9 July 2015
EMA/469409/2015
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for FORTEKOR PLUS (EMEA/V/C/002804/0000)

International non-proprietary name: pimobendan / benazepril

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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Introduction

On 21 November 2013, the applicant Novartis Healthcare A/S submitted an application for a marketing authorisation to the European Medicines Agency (the Agency) for FORTEKOR PLUS, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004 (new active substance). The name of the applicant was subsequently changed during the procedure to Elanco Europe Ltd.

The eligibility to the centralised procedure was agreed upon by the CVMP on 11–13 September 2012 as falling under Article 3(2)(a) of Regulation (EC) No 726/2004 as FORTEKOR PLUS contains a new combination of two existing active substances, pimobendan and benazepril hydrochloride, which were not authorised in combination in the Community on the date of entry into force of the Regulation.

The rapporteur appointed was C. Friis and co-rapporteur C. Muñoz.

The applicant initially applied for the following indication: "For the treatment of congestive heart failure due to atrioventricular valve insufficiency or dilated cardiomyopathy in dogs."

The dossier has been submitted in line with the requirements for submissions under Article 13(b) of Directive 2001/82/EC (fixed combination application).

FORTEKOR PLUS tablets contain two active substances: pimobendan and benazepril hydrochloride. There are two different strength tablets, containing 1.25 mg/2.5 mg and 5 mg/10 mg pimobendan/benazepril hydrochloride respectively. The tablets are contained in blister packs (aluminium/aluminium) which are supplied in outer cartons containing 30 or 60 tablets, for both tablet strengths. The route of administration is oral. The target species is dogs.

The CVMP adopted an opinion and CVMP assessment report on 9 July 2015.

On 8 September 2015, the European Commission adopted a Commission Decision granting the marketing authorisation for FORTEKOR PLUS.

Scientific advice

The applicant received scientific advice from the CVMP on 14 July 2011 and clarification on 10 November 2011. The scientific advice pertained to clinical aspects of the dossier. CVMP advised that a fixed combination product of benazepril and pimobendan is relevant for a certain group of congestive heart failure (CHF) patients, that is, dogs which require treatment with both an angiotensin converting enzyme (ACE) inhibitor and pimobendan. CVMP further advised that the applicant has to demonstrate non-inferiority of the combination product to a treatment protocol comprising all the individual active substances. CVMP also advised that if the intention is to show that the fixed combination product performs similar to the two components given concomitantly in a group of dogs where the need for the two components given at this certain dose level and interval has been confirmed, no field data would be needed provided bioequivalence is shown.

The applicant followed the bioequivalence approach.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (Elanco Animal Health, dated September 2013) which fulfils the requirements of Directive 2001/82/EC. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse event occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

Pimobendan is manufactured in the European Union (EU).

Several sites inside and outside Europe are involved in the manufacture of benazepril hydrochloride (HCl).

The benazepril pellets are manufactured in the EU.

The finished product is manufactured and packaged in the EU. LEK Pharmaceuticals, Ljubljana, Slovenia are responsible for batch release. A manufacturing authorisation was issued on 3 April 2013 by the Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP).

A declaration, signed by the qualified person (QP) at the batch release site, was provided confirming that the suppliers of the active substances, pimobendan and benazepril hydrochloride, operate in compliance with good manufacturing practice (GMP). This declaration is based on audits at the suppliers.

No concerns have been raised during the assessment that would give rise to any manufacturing site inspection prior to authorisation.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system is considered in line with legal requirements.

The GMP status and manufacturing authorisation for both the active substance and dosage form manufacturing sites have been satisfactorily established and are in line with legal requirements.

In addition, the applicant is recommended to provide the following information post authorisation:

- An update of the DDPS that includes a revised flow diagram including suspected transmission of infectious agents in third countries among expedited reports and also the example of a contractual agreement between Elanco and distributors for the exchange of pharmacovigilance data.

Part 2 - Quality

Composition

The proposed veterinary medicinal product is available in two strengths, containing, either 1.25 mg pimobendan and 2.5 mg benazepril HCl, or 5 mg pimobendan and 10 mg benazepril HCl, and is formulated as uncoated bilayered tablets.

FORTEKOR PLUS tablets include the following excipients: succinic acid, polysorbate 80, hypromellose, maize starch, lactose monohydrate, starch pregelatinised, croscarmellose sodium, iron oxide brown, copovidone, silica colloidal anhydrous, magnesium stearate, cellulose microcrystalline, compressible sugar, crospovidone, povidone K-30, basic butylated methacrylate copolymer, sodium laurilsulfate, dibutyl sebacate and artificial special dry flavour. In addition, ethanol (96%) and purified water are used during the manufacture of the finished product.

Container

Aluminium blisters consisting of aluminium blister-forming and aluminium lidding (peel-off) foils are used as primary packaging components to ensure adequate protection of the tablets from moisture.

The proposed pack sizes for both strengths are 30 tablets (3 blister strips, each containing 10 tablets) and 60 tablets (6 blister strips, each containing 10 tablets). The aluminium blisters are supplied in cardboard boxes (secondary packaging).

Appropriate documentation has been provided for the finished product commercial packaging (aluminium blisters). Compliance of the primary packaging materials in contact with the product with Commission Regulation (EU) 10/2011, as amended by Commission Regulation (EU) 1183/2012, has been documented.

Development pharmaceutics

A comprehensive report on development pharmaceutics is presented and indicates that the formulation, method of manufacture and dissolution test have been carefully selected and justified.

The objective was to develop fixed combination tablets of benazepril HCl and pimobendan, as these two active substances are already commercially available as monocomponent products. The formulation development was focused on a bilayer tablet formulation, with the pimobendan and benazepril HCl separated in different layers.

For the pimobendan layer of the tablets, the excipients and their amounts chosen were based on the intended manufacturing process and the physico-chemical characteristics of pimobendan.

For the benazepril monolayer, benazepril pellets were used

The pharmaceutical development section is considered comprehensive.

The choice of the raw materials incorporated in the formulation is discussed and justified.

Method of manufacture

The manufacturing process of the finished product is based on direct compression of both the final granulate of the pimobendan layer and the final mixture for the benazepril layer.

Satisfactory in-process controls are in place at each stage. Full validation has been conducted with production batches for each strength of the tablets.

The manufacturing process is considered reliable and able to produce a consistent finished product.

Control of starting materials

Active substances

Benazepril hydrochloride:

Benazepril hydrochloride is a known active substance, included in veterinary and human medicinal products already authorised in the EU, and is the subject of a monograph in the European Pharmacopoeia (Ph. Eur.). Full documentation is provided in the dossier.

The molecule has the potential for four different isomers. However, the design of the manufacturing process ensures synthesis of one specific isomer with only small amounts of the other isomers. Three crystal forms have been identified which depend on the water content. The complete removal of water in the final purification step ensures that only the anhydrous form is obtained.

The specification includes all the parameters in the Ph. Eur. monograph for this substance plus appropriate tests and limits for identification, heavy metals, identity of impurities and assay by HPLC and particle size. Other test methods are standard pharmacopoeial methods. Descriptions for all analytical methods are presented and the methods have been appropriately validated in accordance with the VICH guidelines.

Comparative batch analysis data is provided for an appropriate number of production scale batches of active substance manufactured with the intermediate from the different suppliers proposed. No significant differences are observed in the quality of the active substance obtained from the different sources as all parameters comply with the active substance specification and the results demonstrate consistency from batch to batch.

Pimobendan:

Pimobendan is also a known active substance and is also the subject of a monograph in the Ph. Eur. The information for this active substance is presented in an active substance master file (ASMF).

Pimobendan exhibits polymorphism. However, all tested batches are concordant with only one polymorph, which complies with the Ph. Eur. reference standard. The pimobendan molecule has one asymmetric carbon atom however pimobendan is optically inactive because neither chiral starting materials nor chiral reagents are used in the manufacturing process.

The specification includes all the parameters in the Ph. Eur. monograph for this substance plus appropriate and limits for residual solvents and particle size. Other test methods are standard pharmacopoeial methods.

Batch analysis data for four production scale batches are provided and all parameters comply with the active substance specification. The results demonstrate consistency from batch to batch.

Excipients

The majority of the excipients used to manufacture the finished product are described in the Ph. Eur: polysorbate 80, hypromellose, maize starch, lactose monohydrate, starch pregelatinised, croscarmellose sodium, copovidone, silica colloidal anhydrous, magnesium stearate, cellulose microcrystalline, crospovidone, povidone K-30, basic butylated methacrylate copolymer and sodium laurilsulfate. These Ph. Eur. excipients are tested according to, and comply with, the requirements of the respective monographs. Certificates of analysis for each of these excipients are presented.

Succinic acid, compressible sugar and dibutyl sebacate are described in the US Pharmacopoeia or US National Formulary (NF) and corresponding certificates of analysis have been presented.

Two non-pharmacopoeial excipients are used in the finished product, iron oxide brown and artificial special dry flavour.

Iron oxide brown (E172) is used as a colorant for the pimobendan layer of the finished product and an in-house specification is provided which is considered appropriate. Iron oxide brown (E172) complies with Directive 94/36/EC (colours for use in foodstuffs) and with the specifications of the Annex of Regulation (EU) 231/2012, laying down specific purity criteria concerning colours for use in foodstuffs.

Artificial special dry flavour is used as a flavour in the finished product. The flavour is a commercially available mixture of known excipients. Although it is not listed in any pharmacopoeia, the individual components are described in the Ph. Eur. and an in-house specification is provided which is considered appropriate.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The only material of animal origin used in the finished product is lactose monohydrate, however confirmation is provided that this is manufactured from bovine milk sourced from healthy animals in the same conditions as milk collected for human consumption.

None of the starting materials used for the two active substances (pimobendan and benazepril HCl) or the finished product are risk materials as defined in the current version of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 Rev.3). The product is therefore out of scope of the relevant Ph. Eur. monograph and the Note for guidance.

TSE declarations for the FORTEKOR PLUS components from each of the manufacturers are submitted accordingly.

Control tests during production

Satisfactory in-process controls are in place at different stages of the manufacturing process.

Stability studies for the pellets have been submitted for one batch of the benazepril pellets in order to support a 6 month retest period for this intermediate product.

Control tests on the finished product

Descriptions of the methods used for the control of the finished product and the specification limits were provided. The specification limits are in accordance with current EU and VICH guidance and are appropriate to control the quality of the finished product. The tests include appearance (visual examination), water content (Ph. Eur. 2.5.12), dissolution (in-house HPLC method), identification and assay of pimobendan and benazepril HCl (in-house HPLC method) plus a second identification method (HPLC/PDA) for both active substances, uniformity of dosage units (Ph. Eur. 2.9.40 and in-house HPLC method), degradation products of pimobendan and of benazepril HCl (in-house HPLC methods), residual solvents (in-house method) and microbial contamination (Ph. Eur. 2.6.12, 2.6.13).

Different limits have been proposed for use at time of release and at end of shelf life for the following tests: assay for pimobendan and benazepril HCl, and impurities related to benazepril HCl. This has been justified.

The shelf life limit of an impurity of benazepril HCl is above the qualification threshold of 1.0% specified in VICH GL11 on Impurities in new veterinary medicinal products. However, based on chronic toxicological data in dogs this impurity is considered qualified. The proposed limit for impurity C is based on the results obtained in stability studies.

The results of the analysis of three batches of each of the two strengths of tablet are provided which comply with the release specifications.

Stability

Benazepril hydrochloride: stability studies have been performed on an appropriate number of batches of the active substance manufactured with the intermediate from each of the suppliers. Results of the tests demonstrate the active substance to be stable with no adverse trends in any of the parameters investigated. A re-test period of 5 years, with no special storage conditions when stored in polyethylene bags within metal containers, is considered to be adequately supported.

Pimobendan: stability studies have been performed on four production batches of the active substance. Results of the tests demonstrate the active substance to be stable with no adverse trends in any of the parameters investigated. A re-test period of 5 years, with no special temperature storage conditions when stored in polyethylene bags within metal containers, is considered to be adequately supported.

Stability studies on the finished product have been performed under VICH real time, intermediate and accelerated conditions (i.e., 25 °C/60% RH, 30 °C/65% RH and 40 °C/75% RH) for up to 36 months, 12 months, and 6 months respectively. To date, 6 months accelerated, 12 months intermediate and 36 months long-term stability data are available for 3 batches of each strength of the product. The analytical procedures used are stability indicating.

Under accelerated testing conditions a substantial decrease in assay and an increase in total degradation products for the benazepril HCl, above the proposed shelf life specification limit, was observed. Furthermore, after storage at long term and intermediate conditions, a high variability in the content of benazepril HCl was detected. A decrease of more than 5% from its initial value was found in 3 out of 6 batches stored at both conditions. Therefore, a shelf life of only 18 months when stored below 25 °C is considered justified.

Photostability: Light stability studies conducted in accordance with VICH Guideline GL5: Photostability testing of new veterinary drug substances and medicinal products, showed that all tested parameters complied with their specifications and the finished product is not considered sensitive to light.

Stability of the product in bulk: Bulk storage was simulated by storing one batch of tablets in aluminium bags under both accelerated and long term stability testing conditions. Two additional batches (one of each proposed strength; stored in the aluminium bags) have been placed at these stability testing conditions and 3 months stability data have been submitted to date confirming the results of the previous study. The results of tablets packed in bulk did not differ from the results of tablets packed in the primary packaging material. Therefore when the bulk tablets are stored in aluminium bags (prior to packaging into blister packs) their proposed shelf life of 12 months has been justified.

A shelf life of 3 years with the special storage condition "Do not store above 25 °C. Store in the original package in order to protect from moisture." was initially proposed by the applicant for the finished product, however the data currently available only support a shelf life of 18 months. Furthermore the age of the pellets (maximum 6 months) is taken into account when calculating the expiration date. This is in accordance with the current EU guidance ('Note for guidance on start of shelf life of the finished dosage

form' (EMEA/CVMP/453/01), annex to the 'Note for guidance on the manufacture of the finished dosage form' (EMEA/CVMP/126/95)) as the first step of the manufacturing process is considered to be pellet production.

In addition, an in-use shelf life of 24 hours for halved tablets was justified by stability data.

Based on the available stability data, the shelf life, in-use shelf life and storage conditions as stated in the SPC (and other product information) are acceptable.

Overall conclusions on quality

Active substances:

Full documentation is provided for the active substance benazepril HCl. The synthesis and control strategy applied during the process have been acceptably described. The active substance is described in Ph. Eur. and is controlled accordingly, with additional justified specific requirements. The justifications for impurities are considered acceptable. Stability studies support a re-test period of 5 years.

An ASMF is provided for the active substance pimobendan. The synthesis and control strategy applied during the process have been acceptably described. Stability studies support a re-test period of 5 years.

Finished product:

The rationale for development of these bilayered tablets and the manufacturing method used is detailed.

The proposed veterinary medicinal product contains either 1.25 mg pimobendan and 2.5 mg benazepril HCl, or 5 mg pimobendan and 10 mg benazepril HCl, and is formulated as bilayered tablets. FORTEKOR PLUS tablets include standard excipients with exception of a flavour (artificial special dry flavour), which is a non-pharmacopoeial excipient. All of the excipients, including the artificial special dry flavour (which is of non-animal origin), appear to have been used previously in the manufacture of EU authorised tablets.

The drug product is manufactured by direct compression of both the final granulate for the pimobendan layer and the final mixture for the benazepril layer. The manufacturing process has been adequately described. Full validation has been conducted on three batches of each of the two strengths of tablets.

The specifications proposed at release and at the end of shelf life are appropriate to control the quality of the finished product. Analytical methods and their validation are adequately described. The relevant EU and VICH guidance and Ph. Eur. requirements are taken into account.

The finished product is packed in aluminium blisters consisting of aluminium blister forms and aluminium lidding (peel off) foil. Stability studies performed according to current VICH requirements support a shelf life of 18 months with the special storage conditions "Do not store above 25 °C. Keep the blisters in the outer carton in order to protect from moisture."

Information on the development, manufacture and control of both the active substances and the finished product has been presented and assessed as satisfactory. The results of tests carried out indicate the consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

In addition, the applicant is recommended to provide further information post authorisation in relation to residual solvents in the manufacture of pimobendan, specification of benazepril hydrochloride, and stability data of benazepril hydrochloride, benazepril pellets, bulk product and half tablets.

Part 3 – Safety

Safety documentation

Pharmacodynamics

Data from peer-reviewed publications were presented. The modes of action of benazepril and pimobendan are well established, and each active ingredient has a different mode of action.

Pimobendan:

Pimobendan exerts its positive inotropic effects with potent vasodilating properties. The inotropic mechanism of action is achieved by an enhancement of the interaction between calcium and the troponin C complex, without an increase in myocardial oxygen consumption. Pimobendan also inhibits phosphodiesterase type III (PDE III) leading potentially to an increased intracellular calcium concentration. However, this second mechanism of action was reported to be minimal at pharmacological doses in dogs with heart failure. Overall, pimobendan enhances systolic function by improving the efficiency of contraction and by limiting the arrhythmogenic side effects seen with other positive inotropes.

Benazepril HCl:

Benazepril HCl is metabolised to the active metabolite benazeprilat. Benazeprilat inhibits angiotensin converting enzyme (ACE) in vitro approximately 200 times more potently than benazepril. In common with other ACE inhibitors, benazeprilat causes vasodilation. This vasodilatation is more pronounced in the renal blood vessels than in the general circulation and leads to increased renal blood flow and glomerular filtration rate, i.e. improved renal excretory capacity. As a consequence of the vasodilatation benazeprilat reduces volume load on the heart in dogs with congestive heart failure. General pharmacodynamic effects include reduced mean arterial pressure, reduced aldosterone secretion leading to increased sodium and water excretion, and increased plasma renin activity.

Pharmacokinetics

Study reports and published literature have been provided to describe the pharmacokinetics and metabolism of pimobendan and benazepril in the dog.

Pimobendan:

Pimobendan is absorbed rapidly with peak plasma concentrations noted within one hour after administration. Oral bioavailability is approximately 60–63% but is reduced in the presence of food. Pimobendan also is highly bound (90–95%) to plasma proteins in the circulation. It is metabolised in the liver to the O-demethyl metabolite (UD-CG 212) and eliminated in the faeces via excretion in the bile. The compound is excreted to a lesser extent in the urine. In dogs and in humans, the demethylated metabolite, which is also active, is a more potent inhibitor of PDE III than pimobendan.

Benazepril HCl:

In dogs, the oral bioavailability of benazepril is about 40%. Peak plasma concentrations are reached rapidly (0.25 to 1.5 hours) after ingestion. In all mammalian species tested, benazepril is rapidly and almost completely metabolised by liver enzymes to benazeprilat, which is the pharmacologically active entity. Benazepril and benazeprilat are both extensively bound to plasma proteins (85–90%). The highest concentrations of benazeprilat and metabolites are found in the lung, followed by the kidney and the liver.

Plasma benazeprilat levels decline rapidly in all species but show a slow terminal elimination phase. Benazeprilat is excreted via the biliary (54%) and urinary (46%) routes in dogs.

Pimobendan and benazepril HCl:

Pimobendan and benazepril HCl were given to healthy dogs via oral administration to evaluate the pharmacokinetic interaction between both compounds (see Part 4). The products were administered separately. Pimobendan was administered (in starch in capsules) at a dose of 0.3 mg/kg bodyweight (bw) and benazepril HCl by gavage at 0.25 mg/kg bw to fasted healthy Beagle dogs. There were no statistically significant pharmacokinetic interactions between pimobendan and benazepril or their metabolites after such oral administration.

Toxicological studies

Single dose toxicity

Literature references were provided to demonstrate the acute toxicity of the two substances. The acute toxicity of pimobendan given orally is low. The oral LD_{50} was reported as 1150 mg/kg bw in male rats and 950 mg/kg bw in female rats.

The acute toxicity of benazepril in rats is very low as no mortality was observed at up to 5000 mg/kg bw.

Acute oral and dermal exposure to the combination product in rats showed no signs of toxicity at a dose of 2000 mg/kg bw.

Repeat dose toxicity

Pimobendan:

Data from peer-reviewed publications were presented. In dogs cardiovascular failure was observed due to the pharmacological effect of the substance. Clinical chemistry changes were neither correlated with clinical dysfunctions nor the histological changes observed in kidney and liver suggesting the findings probably were not biologically relevant. In rats hypertrophy of the parotid glands was noticed at 50 mg/kg bw and a NOAEL has been set to 7 mg/kg bw/day following oral administration for 52 weeks.

Benazepril:

Original toxicological studies on benazepril were presented. In rats and dogs aldosterone-related changes in the blood electrolytes (that is, hyponatraemia, hyperkalaemia) and renal juxtaglomerular hypertrophy secondary to renin overproduction have been found in 52 weeks repeated dose toxicity studies. Mild anaemia and azotaemia were also observed. Possible explanations for the anaemia are chronic occult blood loss, haemolytic anaemia, or reduced erythropoiesis. Azotaemia is most likely secondary to the catabolism of the large quantities of circulating renin (originating in the hypertrophied renal juxtaglomerular cells) and angiotensin I. There is no evidence from animal toxicity studies for adverse effects on the adult kidney at any dose. A dose of 15 mg/kg bw of benazepril was considered to be the no effect level when administered orally daily for 12 months in dogs.

Tolerance in the target species of animal

See part 4.

Reproductive toxicity

Pimobendan:

Studies on reproduction in rats and rabbits reported the no-observed effect level (NOEL) for parental toxicity of pimobendan to 15–30 mg/kg bw for rats and 15 mg/kg bw for rabbits. Exposure during organogenesis and the late gestation period revealed slight retardation of development or decrease in bodyweight of the offspring. However, effects on maturation or reproductive capability of the progeny were not affected. It was concluded that pimobendan was not teratogenic when tested in rats and rabbits.

Benazepril:

In rats, male and female fertility, gestation length, labour and delivery were not affected by benazepril at doses of 50, 250 and 500 mg/kg bw even though there were signs of parental toxicity. Survival of offspring in the early postnatal period and offspring weight gain during lactation were reduced.

Benazepril was found to increase the incidence of urinary system variations in rats (for example, short or absent renal papillae and dilated ureters) even at maternally minimally or non-toxic doses. The effects are probably due to an exaggerated pharmacological effect of renal hypotension in the neonatal kidney. The reduced survival and growth rates seen in neonatal rats may be attributable to these kidney effects. Other laboratory studies did not show any embryotoxic or foetotoxic effects of benazepril, even at maternally toxic doses, and no non-teratogenic effects in mice, rats and rabbits.

In man, perinatal use of ACE inhibitors can cause severe disturbances of foetal and neonatal renal function. For this reason, benazepril is contraindicated in the second and third trimesters of human pregnancy. This effect of benazepril is related to the exaggerated pharmacological activity.

As a consequence of these findings, the product has been contraindicated for use during pregnancy and lactation, and a warning has been included on the SPC for pregnant women to take special care to avoid contact with the product.

Mutagenicity/genotoxicity

Pimobendan:

Data from the public domain showed that pimobendan was negative in an in vitro chromosomal aberration test and in an in vivo micronucleus test. The following mutagenicity tests were provided.

In the standard Ames' test results provided, pimobendan did not induce mutations in five histidine-requiring strains (TA98, TA100, TA1535, TA1537 and TA102) of *Salmonella typhimurium*. Pimobendan also did not induce biologically relevant increases in structural chromosome aberrations in cultured human peripheral blood lymphocytes in both the absence and presence of a rat liver metabolic activation system.

However, in an in vivo micronucleus (MN) test in mice, pimobendan induced micronuclei in the polychromatic erythrocytes of the bone marrow of male mice treated on two consecutive days at oral doses of 1000 and 2000 mg/kg bw, but not at 200 mg/kg bw. Using a comet assay the applicant demonstrated the genotoxic effect did not directly correlate to DNA damage.

The micronucleus test in mice was repeated using oral doses from 100 to 2000 mg/kg bw. An increase in micronuclei positive polychromatic erythrocytes (MN PCE) was observed at dose levels of 1000 mg/kg bw. Fluorescent in situ hybridization (FISH) with mouse pan-centromeric DNA probes confirmed that the majority (75–90%) of micronuclei formed following treatment with pimobendan contained centromeres

(indicating aneuploidity). Benchmark dose calculations showed a point-of-departure of 750 mg/kg bw/day and this threshold offers a sufficient safety margin for both the target species and for users.

Benazepril:

The mutagenicity of benazepril was studied in standard test systems, i.e. for gene mutations in bacterial cells, chromosome aberrations in mammalian cells in vitro, and gene mutations in eukaryotic cells in vitro and in vivo. All in vitro assays were performed with and without metabolic activation using rat liver post-mitochondrial supernatant, which is known to hydrolyse benazepril to benazeprilat. No mutagenic effects of benazepril were found in any of these tests. It can thus be concluded that neither benazepril nor benazeprilat has any mutagenic potential.

Carcinogenicity

Since a genotoxic NOEL for pimobendan is high and no preneoplastic changes have been observed in repeated dose studies the lack of carcinogenicity studies is accepted.

In mice and rats administered benazepril at mean daily doses of 10, 50 and 150 mg/kg bw in feed for at least 104 consecutive weeks, no evidence of carcinogenicity or target organ toxicity was observed.

Studies of other effects

The dermal irritation potential of FORTEKOR PLUS was evaluated in an in vitro skin irritation assay, EpiDerm SIT (EPI-200). This demonstrated that the product did not have the potential to cause irritation to the skin.

The potential for ocular irritation from FORTEKOR PLUS was initially evaluated in a bovine corneal opacity and permeability assay (BCOP). This demonstrated that the test article did not have the potential to cause corrosion or severe irritation to the eye. Subsequently, in an in vivo test in New Zealand White rabbits, slight initial sting reactions and moderate conjunctival irritation ocular reactions were observed for up to 9 days after treatment. Therefore the combination product was considered to be a mild irritant. The skin sensitisation potential of FORTEKOR PLUS 5 mg/10 mg tablets was evaluated at three different concentrations; 10%, 25% and 50% in a local lymph node assay in mice. A clear positive response was noted at concentrations of 10% and 50%. No explanation could be found as to why no response was seen at a concentration of 25%. The local lymph node assay demonstrated that FORTEKOR PLUS 5 mg/10 mg tablets has the potential to cause skin sensitisation.

User safety

A user safety assessment which was conducted in accordance with the CVMP Guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03 Rev.1) was provided.

FORTEKOR PLUS is to be available on prescription only. However, these tablets are for daily administration to dogs at home, therefore pet owners are most likely to be exposed to the product.

Exposure to the two active substances during normal use of the product would be via skin of the hands while handling the tablet. As the final product is considered not to be a dermal irritant, no adverse effects are expected as a result of handling the tablets. As the final product is categorized as only mildly irritant to the eyes, no significant toxic effects are expected following hand-to-eye transfer. It should be noted that the ocular irritation study was conducted with powdered drug while no significant exposure is

expected from the final tablet formulation. Even with the powdered formulation, the combination product did not meet the criteria for classification as an ocular irritant according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). The tablet is not volatile or dusty thus excluding exposure by inhalation.

Oral exposure is considered to represent a relevant risk.

A maximum of two tablets of FORTEKOR PLUS 5 mg/10 mg tablets will be administered to one dog. This may lead to a maximum single exposure to 10 mg of pimobendan and 20 mg of benazepril HCl and safety margins compared to the NOAELs for both pimobendan (7 mg/kg bw from a study in rats) and benazepril (15 mg/kg bw from a study in dogs) of 44 and 46 for adults, and 7 and 7.5 for children, respectively. These margins of exposure for children seem to be quite narrow, however it is to be noted that the NOELs used for the calculation are based on 52-week repeat dose toxicological studies, and that the scenario considers the ingestion of two tablets as a worst case scenario.

In light of the known effects of ACE inhibitors on foetal and neonatal renal function, a warning has been included in the product information for pregnant women to take special care to avoid contact with the product.

In addition, a warning is included in the product information highlighting the need for people with known hypersensitivity to pimobendan or benazepril hydrochloride to avoid contact with the product.

Based on the data presented, the product does not pose an unacceptable risk to users, which are pet-owners (administering the product) and children (who could accidentally access the product), when used in accordance with the SPC.

Environmental risk assessment

An environmental risk assessment (ERA) in accordance with VICH GL6 on environmental impact assessment for veterinary medicinal products - Phase I (CVMP/VICH/592/98) and the CVMP Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1) was provided. The veterinary medicinal product will only be used in individual non-food animals.

Based on the data provided, the ERA can stop at Phase I. FORTEKOR PLUS is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

FORTEKOR PLUS contains two active substances, pimobendan and benazepril hydrochloride. These active ingredients are known and are currently included in authorised monocomponent veterinary medicinal products in the EU.

A pharmacokinetic interaction study did not reveal any significant interaction between the two active substances. Thus the safety of active ingredients was discussed separately, in line with the CVMP Guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005). For pimobendan, published literature in peer reviewed journals was presented. For benazepril, extensive data collected from good laboratory practice (GLP) studies was presented.

Pimobendan: This active substance has been shown to induce hypertrophy of parotid glands in rats and a NOAEL has been set at 7 mg/kg bw/day following oral administration for 52 weeks. Studies on reproduction in rats and rabbits reported a NOEL for parental toxicity of pimobendan as 15–30 mg/kg bw

for rats and 15 mg/kg bw for rabbits. Pimobendan was not teratogenic when tested in rats and rabbits. Finally pimobendan was found to have an aneugenic effect at doses ≥ 750 mg/kg bw. For all effects the thresholds offer sufficient safety margins, both for the target species and for users.

Benazepril: In rats and dogs aldosterone-related changes in blood electrolytes (that is, hyponatraemia, hyperkalaemia) and renal juxtaglomerular hypertrophy secondary to renin overproduction have been reported. A dose of 15 mg/kg bw of benazepril was considered to be the NOEL when administered orally daily for 12 months in dogs.

Benazepril was found to increase the incidence of urinary system variations in the offspring of rats at non-toxic doses. This effect of benazepril is probably due to an exaggerated pharmacological effect of renal hypotension in the neonatal kidney. In man, perinatal use of ACE inhibitors can cause severe disturbances of foetal and neonatal renal function. For this reason, benazepril is contraindicated in the second and third trimesters of human pregnancy. As a consequence of these findings, the product has been contraindicated for use during pregnancy and lactation, and a warning has been included on the SPC accordingly. Neither benazepril nor benazeprilat has any mutagenic potential.

In relation to user safety, a maximum of two tablets of the higher strength (5 mg/10 mg) of FORTEKOR PLUS tablets will be administered to one dog. This could lead to a maximum single exposure to 10 mg of pimobendan and 20 mg of benazepril HCl and safety margins compared to the NOAELs for both pimobendan and benazepril of 44 and 46 for adults, and 7 and 7.5 for children, respectively. When used in accordance with the SPC, FORTEKOR PLUS tablets are not expected to pose an unacceptable risk to the user.

Based on the data provided, the ERA can stop at Phase I. FORTEKOR PLUS is not expected to pose a risk for the environment when used according to the SPC.

Part 4 – Efficacy

The proposed target dosing of the proposed product is to administer 0.25–0.5 mg/kg bw pimobendan and 0.5–1 mg/kg bw benazepril divided into two daily doses, i.e. 0.125–0.25 mg/kg bw pimobendan and 0.25–0.5 mg/kg bw benazepril twice daily.

Justification of fixed combination

Benazepril and pimobendan are two known substances not previously authorised in a combination product.

Benazepril is authorised in the EU (FORTEKOR) for dogs with the following indication: "Treatment of congestive heart failure". Pimobendan is also authorised for use in dogs in the EU (Vetmedin) with the following indication: "For the treatment of canine congestive heart failure originating from valvular insufficiency (mitral and/or tricuspid regurgitation) or dilated cardiomyopathy."

The combination of benazepril and pimobendan in this proposed product is based on the concurrent use of the EU-authorised monocomponent products and the recommendation from the American College of Veterinary Internal Medicine (ACVIM) on the treatment of dogs with heart failure.

The modes of action of benazepril and pimobendan are well established, and each active ingredient has a different mode of action.

Benazepril is a prodrug. The major metabolite of benazepril in all species studied is benazeprilat, which is the pharmacologically active form. Benazeprilat inhibits angiotensin converting enzyme (ACE) and causes

vasodilation in the renal blood vessels which leads to increased renal blood flow and glomerular filtration rate, i.e. improved renal excretory capacity, which is the desired therapeutic effect.

Pimobendan exerts its positive inotropic effects through sensitization of the cardiac contractile system to intracellular calcium. The mechanism of action is achieved by an enhancement of the interaction between calcium and the troponin C complex, without an increase in myocardial oxygen consumption. It also inhibits phosphodiesterase (PDE) III leading potentially to an increased intracellular calcium concentration. However, this second mechanism of action was reported to be minimal at pharmacological doses in dogs with heart failure. Overall, pimobendan enhances the systolic function of the heart by improving the efficiency of contraction and by limiting the arrhythmogenic side effects seen with other positive inotropes.

In a scientific advice procedure, the CVMP advised the applicant that if the intention is to show that the fixed combination product performs similarly to the two individual components given concomitantly in a group of dogs where the need for the two components given at this certain dose level and interval has been confirmed, no field data would be needed provided bioequivalence is shown. The applicant followed this approach and bioequivalence was demonstrated.

In addition a clinical study (JPN-12-001) showed non-inferior efficacy of the proposed tablets (1.25 mg/2.5 mg and 5 mg/10 mg of benazepril HCl and pimobendan respectively) when compared to concurrent use of benazepril (FORTEKOR) and pimobendan (Vetmedin) in dogs with chronic heart failure associated with mitral regurgitation.

The combination of benazepril and pimobendan in the proposed product is considered justified.

Pharmacodynamics

See part 3.

A study was conducted to compare the effects of once versus twice daily administration of benazepril on the plasmatic angiotensin converting enzyme (ACE) in Beagle dogs. Furthermore the interaction of pimobendan with the effect of benazepril to inhibit the plasma ACE activity was examined.

A total of 48 Beagle dogs were randomised into 4 groups. After one week of acclimatisation, treatments were administered orally for 15 consecutive days in a parallel design. Group A received placebo treatment twice daily. Group B was treated with benazepril HCl 0.5 mg/kg bw once a day, group C with benazepril HCl 0.25 mg/kg bw twice a day and group D with benazepril HCl 0.25 mg/kg bw and pimobendan 0.125 mg/kg bw twice a day. Comparison of the average ACE value showed that a dosing regimen of benazepril HCl 0.25 mg/kg bw twice daily produced equivalent (statistically non-inferior) inhibition of plasma ACE activity compared to 0.5 mg/kg bw once daily. Furthermore, addition of 0.125 mg/kg bw pimobendan twice daily had no significant effect on the inhibition of plasma ACE activity produced by benazepril HCl dosed at 0.25 mg/kg bw twice daily.

Development of resistance

Not relevant.

Pharmacokinetics

Although no pharmacokinetic interactions between benazepril and pimobendan were expected, two pharmacokinetic interaction studies were conducted, firstly with the two active ingredients (benazepril

and pimobendan) as single substances, and secondly using authorised or final tablet formulations of benazepril, pimobendan and fixed combination benazepril and pimobendan (the proposed product).

In the first study the pharmacokinetic interaction between benazepril and pimobendan, after single administration of the two active ingredients, was examined. A total of 18 Beagle dogs (9 female and 9 male) were each treated 3 times in a 3-part randomized crossover design with a 14-day washout between each period. In period one, benazepril HCl was the only medication and was administered by gavage at a dose of 0.25 mg/kg bw. In period two, both substances were administered, benazepril HCl (0.25 mg/kg bw) by gavage and pimobendan (0.3 mg/kg bw) in a starch containing capsule. In the third period, pimobendan (0.3 mg/kg bw) was given alone in a starch capsule. Dogs were fasted overnight before each treatment, and blood was sampled 4 hours after treatment.

The results showed bioequivalence between the AUCs of the metabolite benazeprilat, benazepril administered alone and benazepril administered in combination with pimobendan, whereas the C_{maxs} were statistically different. The results also showed no significant differences between the AUCs or C_{max} for pimobendan or O-desmethyl-pimobendan after pimobendan was given alone, or pimobendan was given together with benazepril, showing therefore no evidence for interaction between the substances. However, bioequivalence according to the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00 Rev. 2) was not shown. Limitations of this study were that the active ingredients, and not the final formulation, were used. In addition, benazepril was administered via gavage, and not orally via tablets.

In the second study, the pharmacokinetic interaction between benazepril and pimobendan in the final formulation was examined. Three groups of 12 male dogs were treated with a single dose of benazepril HCl (FORTEKOR), pimobendan (Vetmedin) or both (the proposed product) in a three-phase crossover study. The washout period between phases was 7 days. The theoretical dose of benazepril HCl was 0.50 mg/kg bw. Mean actual doses of benazepril HCl were 0.52 ± 0.05 mg/kg bw (administered alone, R1) and 0.51 ± 0.05 mg/kg bw (co-administered with pimobendan, T). The theoretical dose of pimobendan was 0.25 mg/kg bw. Mean actual doses of pimobendan were 0.27 ± 0.03 mg/kg bw (administered alone, R2) and 0.28 ± 0.03 mg/kg bw (co-administered with benazepril, T). Single doses of test formulations were administered after the dogs were fasted overnight.

Results show that benazepril and benazeprilat plasma concentrations were lower at each time point (in particular at C_{max}) after administration of the fixed combination product in comparison to following the administration of benazepril alone. In contrast, the profiles obtained after administration of the combination tablet and pimobendan (alone) tablet were similar, for both pimobendan and O-demethyl pimobendan. AUC_{last} or AUC_{tot}, AUC_{last_corr} or AUC_{tot_corr}, C_{max}, C_{max_corr}, T_{max} and $T_{1/2}$ were highly variable for benazepril (CV between 53% and 104%) and for benazeprilat (CV between 29% and 130%) and variable for pimobendan (CV between 27% and 69%) and for O-demethyl pimobendan (CV between 26% and 54%). It could be concluded that co-administration of pimobendan resulted in lower values for the C_{max} and AUC of benazeprilat but that benazepril had no pharmacokinetic interaction on pimobendan. The CVMP considered that the observed difference in benazeprilat concentration between the combination product and the monocomponent product may have a minimal impact on benazeprilat effect as maximal benazeprilat effects are achieved at low plasma concentrations controlled by the binding of benazeprilat to circulating ACE. Consequently differences in benazeprilat plasma concentration between these formulations would not be expected to have an impact on the therapeutic use of the product.

The study was performed with tablets containing 2.5 mg/5 mg pimobendan/benazepril HCl whereas the proposed two product tablets strengths contain 1.25 mg/2.5 mg pimobendan/benazepril HCl or 5 mg/10 mg pimobendan/benazepril HCl. According with CVMP Guideline on the conduct of

bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2), additional tests should be provided in order to extrapolate the results from bioequivalence studies for additional strengths. To address this, the clinical equivalence of the 1.25 mg/2.5 mg and 5 mg/10 mg strengths was confirmed in a clinical field study (for full details see 'Fields trials' below).

Dose determination/justification

The proposed dose range of the combination product is 0.125–0.25 mg pimobendan per kg bodyweight and 0.25–0.5 mg benazepril HCl per kg bodyweight twice daily.

Pimobendan:

The proposed dose for the combination product in dogs is based on the dose of the EU authorised monocomponent product containing pimobendan, that is, oral doses of 0.125–0.25 mg pimobendan per kg bodyweight twice daily, approximately 12 hours apart and approximately 1 hour before feeding.

The proposed dose rate for pimobendan in the proposed product is justified based on the data presented with respect to the demonstration of bioequivalence of the pimobendan component in the proposed product formulation and the EU authorised product containing pimobendan alone (Vetmedin).

Benazepril:

Benazepril as a monocomponent product (FORTEKOR) is currently authorised in the EU for the treatment of congestive heart failure in dogs at a minimum starting dose of 0.25 mg benazepril HCl/kg bw once daily. In a PK/PD study it was determined that 0.25 mg benazepril HCl/kg bw was the lowest dose that produced maximal inhibition of plasma ACE over the recommended dosage interval of 24 hours for benazepril in dogs. The once daily dosing frequency was at the time justified based on the duration of action of benazepril, which was determined to be long, with 84% plasma ACE inhibition at 24 hours (versus 97% at E_{max}) with steady state dosing at 0.25 mg/kg bw.

However, in the pharmacodynamic interaction study submitted, where effects on ACE inhibition were compared between benazepril HCl administered once or twice daily at a total daily dose of 0.5 mg/kg bw and benazepril HCl administered twice daily in the pimobendan/benazepril HCl combination, the twice daily administration of benazepril or benazepril plus pimobendan groups lead to comparable levels of ACE inhibition at 24 hours to those seen following once daily dosing.

Although bioequivalence in accordance with the CVMP Guideline on bioequivalence (EMA/CVMP/016/00-Rev.2) was not demonstrated with respect to benazeprilat between the authorised product containing benazepril alone and the combination product containing pimobendan and benazepril, it is accepted that the small difference in the plasma profile of benazeprilat is not expected to have an impact on therapeutic efficacy as maximal benazeprilat effects are achieved at low plasma concentrations controlled by the binding of benazeprilat to circulating ACE.

Target animal tolerance

A recent GLP-compliant pivotal target animal safety study was conducted with the final combination product in accordance with the VICH GL43 on target animal safety.

Thirty two adult Beagle dogs were randomly allocated to four study groups (n=8 per group). FORTEKOR PLUS tablets (final formulation) were administered orally twice daily at 1x, 2x and 4x the highest recommended dose (0.25 mg/kg bw pimobendan and 0.50 mg/kg bw benazepril hydrochloride) for six months to identify potential adverse effects associated with overdose and increased duration of

administration of the product. In this study, the product was in general well tolerated by all dogs. No significant changes in food consumption or bodyweight were observed. Apart from increased heart rates on study days 34/35, 88/89 and 116, and occasional vomiting (observed between study day 61 and 173) in the 1x and 4x treatment groups, no other clinically significant abnormalities attributable to the combination product were detected concerning general health, neurological and ophthalmological functions. Changes observed in electrocardiograms (ECGs) were determined to be within acceptable limits and there were no significant pathological findings related to those ECG abnormalities. Statistically significant differences in clinical pathology revealed no definitive pattern that would indicate an effect of the product, and no changes were associated with any clinical signs of illness in the treated animals. There were no macroscopic or histopathological findings that could be attributed to administration of the product in this study. No statistically significant changes were observed in organ weights between the control and treatment groups.

The results of this study show that FORTEKOR PLUS tablets are well tolerated in Beagle dogs when administered orally, twice daily for 180 days, at 1x, 2x and 4x the maximum recommended dose of 0.25 mg pimobendan and 0.50 mg benazepril HCl per kg bodyweight.

The CVMP noted that the tolerance study was conducted at the higher end of the proposed dose range of pimobendan and benazepril recommended for dogs. That means that the submitted tolerance study cover doses of 2x, 4x and 8x the lowest recommended dose for the proposed product. The Committee agreed that this study showed that benazepril HCl/pimobendan combination tablets are generally well tolerated in Beagle dogs when administered orally, twice daily for 180 days. Some adverse effects such as increased heart rates and occasional vomiting may be associated with overdosing and increased duration of administration of the test item in healthy animals. However, as the affected animals were otherwise clinically normal, the overall conclusion of this study is that the product is generally well tolerated in the target species.

Field trials

One single-blinded randomized GCP-compliant multicentre field study (JPN-12-001) of non-inferiority design was provided, investigating the efficacy and safety of a fixed combination of pimobendan and benazepril for the treatment of chronic heart failure associated with mitral regurgitation in dogs at a total of 26 study sites in Japan.

A total of 67 dogs of various breeds were randomised into three groups in a proportional ratio of 2:1:1. The proposed fixed combination of benazepril HCl and pimobendan was administered twice daily in a single tablet to a group of 34 dogs at target standard doses of 0.25–0.5 mg/kg bw and 0.125–0.25 mg/kg bw respectively. Control group I included a total of 14 dogs. Benazepril (FORTEKOR) was administered twice daily at half the standard dose of benazepril and the standard dose of pimobendan (Vetmedin) twice daily in separate formulations to this group. Control group II included a total of 19 dogs. Benazepril was administered once daily and pimobendan twice daily at their standard doses in separate formulations to this group. The products were administered approximately 1 hour before feeding (if animals were fed) by the owner.

There were no biologically relevant differences in efficacy or safety parameters between the three groups. For the primary (efficacy) endpoint defined as the global clinical score defined as the total score of exercise tolerance, demeanour, appetite, respiratory effort, coughing and nocturnal dyspnoea; there were no significant differences between groups. The scores decreased compared to pre-treatment values in all groups, and this decrease was statistically significant ($p<0.05$, Wilcoxon test) at all-time points (weeks 1, 2, 4 and 8) for the fixed combination, Control II and the combined control groups, and at two

time points only for Control I (weeks 1 and 2 only). Comparison between Control I and Control II also indicated that there was no significant difference between once daily dosing and twice daily dosing of benazepril hydrochloride.

The incidence of adverse events was comparable in the three groups. Adverse events were classified as cardiovascular, digestive, auricular, musculoskeletal, neurological, respiratory, dermatological and systemic conditions. Most of the adverse events were likely associated with the primary disease (CHF) or incidental and not related to the administration of the proposed product or control products.

The study showed non-inferiority of a fixed combination of pimobendan and benazepril when compared to concurrent use of pimobendan and benazepril for the treatment of chronic heart failure associated with mitral regurgitation in dogs.

Two retrospective studies were provided based on field data where an ACE inhibitor and pimobendan were administered in combination with other cardiac drugs to treat mitral regurgitation and congestive heart failure in dogs (DeMadron et al, 2011) (Van Israel, 2009). These data were considered supportive for this application.

In the scientific advice given for this application, prior to its submission, the CVMP considered that if the intention was to show that the fixed combination product performs similarly to the two components given concomitantly in a group of dogs where the need for the two components given at this particular dose level and interval has been confirmed, no field data would be needed, provided that bioequivalence was shown.

The bioequivalence approach has been followed, and the consequence is that the combination product is for use as a replacement/substitution therapy where the treatment of CHF already has been initiated and is controlled by use of both the mono-substance products. In accordance with the scientific advice given this restricts the use of the product to such a subpopulation, which is clearly specified in the indication for the product.

FORTEKOR PLUS is a fixed dose combination and can be used in patients only when clinical signs are successfully controlled by administration of the same doses of both of the individual components (pimobendan and benazepril hydrochloride) given concurrently. The recommended doses are benazepril HCl 0.25 mg/kg bw and 0.125 mg/kg bw, twice daily. To make it clear that the product is only to be used when the same doses of the monocomponent products would be prescribed the acceptable indication is as follows: "For the treatment of congestive heart failure due to atrioventricular valve insufficiency or dilated cardiomyopathy in dogs. FORTEKOR PLUS is a fixed dose combination and should only be used in patients whose clinical signs are successfully controlled by administration of the same doses of the individual components (pimobendan and benazepril hydrochloride) given concurrently."

Overall conclusion on efficacy

The proposed recommendation for the posology of the pimobendan component in the combination product is based on the recommendations for the use of pimobendan authorised as a monocomponent product (Vetmedin) in the dog, i.e., an upper oral dose of 0.25 mg/kg bw twice daily. In the proposed product the recommended dose of pimobendan is 0.125–0.25 mg/kg bw twice daily, which is within the range for the recommended dose of pimobendan in the authorised monocomponent product and which cannot be adjusted.

Benazepril (as the HCl salt) is authorised as a monocomponent product (FORTEKOR) in the dog with recommendations for administration once daily in a dose of 0.25–0.5 mg/kg bw, which may be increased

to 0.5–1 mg/kg if required. The justification of the dose rate and dose frequency proposed for benazepril in FORTEKOR PLUS is based on the comparative pharmacodynamic effects of benazeprilat (active metabolite of benazepril) in the EU-authorised monocomponent product and the proposed combination product, and on a specific study. This study showed that the proposed daily dose of benazepril when administered twice daily is as effective in terms of ACE inhibition as the once daily dose of benazepril as currently recommended for FORTEKOR, and which demonstrated the absence of any interaction in terms of ACE inhibition between pimobendan and benazepril. In the proposed product benazepril (as the HCl) is administered twice daily at a dose of 0.25–0.5 mg/kg bw, which cannot be adjusted.

Although bioequivalence in accordance with the relevant CVMP Guideline was not demonstrated on the basis of pharmacokinetic parameters between the authorised single component and the proposed product for benazeprilat, the small difference in the plasma profile of benazeprilat is expected to have no impact on therapeutic efficacy as maximal benazeprilat effects are achieved at low plasma concentrations controlled by the binding of benazeprilat to circulating ACE.

The clinical efficacy was shown in a GCP-compliant non-inferiority study including a total of 67 dogs of various breeds, of which 34 dogs were treated with the proposed product within the proposed dose range. The study showed non-inferiority of this fixed combination of pimobendan and benazepril when compared to concurrent use of pimobendan and benazepril for the treatment of chronic heart failure associated with mitral regurgitation in dogs.

A tolerance study shows that the combination product is well tolerated in Beagle dogs when administered orally, twice daily for 180 days, at 2x, 4x and 8x the recommended lower dose of 0.125 mg pimobendan and 0.25 mg benazepril HCl per kg bodyweight.

Part 5 – Benefit-risk assessment

Introduction

FORTEKOR PLUS is a bilayered uncoated oral tablet containing two active substances: pimobendan and benazepril hydrochloride. Two strengths of tablets are available containing 1.25 mg/2.5 mg and 5 mg/10 mg pimobendan/benazepril hydrochloride respectively.

The combination is considered a new fixed combination (of two active substances previously authorised within the EU as monocomponent products) and is therefore considered a new active substance.

The product is intended for the treatment of congestive heart failure due to atrioventricular valve insufficiency or dilated cardiomyopathy in dogs and should only be used in patients whose clinical signs are successfully controlled by administration of the same doses of the individual active substances (pimobendan and benazepril hydrochloride) given concurrently.

The application has been submitted in accordance with Article 13(b) of Directive 2001/82/EC.

Benefit assessment

Direct therapeutic benefit

The active substances are both known vasodilators used in EU authorised veterinary medicinal products and pimobendan has, in addition, a positive inotropic effect.

The combination of these two active substances, pimobendan and benazepril hydrochloride, in the proposed product has been justified.

The doses of both substances – benazepril HCl 0.25 mg/kg bw twice daily and pimobendan 0.125 mg/kg bw twice daily - are justified.

The efficacy of the product in the proposed dose and dosing interval is justified on the basis of a bioequivalence study investigating the lower tablet strength (1.25 mg benazepril HCl/2.5 mg pimobendan) of the proposed product in comparison with EU-authorised monocomponent products containing either benazepril HCl or pimobendan alone. The small differences observed in the benazepril plasma profiles between the lower tablet strength and the monocomponent product, were considered not to have any impact on therapeutic efficacy.

Efficacy was further supported by a well-controlled clinical study showing non-inferiority of this fixed combination of pimobendan and benazepril when compared to concurrent use of pimobendan and benazepril for the treatment of chronic heart failure associated with mitral regurgitation in dogs.

In conclusion, the benefit of FORTEKOR PLUS is its efficacy in the treatment of congestive heart failure due to atrioventricular valve insufficiency or dilated cardiomyopathy in dogs. FORTEKOR PLUS is a fixed dose combination product and should only be used in patients whose clinical signs are successfully controlled by administration of established doses of the individual components (pimobendan and benazepril hydrochloride) when given concurrently as monocomponent products.

Additional benefits

The fixed combination facilitates dog handling by reducing the total number of tablets to be given and therefore, treatment compliance.

Risk assessment

Main potential risks

Quality:

The formulation and manufacture of the finished product FORTEKOR PLUS is well described and specifications set will ensure that product of consistent quality will be produced.

Target animal safety:

The safety of FORTEKOR PLUS has been investigated in healthy dogs when used according to the proposed dosing recommendations. Adverse reactions are of non-serious nature and include increased heart rates and occasional vomiting which may be associated with overdosing and the long duration of administration, also incoordination and fatigue. No data were submitted on reproductive toxicity in the target species.

The fixed combination provides a risk that a population of patients with chronical heart failure which do not need both an ACE inhibitor and pimobendan is over-treated.

User safety:

The CVMP concluded that user safety for this product is acceptable when used as recommended and taking into account the safety advice in the SPC.

Environmental safety:

The product is not expected to pose a risk for the environment when used in accordance with the SPC.

Risk management or mitigation measures

Appropriate information has been included in the SPC to inform on the potential risks of this product relevant to the target animal, user and the environment and to provide advice on how to prevent or reduce these risks.

To manage the risk of over-treatment, the product FORTEKOR PLUS should therefore only be used in patients whose clinical signs are successfully controlled by the administration of the same doses (recommended dose benazepril HCl 0.25 mg/kg bw twice daily and pimobendan 0.125 mg/kg bw twice daily) of the individual components given concurrently.

Evaluation of the benefit-risk balance

The benefit of FORTEKOR PLUS is its efficacy in the treatment of congestive heart failure due to atrioventricular valve insufficiency or dilated cardiomyopathy in dogs. The formulation and manufacture of FORTEKOR PLUS tablets is well described and the proposed specifications would ensure that a product of consistent quality will be produced.

It is well tolerated by the target animals.

The product represents an acceptable risk for the user and the environment when used as recommended and appropriate warnings have been included in the SPC.

The product has been shown to have a positive benefit-risk balance overall.

Conclusion on benefit-risk balance

The overall benefit-risk evaluation for the product is deemed positive with a sufficiently clear and complete SPC and product literature.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for FORTEKOR PLUS is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above mentioned medicinal product.

Divergent position on a CVMP opinion on the granting of a marketing authorisation for FORTEKOR PLUS (EMEA/V/C/002804/0000)

FORTEKOR PLUS is a new product which contains two previously authorised substances (benazepril, an angiotensin converting enzyme inhibitor (ACEI), and pimobendan) for the treatment of congestive heart failure due to atrioventricular valve insufficiency or dilated cardiomyopathy in dogs. Sufficient information has not been presented to support the fixed combination of the two substances, pimobendan and benazepril, specifically the clinical benefits as compared to the administration of either pimobendan or benazepril as mono products for the following reasons:

- The benefit of combining the two substances as compared to the administration of either pimobendan or benazepril as mono-substance product has not been confirmed in clinical trials.
- Between-study comparisons of different treatment strategies cannot provide conclusive information due to uncontrolled differences in study conditions.
- Consensus statements given by clinical experts in the field (ACVIM) only recommends concurrent administration to dogs that have certain stages of heart disease. It can be regarded as supportive information but in the absence of confirmatory clinical trial results, such information is of more limited scientific value.
- There is some clinical information available where benazepril and pimobendan given as mono products have been compared head-to-head with the combination. On a short-term basis, no benefit of the combination was indicated. There is no information on the long-term basis, neither on the added benefit of the combination, nor its safety, especially in regards to median survival time in comparison to mono-substance product treatments.
- The identification of the target population that could potentially benefit from the concurrent administration of benazepril and pimobendan is haphazard at best, due to the lack of appropriate studies.
- In addition to above mentioned deficiencies regarding efficacy confirmation, the risk profile for the intended target population is not clarified.
- Pharmacokinetic equivalence between the fixed combination product and mono-substance products (pimobendan and benazepril) provided at the same doses is uncertain.

In the absence of sufficient clinical information to support a benefit of the benazepril/pimobendan combination product as compared to the administration of either of the mono-substance products for the proposed indication and the safe use of the product, then the benefit-risk balance is regarded as negative for FORTEKOR PLUS.

Background

Market authorisation is sought for the combination product FORTEKOR PLUS. The eligibility to the centralised procedure was agreed upon by the EMA/CVMP on 11–13 September 2012 as falling under Article 3(2)(a) of Regulation (EC) No 726/2004 as FORTEKOR PLUS contains a new fixed combination of two existing active substances, pimobendan and benazepril hydrochloride, which are not authorised in combination in the European Union.

CVMP agreed on the following indication:

"For the treatment of congestive heart failure due to atrioventricular valve insufficiency or dilated cardiomyopathy in dogs. FORTEKOR PLUS is a fixed dose combination and should only be used in patients whose clinical signs are successfully controlled by administration of similar doses of the individual components (pimobendan and benazepril hydrochloride) given concurrently".

Justification of the combination

For a fixed combination Directive 2001/82/EG [article 13(b)] states that:

"in the case of new veterinary medicinal products containing known constituents not hitherto used in combination for therapeutic purposes, the results of toxicological and pharmacological tests and of clinical trials relating to that combination must be provided, but it shall not be necessary to provide the relevant documentation for each individual constituent".

Thus, in addition to the demonstration of the lack of pharmacokinetic interaction, the benefit of combining the two substances is required to be confirmed. This would mean that for FORTEKOR PLUS the clinical benefit is required to be demonstrated through clinical trials in that the fixed combination provides a benefit which is superior to the effect obtained when either of the two substances are given as mono therapies. This is a relevant requirement in line with the fixed combination guideline (EMEA/CVMP/83804/2005) which states that "*Any fixed combination product can only be justified, if such a combination offers an advantage over their active substances, when used as single substances products*". For example, the product user will expect that the granting of market authorisation of a combination product provides assurance that the combination product results in a superior clinical effect as compared to the single administration of any of the substances included in the combination.

The fixed combination guideline also states that tolerance can be improved in certain fixed combination products "because the dose of individual substances with a narrow margin of safety can be reduced, without affecting the total level of efficacy,"; it is noted that within this combination, while the pimobendan dosing regime is maintained, benazepril would now be administered twice daily and, in all circumstances, at the maximum recommended dose of the mono-substance product.

One of the main concerns is the fact that there is no study available in which the clinical effect of the fixed combination have been assessed and proven superior to the treatment with either pimobendan or benazepril as mono-substance therapy. Confirmation of the clinical effect through an appropriate clinical study including a relevant comparator is regarded as of pivotal importance for any new product and the waving of such information is normally not accepted.

The applicant provided a report from a multi-centre randomized and blinded study performed in Japan in which the clinical efficacy and safety of FORTEKOR PLUS was compared to Fortekor 2.5mg/5mg flavour (benazepril mono product) and Vetmedin 1.25mg/5mg (pimobendan mono product). The latter two were provided in combination so that benazepril was given either once or twice daily for the treatment of dogs with clinical signs of CHF (chronic heart failure). After an eight week follow-up period, for the primary endpoint which consisted of a composite score of different clinical signs no significant differences were noted between any of the three groups. Similarly, no difference was noted for a number of secondary endpoints. Through non-inferiority analyses it was concluded that the different treatment strategies did not affect clinical efficacy. This study does not provide information regarding the potential benefit of providing the two substances in combination as compared to giving either of them as mono substance therapy. Results from a short term clinical study are available in the public domain in which concomitant treatment of pimobendan and benazepril was compared to pimobendan as mono product. No difference

between the two groups were noted four weeks after the start of treatment (Lombard 2000 (http://www.vetcontact.com/en/art.php?a=417&t=).

In the absence of clinical data including head-to head comparisons of the fixed combination and the mono products, the applicant seeks to justify the combination through between-study comparisons.

In two studies of dogs with CHF secondary to CVHD (canine valvular heart disease) that received both benazepril and pimobendan as well as furosemide and other therapy, a mean survival time of 525 days (95% CI 206–719 days) was noted by Madron et al. (2011), and a median survival time of 640 days (95% CI 472–824 days) was reported by Van Israel (2009). These survival times are longer than what is reported for the use of benazepril alone (mean 436 days, BENCH 1999), or pimobendan alone (median 188 days, Häggström et al., 2008) in dogs with CVHD. A survival analysis may have been a more appropriate statistic to assess survival times between studies. It is recognised that such an analysis is heavily dependent on the stage of disease at the time of inclusion of study animals.

Although longer survival times are reported in the studies where pimobendan and benazepril were provided in combination, between study comparisons are problematic due to uncontrolled between-study variation in the conduct and analyses of the trial (e.g. inclusion criteria, exclusion criteria, concomitant treatment etc) which precludes a scientifically robust comparison. It is noted that the two studies in which pimobendan and an ACEI were given concurrently (Madron *et al* 2011 and Van Israel 2009) are both small (21 and 50 dogs respectively) uncontrolled retrospective studies. The Van Israel study (2009) is only available as a half-page long congress abstract which precludes a proper assessment of the conduct and analyses of the study. In the Madron study (2011) the dogs, in addition to the administration of furosemide, pimobendan and ACEI were also provided spironolactone and amlodipine, implying that the study population was not suitable to assess the specific effect of the sole pimobendan/benazepril combination. Hence, it is not possible to conclude on the potential benefit of the combination as compared to mono treatment from comparisons of published data. Regarding the BENCH study (1999), it is noted that this non-recent result may underestimate current survival times because dogs are treated earlier in the evolution of their disease. Finally, in the study by Häggström et al (2008) it is mentioned in the conclusions that "*Further studies are required to address the impact of combined pimobendan and ACEI therapy*….".

Guidance for the diagnosis and treatment of canine chronic valvular heart disease is given in the ACVIM consensus statement (Atkins et al 2009). For acute Stage C patients (*i.e*. denotes patients with past or current clinical signs of heart failure associated with structural heart disease.) it is mentioned that the evidence supporting an add-on effect of ACEI to pimobendan and furosemide is not clear. For Stage C and Stage D (refers to patients with end-stage disease with clinical signs of heart failure caused by CVHD that are refractory to what they identify as standard therapy) concurrent administration of furosemide, ACEI and pimobendan is recommended by the ACVIM consensus statement. Recommendations given from clinical expert panels may be used as supportive information. However, in the absence of clinical trials which confirm efficacy of a certain treatment strategy, such recommendations are of limited value to support an application for market authorisation. New veterinary medicinal products are normally not authorised on the basis of expert statements and individual clinical experience alone.

Heart failure describes the situation in which the heart cannot maintain cardiac output sufficient to meet the perfusion needs of the metabolizing tissues while maintaining normal venous pressures, and exercise capacity is thus limited. Heart failure can be divided into acute management and chronic therapy with different goals for treatment. The acute management of symptomatic heart failure involves the pharmacologic adjustment of the major determinants of heart function to achieve a new level of hemodynamic compensation in the face of the disease and the body's response to the disease that is present. Chronic therapy of CHF is currently aimed at maintaining those hemodynamic gains while

modulating and blunting the body's neuroendocrine responses in an attempt to minimize the clinical signs of CHF, protect the heart and vascular tissues, and prolong life, survival being the most sensitive measure of treatment success. In dogs presenting with their first onset of heart failure secondary to longstanding mitral valve disease, pimobendan is given to improve contractile function and reduce afterload and preload on the heart.

Angiotensin converting enzyme inhibition (e.g. benazepril) is given for additional mild preload and afterload reduction as well as control of hypertension. Potential problems with the combination of pimobendan and benazepril is that both active substances are heavily protein bound (90–95%), which may have implications in patients suffering from low blood protein levels (hypoproteinemia/hypoalbuminemia) and in patients that are on other concurrent therapies that are also highly protein bound (e.g. furosemide). Both pimobendan and benazepril promote decreases in heart afterload through peripheral vasodilation and lower blood pressure. For example, pimobendan also causes peripheral vasodilation by inhibiting the function of phosphodiesterase III. Thus, this fixed combination is at particular risk of inducing hypotension leading to serious effects in the patient (e.g. lower cardiac output). Blood pressure in relation to congestive heart failure is an independent predictor of mortality and morbidity. Thus, one of the features of good management of CHF is careful management of blood pressure. When using medications as monotherapies then doses can be adjusted for careful management of blood pressure, but this is not possible for a combination product, especially when used on an out-patient basis. Tolerance data available for pimobendan indicates a risk for cardiac muscle pathology and this substance has a narrow safety margin which further emphasizes that careful individual dose adjustment is often necessary when pimobendan is combined with an ACEI. Adapting treatment is an important part of cardiac drug treatment. It is important to understand how a disease which evolves can be treated with a fixed combination product and how eventual changes in dosing regime are feasible with such a product and mono-substance products containing either benazepril or pimobendan which are potentially used in the treatment group. It is recalled that in all cases, for benazepril, the higher, double dose is administered with the current product, leading to higher exposure and a particular risk of hypotension in addition to pimobendan administration, as explained above. In summary, tolerance is not improved and there is no demonstrated benefit on endpoint survival. As previously mentioned, there is no clinical data available which confirms the add-on value of combining the two products at the dose levels given for the fixed combination and furthermore, ensuring acceptable tolerance.

Substitution therapy

In addition to clinical data that confirms an added value of combining the two products at the dose level given for the fixed combination and sufficient tolerance at these dose levels, it needs to be justified that combining the two substances within the same tablet does not cause a negative pharmacokinetic interaction of clinical importance. The applicant aimed to demonstrate lack of pharmacokinetic interaction between pimobendan and benazepril mono-substance products and the combination product FORTEKOR PLUS through PK comparisons. The studies demonstrated variability in bioavailability outside the 80–125 % acceptance limits for benazeprilat, the active metabolite of benazepril, and thus in addition to uncertainty with regard to the clinical relevance of combining the two substances, it is uncertain whether exposure for the two substances is the same when the fixed combination is given, as compared to when the substances are administered concurrently as mono-substance products.

Conclusion

The benefit-risk balance for FORTEKOR PLUS is regarded as negative on the basis that the added clinical value of combining pimobendan and benazepril at the doses given for the fixed combination has not been

confirmed, as compared to administering any of the substances as mono-treatment. Furthermore, safety data to conclude on the tolerance for this combination is lacking which is regarded as a concern in light of potential risks connected to the combination as detailed above. Finally, the lack of significant pharmacokinetic interaction for the combination product has not been sufficiently demonstrated implying that it is put in doubt whether or not the exposure pattern will be the same for the fixed combination as for mono-products provided at corresponding adjusted doses.

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