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Veterinary Medicines and Product Data Management

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Cardalis (EMEA/V/C/002524)

International non-proprietary name: benazepril hydrochloride/spironolactone

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

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Introduction

The applicant Ceva Santé Animale submitted on 29 June 2011 an application for marketing authorisation to the European Medicines Agency (The Agency) for Cardalis, through the centralised procedure falling within Article 3(2)a of Regulation (EC) No 726/2004.

The eligibility to the centralised procedure was agreed upon by the EMA/CVMP at their meeting of 5-7 April 2011 as Cardalis contains a new combination of two existing active substances (spironolactone and benazepril hydrochloride) which was not authorised in the Community on the date of entry into force of the Regulation. Neither spironolactone nor benazepril are new active substances in EU authorised veterinary medicinal products, but inclusion of both in a fixed combination product is a novel presentation.

Cardalis tablets contain a combination of benazepril hydrochloride and spironolactone as active substances. There are three different strengths of Cardalis tablets and each is presented in plastic bottles containing 30 or 90 tablets. The route of administration is oral use. The target species is dogs. The product is indicated for the treatment of congestive heart failure caused by chronic degenerative valvular disease (with diuretic support as appropriate).

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

The CVMP adopted an opinion and CVMP assessment report on 16 May 2012.

On 23 July 2012, the European Commission adopted a Commission Decision for this application.

Scientific advice

The applicant received scientific advice from the CVMP on 19 May 2010 (EMA/CVMP/SA/066/10). The scientific advice concerned non-clinical and clinical aspects of the dossier. The advice was followed by the applicant.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system (DDPS)

The applicant has provided a detailed description of their pharmacovigilance system which fulfils the requirements of Directive 2001/82/EC as amended, and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

Cardalis tablets are manufactured either by Ceva Santé Animale, Loudeac, France or Catalent, Schorndorf, Germany. Secondary packaging and batch release for the EU will also be carried out by those 2 sites. All of the Manufacturing Authorisations and GMP certificates are satisfactory. No inspections are needed for GMP. Testing of the product prior to its authorisation is not recommended as the dosage form is conventional and the method of manufacture is standard.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system and the GMP certification of the manufacturing sites were considered to be in line with legal requirements.

Part 2 - Quality

Composition

The product is presented as oblong, brown, scored uncoated tablets in three different strengths, containing 2.5 mg, 5.0 mg and 10.0 mg benazepril hydrochloride and 20 mg, 40 mg and 80 mg spironolactone respectively.

The tablets are homothetic, having the same percentage composition and are compressed from a common blend. All the excipients are frequently found in many other tablet formulations and include: lactose monohydrate (diluent); microcrystalline cellulose (diluent); povidone K30 (binder); compressible sugar (sweetener); crospovidone (disintegrant); magnesium stearate (lubricant); and an artificial beef flavour. All the excipients are used in the manufacture of other authorised oral veterinary medicines in the EU.

No overages are included in the product.

According to the dosing table in the SPC, both the smallest and largest tablets may need to be divided. Satisfactory data are provided on the uniformity of division.

Container

The tablets are packed in white high density polyethylene (HDPE) bottles with child resistant polypropylene (PP) screw caps equipped with a desiccant insert. There are two pack sizes for each tablet strength, 30 tablets or 90 tablets. Secondary packaging is a cardboard carton. The child-resistant properties of the container have been demonstrated.

Development pharmaceutics

The key development data that would be expected for such a product have been provided, including evidence that the formulation, method of manufacture and dissolution test have been carefully selected and justified. Comparative dissolution studies have been performed between Cardalis and the EU authorised products which contain each active substance on its own. The studies show that the reference products exhibit similar dissolution profiles, independent of strength, for both benazepril and spironolactone. The studies also show that Cardalis exhibits similar dissolution profiles, independent of strength, for both benazepril and spironolactone. As the dissolution was similar regardless of pH and tablet size, and the *in vivo* bioequivalence was proven for the medium strength Cardalis tablet, the *in vivo* bioequivalence for other sizes or strengths was considered justifiably extrapolated.

The polymorphism of both active substances was described and it has been shown that the crystal forms present for routine production are the same as those present in the product used in the bioequivalence studies.

The levels of ingredients are typical of those used in tablet formulations and furthermore the rationale for the choice and concentration of each excipient was adequately explained. A homothetic granule formulation was developed. The manufacturing process consists of 3 steps (granulation of an internal phase, final blend after addition of the external phase, and tabletting). The influence of water content on the tablets was discussed, and due to the tablet sensibility to humidity, HDPE bottles with a

desiccant insert were selected as the primary packaging in order to avoid moisture uptake during storage.

Method of manufacture

Tablets are to be manufactured at the Ceva Santé Animale facility in Loudeac, France or the Catalent facility in Schorndorf, Germany. The manufacturing process is adequately described and a flow chart is provided. The process involves a classical wet granulation method using a high shear vacuum granulator, followed by tabletting using standard rotary tabletting presses. There are no unusual features about the process. Process validation data are provided for the Catalent facility but not for the Ceva Santé Animale facility. The applicant will generate, for this standard process, validation data if and when production commences at the Ceva Santé Animale facility.

Satisfactory in-process controls are in place at each stage.

All validation parameters were satisfactory for all tablet strengths and packaging. The validation data demonstrate that the manufacturing procedure is robust, reproducible and can consistently produce tablets of the desired quality. The process does not cause degradation of the active substances. The manufacturing process is considered validated and suitable for routine production.

Control of starting materials

Active substances

Both active substances have a monograph in the European Pharmacopoeia (Ph. Eur.) and are supported by Certificates of Suitability from the specified suppliers. Copies of the most recent Certificates of Suitability have been submitted.

The applicant's specifications for both active substances are included and are satisfactory and include suitable tests for particle size distribution.

No stability data are provided in the dossier as both active substances are supported by Certificates of Suitability.

Excipients

Appropriate specifications are in place for all of the excipients.

Five of the seven excipients used in the formulation are the subject of monographs in the Ph. Eur. Compressible sugar is the subject of a United States Pharmacopeia (USP) monograph.

The seventh excipient is artificial beef flavour, PC-0125, a material previously used in various veterinary medicinal products, authorised centrally, which is the subject of an in-house specification which is appropriate for this material. The flavour consists of hydrolysed vegetable protein (from soybeans), hydrogenated vegetable oil (from soybeans) and desiccated pork liver powder (from pork livers of swine raised in USA). All three ingredients of the flavour are FDA approved human food ingredients (complying with FDA law and regulations). Gamma irradiation of the artificial powdered beef flavour is carried out and the limits established for microbiological purity are sufficient to guarantee the quality of the tablets.

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

Compliance of all of the substances in the product in accordance with the latest version of the Joint CPMP/CVMP "Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products" (EMEA/410/01 Rev.2) has been confirmed.

Control tests during production

Satisfactory in-process controls are in place at each stage of the granulation and tabletting.

Control tests on the finished product

The specification includes all of the tests expected for a tablet and is in line with VICH GL39. The specifications proposed at release are suitable to control the quality of the finished product. The specification to be applied during shelf-life differs slightly in that the limits for the following parameters are wider: the spironolactone degradation product, canrenone; total spironolactone degradation products; one of the benazepril hydrochloride degradation products, Impurity C; total benazepril degradation products; the assay limits for each of the active substances. These wider shelf-life limits have been justified by batch analyses and stability data, qualified from a safety perspective, and also by a mass balance between the relaxation in the assay limits for each active substance and the permitted increase in related substances.

Analytical methods are fully described and validated in accordance with VICH guidelines.

Stability

Stability studies have been performed under VICH conditions. The dossier contains stability data from several batches stored at 25°C/60% RH, 30°C/65% RH, and accelerated data from storage at 40°C/75% RH. The results comply with specifications for all batches and demonstrate that, even under the accelerated conditions that: the physical characteristics remain unchanged; no significant change in spironolactone or benazepril hydrochloride contents is observed except under accelerated conditions when it remains in accordance with the specification; some increase in canrenone content is observed but remains in accordance with the specification; a slight increase in degradation products of benazepril hydrochloride is observed; the dissolution remains unchanged; and the antimicrobial test complies with specifications.

Additionally, photostability studies have been carried out on both active substances and the finished product which indicate that the active substances do not appear to be sensitive to light.

An in-use stability study has been carried out on a worst case basis, as recommended by the guideline. Two batches have been tested following 6 months storage (the worst case being a 90 tablet container intended for 180 half-tablet treatments). All measured parameters are within the proposed specification limits. Water content is constant, as would be expected with a desiccant in the bottle, demonstrating its efficiency.

In the light of the data available, a shelf-life of 24 months with no special storage condition requirements is acceptable. A shelf-life after opening the container of 6 months is supported by the results of the in-use stability study.

Overall conclusions on quality

Cardalis tablets for dogs are a fixed combination product, available in 3 different strengths of uncoated, scored tablets, containing benazepril hydrochloride and spironolactone.

The tablets are soundly formulated and are prepared from a common tablet blend. Starting materials, including both the active substances and excipients, have been adequately described. All of the excipients, including the beef flavouring, have been used previously in the manufacture of tablets. There is no foreseen risk for the transmission of animal spongiform encephalopathy agents.

The method of manufacture of the tablets is satisfactorily described and considered appropriate for such a formulation. The in-process controls were all well-described, and the process of manufacture is considered as being fully validated.

All of the methods used to control the finished product were sufficiently described and validated, and the limits in the release and shelf-life specifications have been justified. The results of the stability tests justify a 24 months shelf-life for the finished product when it is stored in the original package (HDPE plastic bottles), and a 6 month in-use shelf-life (after first opening the bottle).

The quality of Cardalis tablets for dogs is therefore considered as fully demonstrated and in line with current standards.

Part 3 - Safety documentation

Pharmacodynamics

The pharmacodynamics is reported in more detail in Part 4 of this report.

Pharmacokinetics

Benazepril has been used in veterinary medicines for several years and spironolactone for approximately four years, although it has a long history of use in human medicines. Both active substances have well known pharmacokinetic profiles. The complete data are addressed in Part 4 of this report.

Toxicological studies

Single dose toxicity:

Only limited data are provided for both spironolactone and benazepril hydrochloride, however this is sufficient as both active substances have satisfactory safety profiles following their use in human medicines for many years. The acute oral (LD_{50}) toxicity for spironolactone in the rat, mouse and rabbit is >1000 mg/kg body weight (bw). The acute oral toxicity (LD_{50}) of benazepril hydrochloride in the mouse is 4019 mg/kg body weight and the oral LD_{Lo} (lowest lethal dose) in the dog is 1000 mg/kg body weight. Furthermore, both benazepril and spironolactone have been used (separately) in veterinary medicines for several years; only the fixed combination of these 2 active substances is new. A number of studies investigating user safety with the combination product have been provided.

Repeat dose toxicity:

The repeat dose toxicity is addressed by reference to the target species safety study with the combination product. This is considered acceptable as the product was administered daily to dogs for 6 months at doses up to 5x the therapeutic dose. In terms of user safety, it is noted that effects were

only observed following repeat dosing by the oral route, a scenario which is unlikely for the dog owner. The study is assessed in Part 4 of this report.

Tolerance in the target species of animal:

This section of the dossier is assessed in Part 4 of this report.

Reproductive toxicity:

Data have been provided to address reproductive toxicity for both spironolactone and benazepril hydrochloride. The results of the studies indicate that both actives have an effect on reproductive performance and on developmental toxicity. The doses reported to elicit these adverse effects are not significantly higher than those likely following ingestion of the highest strength Cardalis tablet. The effects were observed with doses similar to the therapeutic dose in human medicines. (See also User Safety below.) For spironolactone, oral doses of 100 mg/kg bw and 10 mg/kg bw caused effects in reproductive toxicity and developmental toxicity studies respectively. The therapeutic dose for humans is up to 200 mg/day, equivalent to 3.33 mg/kg bw for a 60 kg adult. For benazepril hydrochloride, NOELs of 100 mg/kg bw for reproductive toxicity, 100 mg/kg bw for the foetus and 10 mg/kg bw for adults for developmental toxicity were set. The therapeutic dose in humans is 5 to 40 mg/day via the oral route, equivalent to 0.66 mg/kg bw for a 60 kg adult.

Mutagenicity/Genotoxicity:

A comprehensive battery of *in vitro* and *in vivo* genotoxicity studies (Ames, *in vitro* mammalian cell gene mutation and *in vivo* micronucleus test for both individual actives and in addition a UDS assay for spironolactone) has been provided for both active substances. The results for both actives in all assays were negative and neither of the active substances was considered a mutagen.

Carcinogenicity:

No data have been provided for this section of the dossier. This is considered acceptable given the negative results in the genotoxicity studies, the absence of any structural alerts on either molecule and the history of use of both active substances in veterinary and human medicines for many years.

Studies of other effects

Both spironolactone and benazepril hydrochloride have been used in human and veterinary medicines for a number of years, and a number of references were provided addressing potential other effects. However, the results of these studies were not considered to be relevant to the exposure scenarios relating to the dosing of dogs with the proposed tablet formulation, although the Committee acknowledged that they provided reassurance as to the safety profile of the two active substances in Cardalis tablets.

Results from studies on the primary eye and skin irritancy potential of the Cardalis formulation have been provided. The results indicate that Cardalis is slightly irritant to rabbit eyes and skin. The results of a local lymph node assay in mice demonstrated that Cardalis tablets are not skin sensitisers. However, veterinary medicinal products containing spironolactone and benazepril hydrochloride as single active substances do carry hypersensitivity warnings and pre-existing allergies could be triggered by exposure to Cardalis.

User safety

User safety is addressed in the user risk assessment included in the dossier. The potential routes of exposure to the user are identified as dermal and ocular contact as well as accidental ingestion of a tablet.

Ocular contact may result in slight irritation, but dermal exposure arising from users handling the tablet is unlikely to result in any adverse effects for the user. The user warnings included in the SPC address these potential exposure routes by advising users to wash their hands after handling the tablets. This warning adequately addresses accidental ocular and dermal exposure. There is also a warning for individuals who are hypersensitive to any of the ingredients to avoid contact with the product.

In terms of accidental ingestion of a tablet by a child, this is considered unlikely due to the child resistant packaging used and also the bitter taste of the product. The margin of exposure calculations provide reassurance with respect to a single oral exposure of a child of 15 kg bw. In addition, appropriate guidance has been included in the SPC with respect to accidental ingestion of the tablet.

The following user warnings are included in the SPC:

> "People with known hypersensitivity to spironolactone or benazepril should avoid contact with the veterinary medicinal product.
>
> In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
>
> Wash hands after use."

Given the reproductive toxicity profile of benazepril, and the warning carried on human medicines containing benazepril for pregnant women to seek advice from a doctor before taking the medication, the following warning for pregnant women with respect to contact with Cardalis tablets has been included in the SPC (and package leaflet):

> "Pregnant women should take special care to avoid accidental oral exposure because ACE inhibitors have been found to affect the unborn child during pregnancy in humans."

The safety profile of the combination of spironolactone and benazepril hydrochloride is considered acceptable. The Cardalis formulation has been evaluated in terms of potential routes of exposure to the dog owner.

Environmental risk assessment

A Phase I Environmental Risk Assessment (ERA) and expert report on environmental safety were provided in the dossier. The disposal advice provided in section 6.6 of the SPC is the standard disposal advice included for all veterinary medicinal products.

After oral administration of radiolabelled spironolactone to dogs, 80-90% of the dose is recovered in the excreta. Due to the extensive metabolism of spironolactone, a number of metabolites, but no parent compound, is detected in excreta; 20% of the dose is excreted in the urine and 70% in the faeces.

Benazepril hydrochloride is hydrolysed *in vivo* to its active metabolite benazeprilat. Benazeprilat is excreted in dogs by the biliary route (~54%) and in the urine (~46%).

The assessment justifiably ends at Phase I for the following reasons:

- Cardalis is only used in a non food-producing animal species
- Cardalis will only be used to treat a small number of animals
- The active substances are significantly metabolised and the metabolites are recovered mainly from the faeces of treated dogs

- A large proportion of excreta will be deposited in urban areas which may be considered less environmentally sensitive
- Faeces from treated dogs may be removed from the environment in domestic refuse or other waste disposal systems.

A satisfactory ERA was provided which demonstrated that the assessment should end at Phase I as the product was used in non-food animals only. A Phase II assessment was not required.

Overall conclusions on the safety documentation

A satisfactory safety package has been provided and this indicates that the main areas of concern, apart from the expected pharmacological effects of the formulation, relate to reproductive toxicity and the fact that the formulated product is a slight irritant. Although much of the data are derived from old studies, the extensive use of the two active substances (individually) in both human, and more recently veterinary, medicines provides additional reassurance as to the safety profile of the proposed formulation. The study performed with the final Cardalis formulation provides reassurance regarding exposure of the user during treatment of the dog. With the proposed user warnings in place the product is not expected to pose a risk for the user when used as recommended.

A satisfactory ERA has been provided which demonstrates that the product is not expected to pose a risk for the environment when used as recommended.

Residues documentation

As the product is only intended for administration to non-food producing species, there are no requirements for residues data.

Part 4 – Efficacy

Pre-clinical studies

In the Scientific Advice adopted by the CVMP for Cardalis in 2010 (EMA/CVMP/157576/2010), the CVMP agreed with the applicant's approach of relying on already submitted preclinical bibliographic data and the original studies for spironolactone (from the application for Prilactone, which contains spironolactone only and is from the same applicant), and bibliographic preclinical data on benazepril hydrochloride (acknowledging the well-established veterinary use of this active substance).

Pharmacodynamics

Spironolactone acts at the level of the renin angiotensin aldosterone system (RAAS) as an aldosterone antagonist. Its main beneficial effects in dogs with heart failure are thought to result from its antagonism of the deleterious effects of aldosterone on the cardiovascular system (myocardial fibrosis contributing to ventricular diastolic and systolic dysfunction; vascular remodelling and endothelial dysfunction leading to vasoconstriction and increased peripheral resistance). Spironolactone also mediates natriuresis, although this is considered to be of secondary importance in its role in the context of canine heart failure.

The pharmacodynamic profile of benazepril, a well known angiotensin converting enzyme inhibitor (ACEi) in veterinary medicine, is supported by literature references. ACEis also act on the RAAS by inhibiting the conversion of angiotensin I (ATI) to angiotensin II (ATII). This results in reduction of stimulation of aldosterone release mediated by ATII (and therefore also reduction in the adverse

effects of aldosterone) as well as reduction in the direct effects of ATII and consequently blood pressure via dilation of peripheral blood vessels (decrease in systemic vascular resistance) and increased sodium excretion.

No pharmacodynamic interactions were identified in an *in vivo* pharmacokinetic/pharmacodynamic (PK/PD) interaction study (summarised in pharmacokinetics section).

The pharmacodynamic characteristics of each of the active substances in Cardalis have been well documented, and the data are considered sufficient and acceptable.

Pharmacokinetics

A number of references were provided in support of the pharmacokinetics of the two individual active ingredients. Many of these have been previously assessed by the CVMP. Although some of the data provided in these are not in compliance with current standards, the active substances have been used in human medicines for many years. A summary of the pharmacokinetics from all the studies is given below:

The pharmacokinetics of spironolactone are based on its metabolites, as the parent compound is unstable at assay.

Benazepril is a prodrug of the active molecule benazeprilat, the pharmacokinetics for which are supported by literature references as well as new studies.

Absorption:

Spironolactone is well absorbed from the gut. After oral administration of spironolactone to dogs, it was demonstrated that the three metabolites achieved levels of 32 to 49% of the administered dose. Food increases the bioavailability to 80 to 90%. Following oral administration of 2 to 4 mg/kg bw, absorption increases linearly over the range and no accumulation occurs with repeat dosing of 2 mg/kg bw.

After multiple oral doses of 2 mg spironolactone per kg bw (with 0.25 mg benazepril hydrochloride per kg bw) for 7 consecutive days, no accumulation is observed. At steady state, mean C_{max} of 324 µg/l and 66 µg/l are achieved for the primary metabolites, 7-α-thiomethyl-spironolactone (TMS) and canrenone, 2 and 4 hours post-dosing, respectively. Steady-state conditions are reached by day 2.

Benazepril is well absorbed by the oral route, peak levels of benazepril are attained rapidly and decline quickly as the drug is partially metabolised by liver enzymes to benazeprilat. Benazeprilat T_{max} is reported in the literature as 1.25 h after single or repeated doses of 0.5 mg/kg bw. Unchanged benazepril and hydrophilic metabolites account for the remainder. The systemic bioavailability of benazepril is incomplete due to incomplete absorption and first pass metabolism. There is no significant difference in the pharmacokinetics of benazeprilat when benazepril (as hydrochloride) is administered to fed or fasted dogs.

After multiple oral doses of 0.25 mg benazepril hydrochloride per kg bw (with 2 mg spironolactone per kg bw) for 7 consecutive days, a peak benazeprilat concentration (C_{max} of 52.4 ng/ml) is achieved with a T_{max} of 1.4 h. Accumulation occurs during the early stages of repeat dosing (accumulation ratio of 1.47). Dose proportionality over the range 0.125 – 1 mg/kg bw is present after a single dose, but not after repeated dosing, due to saturation of ACE binding.

Distribution:

When spironolactone is administered via the oral route, distribution is preferentially to the gastrointestinal tract, kidneys, liver and adrenal glands; spironolactone is highly protein bound (>89%

in humans). In dogs the mean volumes of distribution of 7-α-thiomethyl-spironolactone and canrenone are approximately 153 litres and 177 litres respectively. The mean residence time of the metabolites ranges from 9 to 14 hours and they are preferentially distributed to the gastro-intestinal tract, kidney, liver and adrenal glands.

Benazepril and benazeprilat are rapidly distributed, mainly in liver and kidney. Benazeprilat is highly protein bound (85-90% reported in the dog), with a reported mean residence time of 15.2 h (range 9.2-22.8) and volume of distribution at steady state of 0.197 ±0.022 l/kg bw.

Metabolism:

Spironolactone is rapidly and completely metabolised by the liver into its active metabolites, 7-α-thiomethyl-spironolactone and canrenone, which are the primary metabolites in the dog. After co-administration of spironolactone (2 mg/kg bw) and benazepril HCl (0.25 mg/kg bw) the terminal plasma half-lives ($t_{½}$) were 7 hours and 6 hours for canrenone and TMS respectively.

Benazeprilat elimination in the dog is primarily via the biliary and renal routes. Concentrations decline biphasically: the initial fast phase represents elimination of free drug, while the terminal phase reflects the release of benazeprilat that was bound to ACE, mainly in the tissues. After co-administration of spironolactone (2 mg/kg bw) and benazepril HCl (0.25 mg/kg bw) the terminal plasma half-life of benazeprilat ($t_{½}$) was 18 hours. Benazepril and benazeprilat are extensively bound to plasma proteins, and in tissues are found mainly in the liver and kidney.

Repeated administration of benazepril leads to slight bioaccumulation of benazeprilat, steady state being achieved within few days.

Elimination:

Spironolactone is mainly excreted via its metabolites. The primary route of elimination in the dog is faecal due to biliary excretion, with a smaller proportion eliminated in the urine. The plasma clearances of canrenone and 7-α-thiomethyl-spironolactone are 1.5 l/h/kg bw and 0.9 l/h/kg bw respectively. After the oral administration of radiolabelled spironolactone to the dog, 70% of the dose is recovered in faeces and 20% in the urine.

Benazeprilat is excreted via the biliary and the urinary route in dogs. Benazeprilat additionally exhibits a slower, terminal elimination phase attributed to slow dissociation of benazeprilat from target receptors. The clearance of benazeprilat is not affected in dogs with impaired renal function and therefore no adjustment of benazepril dose is required in cases of renal insufficiency.

An *in vivo* three period, three treatment, six sequence crossover study to evaluate PK/PD interactions between spironolactone (2 mg/kg bw) and benazepril (0.5 mg/kg bw) was conducted in Beagle dogs. An established, validated acute hyperaldosteronism model was used to enable evaluation of the pharmacodynamic effect of spironolactone on urine Na^+:K^+ ratio. The products administered were authorised veterinary medicinal products containing spironolactone and benazepril as single active substances; Cardalis was not administered in this study. Measurements were taken after single administration and at steady state. The pharmacokinetics and pharmacodynamics of spironolactone were unmodified by co-administration of benazepril. Benazepril had a slight effect on the urine Na^+:K^+ ratio but less so than spironolactone. The pharmacokinetics of benazeprilat were modified by co-administration with spironolactone, manifested as statistically significant increases in the values for C_{max} and AUC. Nevertheless, the pharmacodynamics of benazeprilat (measured using plasma ACE activity) was unaffected by co-administration with spironolactone and this study finding was not judged to be clinically significant.

An *in vivo* two treatment, two period, crossover bridging bioequivalence study comparing the pharmacokinetics after co-administration of two authorised veterinary medicinal products containing spironolactone and benazepril as single active substances with Cardalis was conducted in 24 Beagle dogs. The doses of spironolactone and benazepril administered were 2.4 mg/kg bw and 0.3 mg/kg bw, respectively. Measurements were taken after single administration and at steady state. Bioequivalence within the narrow (0.8-1.25) 90% confidence interval limits was demonstrated for all pivotal parameters. Extrapolation of these results to other tablet strengths was supported by *in vitro* dissolution studies.

The pharmacokinetic data provided adequately support the application, and the omission of data on the combination product is justified as it is not needed for a fixed combination product.

Dose determination/justification

The rationale for the fixed spironolactone-benazepril combination for the treatment of heart failure is based on (i) pharmacological grounds (both substances act on the RAAS, but at different levels), and (ii) in clinical terms in that it is proposed that benazepril and spironolactone have an additive effect in reducing the risk of cardiac mortality in dogs with congestive heart failure. As the dosing regimen is based on the authorised dose of spironolactone (2 mg/kg bw/day) and the lower end of the authorised dose range for benazepril (0.25 – 0.5 mg/kg bw/day), no new dose determination/justification data were submitted. This is consistent with the approach proposed and accepted in the Scientific Advice adopted by the CVMP for Cardalis in 2010.

Target animal tolerance

A six month target animal safety study using Cardalis was conducted in healthy Beagle dogs at 0x, 1x, 3x and 5x the dose achieved at the highest end of the dose band (mean actual doses received 1x: 4.54 mg/kg bw spironolactone/0.57 mg/kg bw benazepril, 3x: 13.93/1.74 mg/kg bw; 5x: 22.53/2.82 mg/kg bw). Mild, treatment-related decreases in red cell mass were observed which were statistically significant in the 3x and 5x groups. These are unlikely to be clinically relevant as red cell counts remained within the reference range, and no adverse events relating to anaemia or other blood disorders were documented in the field safety data; however a statement has been added to section 4.10 of the SPC to reflect this effect. Increases in serum K^+ were seen but mean values remained within the reference range; this was considered to be a pharmacological effect and was investigated more fully in the clinical study analysis. Significantly decreased prostate weights were identified at necropsy in male dogs in the 3x and 5x groups. This effect may be associated with the administration of spironolactone and is documented in section 4.6 of the SPC. Hypertrophy of the zona glomerulosa of the adrenal glands was seen in the 3x and 5x groups, but it was considered that this was a physiological effect only and a statement is included in section 4.10 of the SPC. No mortality occurred during the study and no clinically relevant adverse events were recorded in any group.

In the clinical trials presented (spironolactone and benazepril administered concomitantly as separate single active substance formulations), the adverse events documented in the field safety data were approximately evenly distributed between the spironolactone/benazepril test group and the placebo/benazepril reference group. Most adverse events were due to diagnosed concomitant pathologies, age-related or non-specific signs. Mild to moderate hyperkalaemia was reported in small numbers of dogs in both the test and reference groups, but these findings were generally transient and suspected to be related to underlying renal disease. Results of blood biochemical analyses confirmed good field safety of the benazepril/spironolactone combination.

Field trials

No field studies conducted using Cardalis were presented at the time of application. This was acceptable for the following reasons:

- The mode of action of both active substances is based on additive and complementary effects;
- The combination formulation, Cardalis, has been shown to be bioequivalent to the administration of the separate actives;
- Long term field efficacy data are available in dogs treated with both active substances at the same dosage as proposed for the combination.

Field efficacy data from four studies, previously assessed by CVMP during the authorisation procedure for Prilactone (spironolactone alone, from the same applicant), have been presented:

Mid-term study GCP	3 month study enrolling cases not receiving furosemide at time of inclusion
Mid-term study GCP	2 month study enrolling cases receiving furosemide at the time of inclusion
Long-term study GCP	12 month study enrolling cases having completed either of the mid-term studies (above) and whose owners were willing to continue in follow up for a further year
Life-span study	Enrolled cases having completed the long-term study (above) and whose owners were willing to continue follow up until death of their dog

Field efficacy data for Cardalis is thus supported by a pooled data analysis from the results of the above studies. The objective of this analysis was to evaluate the long term efficacy (survival and reduction of clinical signs) of the co-administration of spironolactone and benazepril in dogs with congestive heart failure, compared with benazepril alone. In total, 222 dogs were recruited to these studies; of these, 109 cases were treated with spironolactone and benazepril, or placebo and benazepril for the whole follow-up period but only 80 met the inclusion criteria for the pooled data analysis (dose range administered consistent with that of each active in the proposed Cardalis SPC). Of the 80 dogs in the pooled data analysis, 41 dogs received spironolactone and benazepril (test group), and 39 dogs received benazepril plus placebo (reference group). The primary outcome in the survival analysis was death (spontaneous or euthanasia) for cardiac causes, "cardiac mortality". The study was limited by the fact that the analysis was conducted retrospectively and that the number of animals included was quite small, especially towards the end of the study. However, the applicant investigated the assumption of proportional hazards by checking the log minus log survival plot; the data were consistent with the assumption that the ratio of the risk in the test group to that in the reference group was constant throughout the follow-up time, and therefore the small number of dogs did not cause problems for the estimate of the treatment effect. The proportion of censored cases was high compared to the proportion of events, which can increase the potential for bias; however, the proportion of censored cases in the treatment and placebo groups was similar. A statistically significant survival benefit was shown for spironolactone in combination with benazepril compared to benazepril alone for both cardiac mortality (Log rank test p=0.011) and cardiac mortality-morbidity (Log rank test p=0.035) in a population of dogs with congestive heart failure predominantly due to valvular degeneration. In clinical terms, a relevant reduction in the risk of mortality from cardiac

causes of 89% (hazard ratio (HR)=0.11 [0.01, 0.87]) was demonstrated for the spironolactone/benazepril group compared to treatment with benazepril alone. As regards secondary outcomes, the reduction in risk of cardiac morbidity-mortality was 68% (HR=0.32 [0.10, 0.98]). When the survival was investigated in regard to combined renal-cardiac events, and all cause mortality, the trend was consistently towards a benefit for the spironolactone/benazepril group compared to benazepril alone, although statistical significance was not achieved for all analyses. These findings support the proposed indication.

Overall conclusion on efficacy

The rationale for this fixed combination is based on the complementary pharmacodynamic actions of the two active substances, and is considered sound. The pharmacokinetic and pharmacodynamic characteristics of each active are well documented and the potential for PK/PD interaction has been satisfactorily evaluated. Dose determination/confirmation is based on the dose regimens established for authorised veterinary medicinal products and linked to the final formulation by the bridging bioequivalence study. Target animal safety is conclusively addressed for each active substance, and for the Cardalis combination formulation; in a target animal safety study, the combination of spironolactone and benazepril had a good safety profile in the target species. Efficacy of the fixed combination is supported by pooled analysis of field study data from trials where the individual actives were administered as separate tablets; confirmation that these data can be extrapolated to Cardalis is provided by the bridging bioequivalence study and accepted by the CVMP.

It is noted that Scientific Advice was provided by CVMP in regard to this application and that it has been followed in relation to the key issues concerning pharmacology, dose determination and dose confirmation.

Part 5 – Benefit risk assessment

Cardalis contains spironolactone and benazepril in a fixed combination ratio of 1:8 and the product is presented as three strengths of tablets for oral administration: 2.5 mg/20 mg; 5 mg/40 mg; and, 10 mg/80 mg. The application is made under Article 13(b) (fixed combination) of Directive 2001/82/EC as amended. The product is indicated for the treatment of congestive heart failure caused by chronic degenerative valvular disease in dogs (with diuretic support as appropriate).

Neither spironolactone nor benazepril are new active substances in EU authorised veterinary medicinal products, but the inclusion of both in a fixed combination product is a novel presentation.

Benefit assessment

Direct therapeutic benefit

The two active substances in this fixed combination product are each authorised individually in veterinary medicinal products in the EU. Spironolactone is authorised for the treatment of congestive heart failure caused by valvular regurgitation in dogs, in combination with standard therapy, while benazepril is authorised for the treatment of congestive heart failure in dogs.

Both spironolactone and benazepril exert their pharmacodynamic effects on the renin angiotensin aldosterone system (RAAS), however their direct activities have different targets: spironolactone is an aldosterone antagonist, while benazepril is an angiotensin converting enzyme inhibitor (ACEi). Field studies submitted in support of this combination have demonstrated an increased survival in dogs treated concurrently with spironolactone and benazepril compared to benazepril alone.

The justification for this fixed combination of active substances centres on the rationale that both substances act in a complementary way on the RAAS, and that the indication for Prilactone (spironolactone only) states that it should be administered in combination with standard therapy for the treatment of heart failure. The suitability of co-administration of both actives in target patients has been supported by field studies where treatment with benazepril + spironolactone was found to improve survival compared to treatment with benazepril alone in dogs with congestive heart failure caused by chronic degenerative valve disease, and a bridging bioequivalence study has demonstrated that the fixed combination product is bioequivalent to the actives as administered in the field studies.

Additional benefits

As a fixed combination product, administration of one Cardalis tablet replaces administration of two single-active tablets, which may increase compliance.

Risk assessment

Both active ingredients have been used in human medicines for many years and in veterinary medicines now for several years, and the proposed dose for dogs is not significantly different to the human therapeutic dose. Spironolactone and benazepril hydrochloride were shown to have effects on developmental aspects following administration to pregnant animals at relevant stages of gestation, although the doses eliciting effects on foetal development for both active substances are in excess of the doses likely to be encountered in routine handling of the product.

Although dermal contact with the product is unlikely to result in any adverse effects for the user, ocular contact may result in slight irritation, therefore potential exposure of the user has been addressed through appropriate standard warnings in the SPC (and package leaflet). Due to the reproductive toxicity profile of benazepril, an additional warning is included that women should take special care to avoid accidental oral exposure to the product because ACE inhibitors have been found to affect the unborn child during pregnancy in humans. The risk to children from accidental ingestion is addressed by the child-resistant packaging and also by the bitter taste of the tablets.

As the product is only intended for administration to non-food producing species there is no consumer safety risk.

It is not considered that the product will pose a risk for the environment when used as recommended.

Risks to the target species related to adverse effects are appropriately documented in the proposed SPC. Both active substances have a good safety profile which is well reported in the literature, and this has been supported by a target animal safety study using the final fixed combination product. Despite the potential for combined therapy to lead to effects such as hypotension and hyperkalaemia, these are not widely observed *in vivo* as clinically significant effects in the target population.

Risk management or mitigation measures

The user safety warnings included in the SPC (and package leaflet) mitigate any potential risks to the dog owner. The risk to pregnant women from exposure to ACE inhibitors is addressed by the inclusion of a specific warning.

Standard disposal advice has been included in the SPC to mitigate any environmental impact of the product.

For target animal safety, the potential risk areas are mitigated by appropriate warnings in the proposed SPC (and package leaflet). The product is contraindicated in dogs used for breeding, and in

dogs suffering from hypoadrenocorticism, hyperkalaemia or hyponatraemia. Kidney function and serum potassium levels should be evaluated before initiating treatment.

Evaluation of the benefit risk balance

The formulation and manufacture of Cardalis is well described and specifications set will ensure that product of consistent quality will be produced.

Sufficient data have been provided for the product to support the indication "Treatment of congestive heart failure caused by chronic degenerative valvular disease in dogs (with diuretic support as appropriate)".

The product is well tolerated by the target animals and presents a low risk for users and the environment. Appropriate warnings have been included in the SPC (and package leaflet) to mitigate any risks.

The Committee concluded that the product has been shown to have a positive benefit risk balance overall for the approved indication.

Conclusion

Based on the original and complementary data presented the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the quality, safety and efficacy of Cardalis tablets for dogs are considered to be in accordance with the requirements of Directive 2001/82/EC, as amended. The overall benefit/risk evaluation is deemed positive with a sufficiently clear and complete SPC and product literature.