, 132, ... 138, 139, 140 etc; 141, 142, ... 148, 149, 150 etc; 151, 152, ... 158, 159, 160 etc; 161, 162, ... 168, 169, 170 etc; 171, 172, ... 178, 179, 180 etc; 108, 182, ... 188, 189, 190 etc; 191, 192, ... 198, 199, 200 mg for each 400 mg of total weight of the solid formulation, preferably a tablet, comprising about 1 mg pimobendan. In the same manner the amount of corn starch may be 100, 101, 102, ... 108, 109, 110 etc.; 111, 112, ... 118, 119, 120 etc; 121, 122, ... 128, 129, 120 etc; 131, 132, ... 138, 139, 140 etc; 141, 142, ... 148, 149, 150 etc; 151, 152, ... 158, 159, 160 etc; 161, 162, ... 168, 169, 170 etc; 171, 172, ... 178, 179, 180 etc; 108, 182, ... 188, 189, 190 etc; 191, 192, ... 198, 199, 200 mg for each 400 mg of total weight of the solid formulation, preferably a tablet, comprising about 1 mg pimobendan. Furthermore, the amount of citric acid anhydrous may be 10, 11, 12, ... 18, 19, 20 etc.; 21, 22, ... 28, 29, 30 etc; 31, 32, ... 38, 39, 40 mg for each 400 mg of total weight of the solid formulation, preferably a tablet comprising about 1 mg pimobendan. Furthermore, the amount of artificial beef flavor may be 20, 21, 22, ... 28, 29, 30 etc.; 31, 32, ... 38, 39, 40 etc; 41, 42, ... 48, 49, 50 etc; 50, 51, 52, ... 58, 59, 60 etc.; 61, 62, ... 68, 69, 70 etc; 71, 72, ... 78, 79, 80 etc, 81, 82, 83,... 88, 89, 90 etc.; 91, 92, ... 98, 99, 100 etc; 101, 102, ... 108, 109, 110 etc; 111, 112, ... 118, 119, 120 mg for each 400 mg of total weight of the solid formulation, preferably a tablet, comprising about 1 mg pimobendan. Furthermore, the amount of polyvidone may be 4, 5, 6, ... 8, 9, 10 etc.; 11, 12, ... 18, 19, 20 mg for each 400 mg of total weight of the solid formulation, preferably a tablet, comprising about 1 mg pimobendan. Furthermore, the amount of croscarmellose-sodium may be 4, 5, 6, ... 8, 9, 10 etc.; 11, 12, ...

18, 19, 20 mg for each 400 mg of total weight of the solid formulation, preferably a tablet, comprising 1 mg pimobendan. Furthermore, the amount of magnesium stearate may be 1.0, 1.1, 1.2, ... 1.8, 1.9, 2.0 etc.; 2.1, 2.2, ... 2.8, 2.9, 3.0 etc; 3.1, 3.2, ... 3.8, 3.9, 40 etc; 4.0, 4.1, 4.2, ... 4.8, 4.9, 5.0 etc.; 5.1, 5.2, ... 5.8, 5.9, 6.0 mg for each 400 mg of total weight of the solid formulation, preferably a tablet, comprising about 1 mg pimobendan. Furthermore, the amount of colloidal anhydrous silica may be 0.4, 0.5, 0.6, 0,7,0.8, 0.9 1.0, 1.1, 1.2, ... 1.8, 1.9, 2.0 etc.; 2.1, 2.2, ... 2.8, 2.9, 3.0 etc; 3.1, 3.2, ... 3.8, 3.9, 4.0 mg for each 400 mg of total weight of the solid formulation, preferably a tablet, comprising about 1 mg pimobendan. A skilled man is in a position to prepare any of such inventive solid formulation, preferably as a tablet.

In another important embodiment, the invention relates to a fluid-bed granulation process comprising, preferably consisting of the steps:

a) an aqueous solution of pimobendan and a binder as defined above is sprayed onto a solid carrier bed comprising one or several carriers and/or excipients as defined above, flavor and citric acid anhydride and
b) the mixture of a) is dried and
c) the mixture of b) is sieved and de-agglomerated and
d) a flow regulator is added to the mixture of c) and
e) a lubricant is added to the mixture of d) and
f) the mixture of e) is blended for uniformity of granules to obtain final granules and/or
g) the final granules of f) are compressed to solid formulations.

Step g) is omitted if the solid formulation is a granule. If the solid formulation is a tablet, step g) is carried out.

The invention preferably relates to a fluid-bed granulation process comprising, preferably consisting of the steps:

a) an aqueous solution of pimobendan and polyvidone is sprayed onto a solid support comprising lactose, starch, flavor and citric acid anhydride and
b) the mixture of a) is dried and
c) the mixture of b) is sieved and de-agglomerated and
d) a flow regulator is added to the mixture of c) and
e) a lubricant is added to the mixture of d) and
f) the mixture of e) is blended for uniformity of granules to obtain final granules and/or
g) the final granules of f) are tabletted.

Step g) is omitted if the solid formulation is a granule. If the solid formulation is a tablet, step g) is carried out.

Another embodiment is a method of prevention and/or treatment of diseases wherein cardiotonic, hypotensive and anti-thrombotic substances have a therapeutic benefit, comprising administering to a mammal in need of such treatment a therapeutically effective amount of a solid formulation according to the invention as disclosed above. Preferred is a method of prevention and/or treatment of congestive heart failure, comprising administering to a mammal in need of such treatment a therapeutically effective amount of a solid formulation according to the invention as disclosed above. Most preferably, the method comprises administering a tablet according to the invention, characterized in that the tablet comprises, preferably consists of 1.25 mg, 2.5 mg, 5 mg or 10 mg pimobendan, and further comprises, preferably consists of lactose, corn starch, croscarmellose-sodium, citric acid preferably at an amount of 50 mg / g, artificial beef flavor, polyvidone, colloidal anhydrous silica and magnesium stearate. Preferably also, such treatment is by orally applying the solid formulation according to the invention.

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

Furthermore, the invention relates to a method for manufacturing a medicament for the prevention and/or treatment of congestive heart failure, characterised in that a solid formulation according to the invention is used. Preferably, the invention relates to a method for manufacturing a medicament for the prevention and/or treatment of congestive heart failure, characterised in that a tablet consisting of 1.25 mg, 2.5 mg, 5 mg or 10 mg pimobendan and further consisting of lactose, corn starch, croscarmellose-sodium, 50 mg / g citric acid, artificial beef flavor, polyvidone, colloidal anhydrous silica and magnesium stearate is used.

The present invention furthermore relates to a kit, comprises a solid formulation, preferably a tablet according to the present invention described herein, and a package leaflet or user instruction including the information that the solid formulation, preferably the tablet is to used, preferably via the oral route for the prevention and/or treatment of congestive heart failure in a mammal in need of such prevention or treatment, preferably in a dog, cat or rodent.

5. EXAMPLES

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

EXAMPLE 1: Compositions

Composition A

Ingredients	mg/tablet 1.25 mg chewable	mg/tablet 2.5 mg chewable	mg/tablet 5.0 mg chewable	Volatile ingre-dient	kg/batch
(01) Pimobendan	1.250	2.500	5.000		0.175
(02) Citric acid anhydrous < 200 µm	25.000	50.000	100.000		3.500
(03) Starch	163.125	326.250	652.500		22.8375

(04)	Lactose, coarse	163.125	326.250	652.500		22.8375
(05)	Polyvidon	20.000	40.000	80.000		2.800
(06)	Croscarmellose Sodium	20.000	40.000	80.000		2.800
(07)	Artificial Powdered Beef Flavour	100.000	200.000	400.000		14.000
(08)	Silica, colloidal anhydrous	2.500	5.000	10.000		0.350
(09)	Magnesium stearate	5.000	10.000	20.000		0.700
(10)	Purified water				+	
		500.000	1000.000	2000.000	-	70.000

Composition B

Ingredients	mg/tablet 1.25 mg chewable	mg/tablet 2.5 mg chewable	mg/tablet 5.0 mg chewable	Volatile ingre-dient	kg/batch
Pimobendan	1.250	2.500	5.000		0.175
Citric acid anhydrous < 200 μm	25.000	50.000	100.000		3.500
Starch	163.125	326.250	652.500		22.8375
Lactose, coarse	238.125	476.250	952.500		22.8375
Polyvidon	20.000	40.000	80.000		2.800
Croscarmellose Sodium	20.000	40.000	80.000		2.800
Meat Flavour	25.000	50.000	100.000		14.000
Silica, colloidal anhydrous	2.500	5.000	10.000		0.350
Magnesium stearate	5.000	10.000	20.000		0.700
Purified water				+	
	500.000	1000.000	2000.000	-	70.000

EXAMPLE 2: Raw Materials

(01) Pimobendan
Function: Active ingredient

(02) Citric acid anhydrous < 200 µm
Function: Diluent ,Disintegrant

(03) Starch
Function: Carrier,Disintegrant

(04) Lactose coarse
Function: Carrier, Disintegrant

(05) Povidone
Function: Binder

(06) Croscarmellose Sodium
Function: Disintegrant

(07) Artificial Powdered Beef Flavour
Function: Flavour

(08) Silica, colloidal anhydrous
Function: Flow regulator; Disintegrant

(09) Magnesium stearate
Function: Lubricant

(10) Purified water
Function: Solvent

EXAMPLE 3: Product description

Appearance: brownish, oblong tablets, with breakline.

	Tablet	Tablet	Tablet
Weight	500 mg	1000 mg	2000 mg
Length	About 19.0 mm	About 24.0 mm	About 25.0 mm
Width	About 7.0 mm	About 7.5 mm	About 15.0 mm
Thickness	About 4.2 mm	About 5.6 mm	About 6.0 mm

EXAMPLE 4: Manufacturing Process

1 batch = 140000 tablets (1.25 mg Dosage)
1 batch = 70000 tablets (2.50 mg Dosage)
1 batch = 35000 tablets (5.00 mg Dosage)

1. Granulating

	Transfer in a suitable Granulator after prescreening:	
(01)	Starch (e.g. 18 mesh sieve)	22.8375 k
(02)	Lactose (e.g. 18 mesh sieve)	22.8375 k
(03)	Citric acid anhydrous (e.g. 18 mesh sieve)	3.500 k
(04)	Croscarmellose sodium (e.g. 18 mesh sieve)	2.800 k
(05)	Artificial Beef Flavour (e.g. 45 mesh sieve)	14.000 k
(05)	Povidone (Spray solution)	2.800 k
(06)	UDCG 115 BS (Spray liquid)	0.175 k
	Premix in the granulator and granulate	
		68.950 k

Purified water (e.g. 16.8 kg, range: 12.0 – 18.0 kg) is used as a solvent for the spray solution of povidone and dispersion of pimobendan.

2. Screening

	Screen the premixture	1.	68.950 kg
			68.950 kg

3. Final mixing

	Add	
(07)	Sillica, colloidal anhydrous (e.g. 25 mesh sieve)	0.350 kg
(08)	Magnesium stearate (e.g. 25 mesh sieve)	0.700 kg
	In a tumbling mixer, mix the screened premixture (2.) and the two ingredients	70.000 kg
		70.000 kg

4. Compression

Using a rotary press, compress the final mixture (3.) into tablets of 500 mg, 1000mg, 2000 mg.	70.000 kg
	70.000 kg

5. Packaging

Transfer the tablets in a suitable container.
The tablets can be packed e.g. by blistering of the tablets in a suitable machine.

EXAMPLE 5: In process controls

1. Granules

1.1	Appearance:	Brownish, white-speckled granules
1.2	Loss on Drying:	Determine the loss on drying e.g.: HR73; 3 g /105 °C / 5 min Target: approx. 3.0 % Tolerance limits: below 5.0 %

2. Tablets

2.1	Appearance:	Brownish, white-speckled, oblong tablets with breakline	
2.2	Weight uniformity:	1) 1.25 mg chewable	Average weight: 475 – 525 mg
		2) 2.5 mg chewable	Average weight: 950 – 1050 mg
		3) 5 mg chewable	Average weight: 1900 – 2100 mg
2.3	Hardness:	Determine the hardness	
		1) 1.25 mg	Target: 140 N Tolerance: 60 – 250 N
		2) 2.5 mg	Target: 160 N Tolerance: 60 – 250 N
		3) 5.0 mg	Target 190 N Tolerance: 60 – 300 N
2.4	Disintegration time:	Determine the disintegration time according to USP/EP Tolerance limits: $\leq$ 15 minutes with water at 37°C, with disks	

EXAMPLE 6: Palatability study

A study to investigate the palatability of pimobendan-containing tablets was carried out. For a period of four days, two products were given to twenty or ten dogs, respectively, for voluntary uptake. For example, the following formulations with a content of 5 mg / 500 mg active ingredient were examined:

Ch. 010122 (tablets with 10 % content of artificial beef flavor)		Ch. 010123 (tablets with 10 % content of artificial beef flavor)	
Pimobendan (UD-CG 115 BS)	5 mg	Pimobendan (UD-CG 115 BS)	5 mg
Lactose	85,5 mg	Lactose	55,5 mg
Corn starch	199,5 mg	Corn starch	129,5 mg
Croscarmellose-Sodium	20 mg	Croscarmellose-Sodium	20 mg
Citric acid	100 mg	Citric acid	100 mg
Artificial Beef Flavor	50 mg	Artificial Beef Flavor	150 mg
Polyvidone	25 mg	Polyvidone	25 mg
Macrogol 6000	15 mg	Macrogol 6000	15 mg
	Total: 500 mg		Total: 500 mg

In case of Ch. 010123 in competition with the identical formulation in granulated format, a voluntary uptake was observed in 36 out of 40 possible opportunities (i.e. when offered to 10 dogs for 10 days),. This compares to an acceptance rate of 90,0 %.

In case of Ch. 010222 in competition with a formulation in granulated format of equal quantity with 30% flavor, a voluntary uptake was observed in 31 out of 40 possible opportunities. This compares to an acceptance rate of 77,5%.

EXAMPLE 7: Dissolution profiles

Examples for representative dissolution profiles of the tablet according to this invention are as disclosed in Fig. 3.

DISSOLUTION PROFILES, PIMOBENDAN 1.25 MG TABLETS
SHOWING 95 % CONFIDENCE INTERVALS OF THE MEAN

USP APPARATUS 2 (PADDLE), ROTATION SPEED 75 RPM, BUFFER pH 4.0
COMPARISON OF DISSOLUTION PROFILES OF TABLETS WHICH WERE STORED 1 AND 6 MONTHS AT 40°C/75 % IN HDPE BOTTLES

BATCH NO. PB020049

Examples for representative dissolution profiles of the tablet according to this invention are as disclosed in Fig. 4.

DISSOLUTION PROFILES, PIMOBENDAN 1.25 MG TABLETS
SHOWING 95 % CONFIDENCE INTERVALS OF THE MEAN

USP APPARATUS 2 (PADDLE), ROTATION SPEED 75 RPM, BUFFER pH 4.0
COMPARISON OF DISSOLUTION PROFILES OF TABLETS WHICH WERE STORED 12 DAYS AT 25°C/60% IN OPEN GLASS BOTTLES

BATCH NO. PB010080

DISSOLUTION PROFILES, PIMOBENDAN 1.25 MG TABLETS

MANUFACTURING VARIABLE: DIFFERENT COMPRESSION FORCES

Batch No.	Time (min)	% Dissolved, mean (n = 6) Tablet hardness			
		70 N	105 N	135 N	157 N
020102	10	82	82	81	84
	20	98	97	97	98
	30	101	99	100	100
	45	101	101	102	102

Examples for representative dissolution profiles of the tablet according to this invention are as disclosed in Fig. 5.

DISSOLUTION PROFILES, PIMOBENDAN 2.5 MG TABLETS
SHOWING 95 % CONFIDENCE INTERVALS OF THE MEAN

USP APPARATUS 2 (PADDLE), ROTATION SPEED 75 RPM, BUFFER pH 4.0
COMPARISON OF DISSOLUTION PROFILES OF TABLETS WHICH WERE STORED 3 AND 6 MONTHS AT 40°C/75 % IN ALU-ALU BLISTER

BATCH NO. PB010076

Examples for representative dissolution profiles of the tablet according to this invention are as disclosed in Fig. 6.

DISSOLUTION PROFILES, PIMOBENDAN 5.0 MG TABLETS
SHOWING 95 % CONFIDENCE INTERVALS OF THE MEAN

USP APPARATUS 2 (PADDLE), ROTATION SPEED 75 RPM, BUFFER pH 4.0
COMPARISON OF DISSOLUTION PROFILES OF TABLETS WHICH WERE STORED 6 MONTHS AT 40°C/75 % IN HDPE BOTTLES

BATCH NO. PB020059

Examples for representative dissolution profiles of the tablet according to this invention are as disclosed in Fig. 7.

DISSOLUTION PROFILES, PIMOBENDAN 5.0 MG TABLETS
SHOWING 95 % CONFIDENCE INTERVALS OF THE MEAN

USP APPARATUS 2 (PADDLE), ROTATION SPEED 75 RPM, BUFFER pH 4.0
MANUFACTURING VARIABLE: DIFFERENT COMPRESSION FORCES

BATCH NO. 020205

Batch No.	Time (min)	% Dissolved, mean (n = 6) Tablet hardness			
		117 N	150 N	186 N	222 N
020205	10	56	56	56	56
	20	76	75	76	76
	30	79	79	80	80
	45	80	80	81	81

Analytical Results for Pimobendan Chewable Tablet Batches Used in Stability Study

Tablet strength	Batch No.	Packaging	% dissolved in t = 30 minutes, mean (n = 6)			
			Initial value	6 Months 25°C/60 %	6 Months 30°C/70 %	6 Months 40°C/75 %
1.25 mg	PB020049	HDPE bottle	97	95	94	93
	PB020049	Alu-Alu blister		95	93	94
	PB020049	PVC/PVDC blister		94	93	93
	PB020050	HDPE bottle	94	92	93	91
	PB020050	Alu-Alu blister		92	92	91
	PB020050	PVC/PVDC blister		93	93	92
	PB020051	HDPE bottle	94	93	92	92
	PB020051	Alu-Alu blister		94	93	92
	PB020051	PVC/PVDC blister		93	93	91
2.5 mg	PB020052	HDPE bottle	98	n.d.	n.d.	93
	PB020052	Alu-Alu blister		n.d.	n.d.	94
	PB020052	PVC/PVDC blister		n.d.	n.d.	92
	PB020053	HDPE bottle	97	n.d.	n.d.	91
	PB020053	Alu-Alu blister		n.d.	n.d.	91
	PB020053	PVC/PVDC blister		n.d.	n.d.	91
	PB020054	HDPE bottle	97	n.d.	n.d.	91
	PB020054	Alu-Alu blister		n.d.	n.d.	92
	PB020054	PVC/PVDC blister		n.d.	n.d.	91
5.0 mg	PB020059	HDPE bottle	95	93	92	92
	PB020059	Alu-Alu blister		93	92	92
	PB020059	PVC/PVDC blister		92	92	91
	PB020060	HDPE bottle	92	91	90	89
	PB020060	Alu-Alu blister		91	91	90
	PB020060	PVC/PVDC blister		91	91	89
	PB020061	HDPE bottle	94	91	91	89
	PB020061	Alu-Alu blister		92	92	90
	PB020061	PVC/PVDC blister		91	91	89

n.d. = not determined

EXAMPLE 8: Content uniformity

Samples were taken from both the final blend before tabletting and from the tabletting process. The following results demonstrate the uniformity of pimobendan content.

Blend Uniformity

Batch	Assay[mg/g]	% Target
0007LP - A	2,37	94,8
0007LP - B	2,48	99,2
0007LP - C	2,43	97,2
0007LP - D	2,44	97,6
0007LP - E	2,47	98,8
0007LP - F	2,50	100,0
0007LP - G	2,49	99,6
0007LP - H	2,49	99,6
0007LP - I	2,50	100,0
0007LP - J	2,43	97,2
Average	**2,46**	**98,4**
0008LP - A	2,41	96,4
0008LP - B	2,48	99,2
0008LP - C	2,45	98,0
0008LP - D	2,45	98,0
0008LP - E	2,46	98,4
0008LP - F	2,43	97,2
0008LP - G	2,46	98,4
0008LP - H	2,44	97,6
0008LP - I	2,47	98,8
0008LP - J	2,50	100,0
Average	**2,46**	**98,2**

Uniformity of Process

Batch	Assay [mg/g]	% Target
PM020080 - 1	2,48	99,2
PM020080 - 2	2,52	100,8
PM020080 - 3	2,50	100,0
PM020080 - 4	2,52	100,8
PM020080 - 5	2,49	99,6
PM020080 - 6	2,52	100,8
Average	**2,51**	**100,2**
PM020081 - 1	2,45	98,0
PM020081 - 2	2,51	100,4
PM020081 - 3	2,48	99,2

PM020081 - 4	2,45	98,0
PM020081 - 5	2,47	98,8
PM020081 - 6	2,45	98,0
Average	**2,47**	**98,7**

EXAMPLE 9: Accuracy of broken tablets

The tablets according to this invention were part of an content uniformity test for the broken tablets. 10 tablets were taken from the beginning, middle and end of the tabletting process and broken into two halves. The pimobendan content was determined.

Pimobendan 5 mg tablet, batch no. 0000251607				
	Specification	Start	Middle	End
CU min. (mg)	≥ 2,13	2,44	2,43	2,41
CU max. (mg)	≤ 2,87	2,61	2,57	2,57
CU average (mg	2,25 – 2,62	2,52	2,51	2,50
RSD (%)	≤ 6,0	2,3	1,9	2,0

Pimobendan 1,25 mg tablet, batch no. 0000251604				
	Specification	Start	Middle	End
CU min. (mg)	≥ 0,532	0,577	0,590	0,582
CU max. (mg)	≤ 0,718	0,664	0,650	0,645
CU average (mg	0,563 – 0,656	0,621	0,621	0,616
RSD (%)	≤ 6,0	5,4	3,4	3,6

EXAMPLE 10: Stability data after 24 months (dissolution/ assay of pimobendan/ degradation of pimobendan)

Product: Pimobendan chewable tablets 1.25 mg				
		Batch No.: PB020049		
		HDPE bottle (m)	**PVC/PVDC (m)**	**Aluminium blister (m)**
Dissolution	**25°C/60°C**	0 months 95(min)-102(max)/97(avg); 24 months 96-99/97	0 months 95(min)-102(max)/97(avg); 24 months 96-99/97	0 months 95(min)-102(max)/97(avg); 24 months 92-96/94
	30°C/70°C	0 months 95(min)-102(max)/97(avg); 24 months 96-97/97	0 months 95(min)-102(max)/97(avg); 24 months 96-98/97	0 months 95(min)-102(max)/97(avg); 24 months 95-99/97
	40°C/75°C	0 months 95(min)-102(max)/97(avg); 6 months 92-94/93	0 months 95(min)-102(max)/97(avg); 6 months 91-94/93	0 months 95(min)-102(max)/97(avg); 6 months 92-95/94
		Batch No.:PB020049		
		HDPE bottle (m)	**PVC/PVDC (m)**	**Aluminium blister (m)**
Assay of Pimobendan	**25°C/60°C**	0 months 1.251; 24 months 1.233	0 months 1.251; 24 months 1.236	0 months 1.251; 24 months 1.237
	30°C/70°C	0 months 1.251; 24 months 1.229	0 months 1.251; 24 months 1.242	0 months 1.251; 24 months 1.236
	40°C/75°C	0 months 1.251; 6 months 1.221	0 months 1.251; 6 months 1.214	0 months 1.251; 6 months 1.231
		Batch No.:PB020049		
		HDPE bottle (m)	**PVC/PVDC (m)**	**Aluminium blister (m)**
Degradation of Pimobendan	**25°C/60°C**	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total); 24 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total); 24 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total); 24 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10
	30°C/7°C	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total); 24 months 1)<0.10; 2)0.10; 3)<0.10; 4)0.10	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total); 24 months 1)0.35; 2)<0.10; 3)<0.10; 4)0.35	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total); 24 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10
	40°C/75°C	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total); 6 months 1)0.10; 2)0.11; 3)<0.10; 4)0.21	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total);6 months 1)0.55; 2)<0.10; 3)<0.10; 4)0.55	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total); 6 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10

Product: Pimobendan chewable tablets 1.25 mg				
		Batch No.:PB020050		
		HDPE bottle (m)	**PVC/PVCD (m)**	**Aluminium blister (m)**
Dissolution	**25°C/60°C**	0 months 91(min)-96(max)/94(avg); 24 months 96-104/99	0 months 91(min)-96(max)/94(avg); 24 months 84-101/95	0 months 91(min)-96(max)/94(avg); 24 months 92-96/94
	30°C/70°C	0 months 91(min)-96(max)/94(avg); 24 months 94-102/97	0 months 91(min)-96(max)/94(avg); 24 months 93-102/97	0 months 91(min)-96(max)/94(avg); 24 months 97-105/99
	40°C/75°C	0 months 91(min)-96(max)/94(avg); 6 months 91-92/91	0 months 91(min)-96(max)/94(avg); 6 months 91-93/92	0 months 91(min)-96(max)/94(avg); 6 months 91-92/91
		Batch No.: PB020050		
		HDPE bottle (m)	**PVC/PVCD (m)**	**Aluminium blister (m)**
Assay of Pimobendan	**25°C/60°C**	0 months 1.231; 24 months 1.224	0 months 1.231; 24 months 1.201	0 months 1.231; 24 months 1.228
	30°C/70°C	0 months 1.231; 24 months 1.213	0 months 1.231; 24 months 1.217	0 months 1.231; 24 months 1.230
	40°C/75°C	0 months 1.231; 6 months 1.205	0 months 1.231; 6 months 1.202	0 months 1.231; 6 months 1.215
		Batch No.:PB020050		
		HDPE bottle (m)	**PVC/PVCD (m)**	**Aluminium blister (m)**
Degradation of Pimobendan	**25°C/60°C**	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total); 24 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total); 24 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total); 24 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10
	30°C/7°C	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total); 24 months1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total); 24 months 1)0.37; 2)<0.10;3)<0.10; 4)0.37	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total); 24 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10
	40°C/75°C	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total); 6 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total); 6 months 1)0.58; 2)<0.10; 3)<0.10; 4)0.58	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total); 6 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10

Product: Pimobendan chewable tablets 1.25 mg				
		Batch No.: PB020051		
		HDPE bottle (m)	**PVC/PVDC (m)**	**Aluminium blister (m)**
Dissolution	**25°C/60°C**	0 months 92(min)-95(max)/94(avg); 24 months 92-100/96	0 months 92(min)-95(max)/94(avg); 24 months 94-101/97	0 months 92(min)-95(max)/94(avg); 24 months 91-100/95
	30°C/70°C	0 months 92(min)-95(max)/94(avg); 24 months 92-99/96	0 months 92(min)-95(max)/94(avg); 24 months 95-98/97	0 months 92(min)-95(max)/94(avg); 24 months 92-100/97
	40°C/75°C	0 months 92(min)-95(max)/94(avg); 6 months 91-93/92	0 months 92(min)-95(max)/94(avg); 6 months 90-92/91	0 months 92(min)-95(max)/94(avg); 6 months 91-94/92
		Batch No.: PB020051		
		HDPE bottle (m)	**PVC/PVDC (m)**	**Aluminium blister (m)**
Assay of Pimobendan	**25°C/60°C**	0 months 1.230; 24 months 1.222	0 months 1.230; 24 months 1.225	0 months 1.230; 24 months 1.228
	30°C/70°C	0 months 1.230;24 months 1.214	0 months 1.230; 24 months 1.221	0 months 1.230; 24 months 1.230
	40°C/75°C	0 months 1.230;6 months 1.210	0 months 1.230; 6 months 1.202	0 months 1.230; 6 months 1.218
		Batch No.PB020051		
		HDPE bottle (m)	**PVC/PVDC (m)**	**Aluminium blister (m)**
Degradation of Pimobendan	**25°C/60°C**	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total); 24 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total); 24 months1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total);
	30°C/7°C	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total); 24 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total); 24 months 1)<0.33; 2)<0.10; 3)<0.10; 4)0.33	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total);
	40°C/75°C	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total); 6 months 1)<0.10; 2)0.10; 3)<0.10; 4)0.10	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total); 6 months 1)<0.54; 2)<0.10; 3)<0.10; 4)<0.54	0 months 1)<0.10(K 2006a);2)<0.10(DU-CG 134 BS);3)<0.10(any unspecified);4)<0.10(total);

Product: Pimobendan chewable tablets 2.5 mg				
		Batch No.: PB020052		
		HDPE bottle (m)	**PVC/PVDC (m)**	**Aluminium blister (m)**
Dissolution	**30°C/70°C**	0 months 97(min)-99(max)/98(avg); 12 Months 93-95/94	0 months 97(min)-99(max)/98(avg); 12 months 93-94/94	0 months 97(min)-99(max)/98(avg); 12 months 94-97/96
	40°C/75°C	0 months 97(min)-99(max)/98(avg); 6 months 93-94/93	0 months 97(min)-99(max)/98(avg); 6 months 91-93/92	0 months 97(min)-99(max)/98(avg); 6 months 93-95/94
		Batch No.:PB020052		
		HDPE bottle (m)	**PVC/PVDC (m)**	**Aluminium blister (m)**
Assay of Pimobendan	**30°C/70°C**	0 months 2.49; 12 months 2.49	0 months 2.49; 12 months 2.47	0 months 2.49; 12 months 2.50
	40°C/75°C	0 months 2.49; 6 months 2.41	0 months 2.49; 6 months 2.41	0 months 2.49; 6 months 2.45
		Batch No.:PB020052		
		HDPE bottle (m)	**PVC/PVDC (m)**	**Aluminium blister (m)**
Degradation of Pimobendan	**30°C/7°C**	0 months 1)<0.10(K2006a); 2)<0.10(UDCG 134 BS); 3)<0.10 (any unspecified); 4)<0.10(total); 12 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10	0 months 1)<0.10(K2006a); 2)<0.10(UDCG 134 BS); 3)<0.10 (any unspecified); 4)<0.10(total); 12 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10	0 months 1)<0.10(K2006a); 2)<0.10(UDCG 134 BS); 3)<0.10 (any unspecified); 4)<0.10(total); 12 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10
	40°C/75°C	0 months 1)<0.10(K2006a); 2)<0.10(UDCG 134 BS); 3)<0.10 (any unspecified); 4)<0.10(total); 6 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10	0 months 1)<0.10(K2006a); 2)<0.10(UDCG 134 BS); 3)<0.10 (any unspecified); 4)<0.10(total); 6 months 1)0.43; 2)<0.10; 3)<0.10; 4)0.43	0 months 1)<0.10(K2006a); 2)<0.10(UDCG 134 BS); 3)<0.10 (any unspecified); 4)<0.10(total); 6 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10

Product: Pimobendan chewable tablets 2.5 mg				
		Batch No.:PB020053		
		HDPE bottle (m)	**PVC/PVCD (m)**	**Aluminium blister (m)**
Dissolution	**30°C/70°C**	0 months 96(min)-98(max)/97(avg); 12 months 92-94/93	0 months 96(min)-98(max)/97(avg); 12 months 90-93/92	0 months 96(min)-98(max)/97(avg);12 months 91-95/93
	40°C/75°C	0 months 96(min)-98(max)/97(avg); 6 months 89-93/91	0 months 96(min)-98(max)/97(avg); 6 months 91-91/91	0 months 96(min)-98(max)/97(avg); 6 months 90-92/91
		Batch No.: PB020053		
		HDPE bottle (m)	**PVC/PVCD (m)**	**Aluminium blister (m)**
Assay of Pimobendan	**30°C/70°C**	0 months 2.44;12 months 2.44	0 months 2.44; 12 months 2.41	0 months 2.44; 12 months 2.46
	40°C/75°C	0 months 2.44; 6 months 2.41	0 months 2.44; 6 months 2.40	0 months 2.44; 6 months 2.40
		Batch No.:PB020053		
		HDPE bottle (m)	**PVC/PVCD (m)**	**Aluminium blister (m)**
Degradation of Pimobendan	**30°C/7°C**	0 months 1)<0.10(K2006a); 2)<0.10(UDCG 134 BS); 3)<0.10 (any unspecified); 4)<0.10(total); 12 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10	0 months 1)<0.10(K2006a); 2)<0.10(UDCG 134 BS); 3)<0.10 (any unspecified); 4)<0.10(total); 12 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10	0 months 1)<0.10(K2006a); 2)<0.10(UDCG 134 BS); 3)<0.10 (any unspecified); 4)<0.10(total); 12 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10
	40°C/75°C	0 months 1)<0.10(K2006a); 2)<0.10(UDCG 134 BS); 3)<0.10 (any unspecified); 4)<0.10(total); 6 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10	0 months 1)<0.10(K2006a); 2)<0.10(UDCG 134 BS); 3)<0.10 (any unspecified); 4)<0.10(total); 6 months 1)0.39; 2)<0.10; 3)<0.10; 4)0.39	0 months 1)<0.10(K2006a); 2)<0.10(UDCG 134 BS); 3)<0.10 (any unspecified); 4)<0.10(total); 6 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10

Product: Pimobendan chewable tablets 2.5 mg				
		Batch No.: PB020054		
		HDPE bottle (m)	**PVC/PVDC (m)**	**Aluminium blister (m)**
Dissolution	**30°C/70°C**	0 months 96(min)-98(max)/97(avg); 12 months 93-95/94	0 months 96(min)-98(max)/97(avg); 12 months 90-93/91	0 months 96(min)-98(max)/97(avg); 12 months 93-94/94
	40°C/75°C	0 months 96(min)-98(max)/97(avg); 6 months 90-92/91	0 months 96(min)-98(max)/97(avg); 6 months 90-92/91	0 months 96(min)-98(max)/97(avg); 6 months 91-93/92
		Batch No.: PB020054		
		HDPE bottle (m)	**PVC/PVDC (m)**	**Aluminium blister (m)**
Assay of Pimobendan	**30°C/70°C**	0 months 2.45; 12 months 2.47	0 months 2.45; 12 months 2.45	0 months 2.45; 12 months 2.44
	40°C/75°C	0 months 2.45; 6 months 2.40	0 months; 6 months 2.39	0 months 2.45; 6 months 2.41
		Batch No.PB020054		
		HDPE bottle (m)	**PVC/PVDC (m)**	**Aluminium blister (m)**
Degradation of Pimobendan	**30°C/7°C**	0 months 1)<0.10(K2006a); 2)<0.10(UDCG 134 BS); 3)<0.10 (any unspecified); 4)<0.10(total); 12 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10	0 months 1)<0.10(K2006a); 2)<0.10(UDCG 134 BS); 3)<0.10 (any unspecified); 4)<0.10(total); 12 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10	0 months 1)<0.10(K2006a); 2)<0.10(UDCG 134 BS); 3)<0.10 (any unspecified); 4)<0.10(total); 12 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10
	40°C/75°C	0 months 1)<0.10(K2006a); 2)<0.10(UDCG 134 BS); 3)<0.10 (any unspecified); 4)<0.10(total); 6 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10	0 months 1)<0.10(K2006a); 2)<0.10(UDCG 134 BS); 3)<0.10 (any unspecified); 4)<0.10(total); 6 months 1)0.36; 2)<0.10; 3)<0.10; 4)0.36	0 months 1)<0.10(K2006a); 2)<0.10(UDCG 134 BS); 3)<0.10 (any unspecified); 4)<0.10(total); 6 months 1)<0.10; 2)<0.10; 3)<0.10; 4)<0.10

Product: Pimobendan chewable tablets 5 mg				
		Batch No.: PB020059		
		HDPE bottle (m)	**PVC/PVDC (m)**	**Aluminium blister (m)**
Dissolution	**25°C/60%**	0 months 94 (min)-96 (max)/95 (avg); 24 months 83-90/88	0 months 94 (min)-96 (max)/95 (avg); 24 months 83-92/88	0 months 94 (min)-96 (max)/95 (avg); 24 months 85-89/87
	30°C/70°C	0 months 94 (min)-96 (max)/95 (avg); 24 months 83-95/89	0 months 94 (min)-96 (max)/95 (avg); 24 months 82-97/88	0 months 94 (min)-96 (max)/95 (avg); 24 months 83-91/87
	40°C/75°C	0 months 94 (min)-96 (max)/95 (avg); 6 months 91-92/91	0 months 94 (min)-96 (max)/95 (avg); 6 months 90-92/91	0 months 94 (min)-96 (max)/95 (avg); 6 months 81-93/92
		Batch No.: PB020059		
		HDPE bottle (m)	**PVC/PVDC (m)**	**Aluminium blister (m)**
Assay of Pimobendan	**25°C/60%**	0 month 4.95; 24 month 4.94	0 month 4.95; 24 month 4.92	0 month 4.95; 24 month 4.92
	30°C/70°C	0 month 4.95; 24 month 4.90	0 month 4.95; 24 month 4.92	0 month 4.95; 24 month 4.96
	40°C/75°C	0 month 4.95; 6 month 4.88	0 month 4.95; 6 month 4.91	0 month 4.95; 6 month 4.95
		Batch No.:PB020059		
		HDPE bottle (m)	**PVC/PVDC (m)**	**Aluminium blister (m)**
Degradation of Pimobendan	**25°C/60%**	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 24 months 1) <0.10; 2) <0.10; 3) <0.10; 4) <0.10	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 24 months 1) <0.10; 2) <0.10; 3) <0.10; 4) <0.10	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 24 months 1) <0.10; 2) <0.10; 3) <0.10; 4) <0.10
	30°C/7°C	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 24 months 1) <0.10; 2) <0.10; 3) <0.10; 4) <0.10	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 24 months 1) <0.10; 2) <0.10; 3) <0.10; 4) <0.10	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 24 months 1) <0.10; 2) <0.10; 3) <0.10; 4) <0.10
	40°C/75°C	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 6 months 1) <0.10; 2) <0.10; 3) <0.10; 4) < 0.10	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 6 months 1) 0.23; 2) <0.10; 3) <0.10; 4) 0.23	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 6 months 1) <0.10; 2) <0.10; 3) <0.10; 4) <0.10

Product: Pimobendan chewable tablets 5 mg				
		Batch No.:PB020060		
		HDPE bottle (m)	**PVC/PVCD (m)**	**Aluminium blister (m)**
Dissolution	**25°C/60%**	0 months 91 (min)-94 (max)/92 (avg); 24 months 85-90/87	0 months 91 (min)-94 (max)/92 (avg); 24 months 84-90/86	0 months 91 (min)-94 (max)/92 (avg); 24 months 82-88/86
	30°C/70°C	0 months 91 (min)-94 (max)/92 (avg); 24 months 85-90/87	0 months 91 (min)-94 (max)/92 (avg); 24 months 82-90/87	0 months 91 (min)-94 (max)/92 (avg); 24 months 86-90/88
	40°C/75°C	0 months 94 (min)-96 (max)/95 (avg); 6 months 88-89/89	0 months 91 (min)-94 (max)/92 (avg); 6 months 88-90/89	0 months 91 (min)-94 (max)/92 (avg); 6 months 89-92/90
		Batch No.: PB020060		
		HDPE bottle (m)	**PVC/PVDC (m)**	**Aluminium blister (m)**
Assay of Pimobendan	**25°C/60%**	0 month 4.87; 24 month 4.88	0 month 4.87; 24 month 4.86	0 month 4.87; 24 month 4.90
	30°C/70°C	0 month 4.87; 24 month 4.83	0 month 4.87; 24 month 4.86	0 month 4.84; 24 month 4.89
	40°C/75°C	0 month 4.87; 6 month 4.86	0 month 4.87; 6 month 4.87	0 month 4.87; 6 month 4.86
		Batch No.:PB020060		
		HDPE bottle (m)	**PVC/PVCD (m)**	**Aluminium blister (m)**
Degradation of Pimobendan	**25°C/60%**	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 24 months 1) <0.10; 2) <0.10; 3) <0.10; 4) <0.10;	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 24 months 1) <0.10; 2) <0.10; 3) <0.10; 4) <0.10;	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 24 months 1) <0.10; 2) <0.10; 3) <0.10; 4) <0.10;
	30°C/7°C	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 24 months 1) <0.10; 2) <0.10; 3) <0.10; 4) <0.10;	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 24 months 1) <0.10; 2) <0.10; 3) <0.10; 4) <0.10;	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 24 months 1) <0.10; 2) <0.10; 3) <0.10; 4) <0.10;
	40°C/75°C	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 6 months 1) <0.10; 2) <0.10; 3) <0.10; 4) <0.10	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 24 months 1) <0.10; 2) <0.10; 3) <0.10; 4) <0.10; 6 months 1) 0.22; 2) <0.10; 3) <0.10; 4) 0.22	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 6 months 1) <0.10; 2) <0.10; 3) <0.10; 4) <0.10

Product: Pimobendan chewable tablets 5 mg				
		Batch No.: PB020061		
		HDPE bottle (m)	**PVC/PVDC (m)**	**Aluminium blister (m)**
Dissolution	**25°C/60%**	0 months 92 (min)-95 (max)/94 (avg); 24 months 83-90/87	0 months 92 (min)-95 (max)/94 (avg); 24 months 86-91/88	0 months 92 (min)-95 (max)/94 (avg); 24 months 65-92/84
	30°C/70°C	0 months 92 (min)-95 (max)/94 (avg); 24 months 84-88/87	0 months 92 (min)-95 (max)/94 (avg); 24 months 81-87/85	0 months 92 (min)-95 (max)/94 (avg); 24 months 88-91/90
	40°C/75°C	0 months 92 (min)-95 (max)/94 (avg); 6 months 88-90/89	0 months 92 (min)-95 (max)/94 (avg); 6 months 88-90/89	0 months 92 (min)-95 (max)/94 (avg); 6 months 88-91/90
		Batch No.:PB020061		
		HDPE bottle (m)	**PVC/PVCD (m)**	**Aluminium blister (m)**
Assay of Pimobendan	**25°C/60%**	0 month 4.87; 24 month 4.83	0 month 4.87; 24 month 4.85	0 month 4.87; 24 month 4.88
	30°C/70°C	0 month 4.87; 24 month 4.82	0 month 4.87; 24 month 4.80	0 month 4.87; 24 month 4.90
	40°C/75°C	0 month 4.87; 6 month 4.83	0 month 4.87; 6 month 4.82	0 month 4.87; 6 month 4.88
		Batch No.PB020061		
		HDPE bottle (m)	**PVC/PVDC (m)**	**Aluminium blister (m)**
Degradation of Pimobendan	**25°C/60%**	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 24 months 1) <0.10; 2) <0.10; 3) <0.10; 4) <0.10;	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 24 months 1) <0.10; 2) <0.10; 3) <0.10; 4) <0.10;	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 24 months 1) <0.10; 2) <0.10; 3) <0.10; 4) <0.10
	30°C/7°C	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 24 months 1) <0.10; 2) <0.10; 3) <0.10; 4) <0.10;	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 24 months 1) <0.10; 2) <0.10; 3) <0.10; 4) <0.10;	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 24 months 1) <0.10; 2) <0.10; 3) <0.10; 4) <0.10
	40°C/75°C	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 6 months 1) <0.10; 2) <0.10; 3) <0.10; 4) <0.10	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 6 months 1) 0.22; 2) <0.10; 3) <0.10; 4) 0.22	0 months 1)<0.10 (K 2006a); 2) <0.10 (UD-CG 134 BS); 3) <0.10 (any unspecified); 4) <0.10 (total); 6 months 1) <0.10; 2) <0.10; 3) <0.10; 4) <0.10

CLAIMS

1. A solid formulation, comprising pimobendan or a pharmaceutically acceptable salt thereof which is homogenously dispersed in a polyvalent acid selected from the group of citric acid, tartaric acid or its anhydride, and a flavor for small animals.

2. A solid formulation according to claim 1, further comprising pharmaceutically acceptable carriers and/or excipients.

3. A solid formulation according to claim 1 or 2, ***characterized*** in that the carriers and/or excipients are selected from the group consisting of diluents, disintegrants, carriers, binders, flow regulators, lubricants and solvents.

4. A solid formulation according to any one of claims 1 to 3, ***characterized*** in that the carriers are starch and lactose.

5. A solid formulation according to any one of claims 1 to 4, ***characterized*** in that the starch or various starches are selected from the group consisting of native starch, gelatinized starch, partly gelatinized starch, starch powder, starch granules, chemically modified starch and swellable physically modified starch.

6. A solid formulation according to any one of claims 1 to 5, ***characterized*** in that the starch is corn starch.

7. A solid formulation according to any one of claims 1 to 6, ***characterized*** in that the lactose consists of coarse particles greater than 200, μm in size.

8. A solid formulation according to any one of claims 1 to 7, comprising 0,5 to 20 mg of pimobendan

9. A solid formulation according to any one of claims 1 to 8, comprising 1,25 mg, 2,5 mg, 5 mg or 10 mg of pimobendan.

10. A solid formulation according to any one of claims 1 to 9, ***characterized*** in that the weight of the whole solid formulation is in the range of 250 to 3000 mg.

11. A solid formulation according to any one of claims 1 to 10, ***characterized*** in that the solid formulation or tablet consists of 1.25 mg, 2.5 mg, 5 mg or 10 mg pimobendan, and further consists of lactose, corn starch, croscarmellose-sodium, 50 mg/g citric acid, artificial beef flavor, polyvidone, colloidal anhydrous silica and magnesium stearate.

12. A solid formulation according to any one of claims 1 to 11, ***characterized*** in that the solid formulation is a tablet or a granule.

13. Fluid-bed granulation process comprising the steps:
a) an aqueous solution of pimobendan and a binder is sprayed onto a solid support comprising one or several carriers and/or excipients, flavor and citric acid anhydride and
b) the mixture of a) is dried and
c) the mixture of b) is sieved and de-agglomerated and
d) a flow regulator is added to the mixture of c) and
e) a lubricant is added to the mixture of d) and
f) the mixture of e) is blended for uniformity of granules to obtain final granules and/or
g) the final granules of f) are tabletted.

14. Fluid-bed granulation process according to claim 13, comprising the steps:
a) an aqueous solution of pimobendan and povidone is sprayed onto a solid support comprising lactose, starch, flavor and citric acid anhydride and
b) the mixture of a) is dried and

c) the mixture of b) is sieved and de-agglomerated and

d) a flow regulator is added to the mixture of c) and

e) a lubricant is added to the mixture of d) and

f) the mixture of e) is blended for uniformity of granules to obtain final granules and/or

g) the final granules of f) are tabletted.

15. A solid formulation according to any one of claims 1 to 12 for treating congestive heart failure.