FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

TEMPORA 10 MG CHEWABLE TABLETS FOR DOGS
TEMPORA 50 MG CHEWABLE TABLETS FOR DOGS
TEMPORA 100 MG CHEWABLE TABLETS FOR DOGS

Date: 22/10/2012

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0235/001-003/DC
Name, strength and pharmaceutical form	TEMPORA 10 MG/50 MG/100 MG CHEWABLE TABLETS FOR DOGS
Applicant	Laboratoires SOGEVAL ROUTE DE MAYENNE ZI DES TOUCHES 53000 LAVAL FRANCE
Active substance(s)	Spironolactone
ATC Vetcode	QC03DA01
Target species	Dogs
Indication for use	Treatment of congestive heart failure caused by valvular regurgitation in dogs in combination with standard therapy.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the website http://www.anmv.anses.fr/

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Full application in accordance with Article 12 (3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	15/06/2012
Concerned Member States for original procedure	AT – BE – CZ – DE – DK – EL – ES – FI – HU – IE – IT – LU – NL – NO – PL – PT – RO –SE - UK

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.
It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC.
The product is safe for the user and for the environment, when used as recommended.
Suitable warnings and precautions are indicated in the SPC.
The efficacy of the product was demonstrated according to the claims made in the SPC. The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains 10, 50 or 100 mg/tablet active spironolactone and the excipients artificial chicken flavor, yeast, crospovidone type A, sodium lauryl sulfate, maltodextrine, magnesium stearate, silica colloidal anhydrous, silicified microcrystalline cellulose and lactose monohydrate.

The container is a blister made of OPA/AL/PVC – aluminium heat sealed. The particulars of the containers and controls performed are provided and conform to the regulation.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post-authorisation.

C. Control of Starting Materials

The active substance is spironolactone, an established active substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.
The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

E. Control on intermediate products

Not applicable.

F. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

G. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

An in-use shelf-life as detailed on the SPC has been supported by appropriate data.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Toxicological Studies

Single dose toxicity

Published data on the effects of a single dose of spironolactone by intraperitoneal in laboratory animals, intravenous or intragastric routes were provided. In rats, mice and rabbits, oral LD_{50} were greater than 1000 mg/kg. Spironolactone can be considered as being of low acute toxicity after a single oral administration.

Repeated dose toxicity

Published reports of studies conducted in rats, dogs and monkeys, and a 90-day tolerance study in dogs were provided.
Published reports were old and not sufficiently detailed for the establishment of a NOEL. However, observed changes were slight and reversible at the withdrawal of spironolactone administration. These changes were consistent with stimulation of liver metabolism and with hormonal anti-androgenic effects of spironolactone.
In rats fed with spironolactone, thyroid hypertrophy was reported. It was probably a compensatory reaction to lowered thyroid hormone levels.
No NOEL can be retained from the tolerance study in which anti androgenic and estrogenic effects (increased progesterone levels, atrophy of the prostate) were observed in dogs even at the therapeutic dose of 2 mg/kg/day.

Reproductive toxicity

A number of old published reports conducted in rats and mice and human data were provided. Effects of spironolactone on sexual organs were also assessed in the tolerance study in dogs.
Spironolactone caused infertility in female rats and mice by preventing ovulation and decreasing the number of embryos. In male rats, spironolactone induced an increase of the weight of testes associated with maturation arrest.
Data from human studies showed that spironolactone induced impotence and breast development in men and menstrual cycle changes and changes in breasts and lactation in women.
In the tolerance study in dogs, atrophy of the prostate and increased progesterone levels were observed at the therapeutic dose of 2 mg/kg/day. These findings were reversible at the withdrawal of spironolactone administration.
Because of the absence of conventional studies on developmental toxicity, no significant conclusion can be drawn on the effects of spironolactone on reproduction and developmental effects.
Since the applicant proposed to contra-indicate the use of the product in pregnant and lactating bitches and in dogs intended or used for breeding, no further data were requested.

Mutagenicity

Spironolactone was devoid of mutagenic potential in well conducted GLP bone marrow micronucleus in rat test, a chromosomal aberration test in human lymphocytes and a micronucleus assay in mouse bone marrow cell.
The final formulation showed positive results in 2 GLP *in vivo* mammalian erythrocyte micronucleus tests. These results were possibly due to one solvent of the formulation: DMSO. Two new GLP *in vivo*

mammalian erythrocyte micronucleus tests were conducted with methylcellulose or polypropylene glycol 400 as vehicle. In both tests, the product was shown to be devoid of mutagenic potential.
Furthermore, the final formulation was shown to be devoid of mutagenic potential in a GLP reverse mutations in *Salmonella typhimurium* TA 100 study B-01323 and in an *in vitro* mammalian chromosome aberration test in human peripheral blood lymphocytes. It can be concluded that the product, should not raise any mutagenic concerns.

Carcinogenicity

A rat study (1978) showed that spironolactone induced an increase in thyroid adenoma, testicular adenoma and liver nodules.
IARC (International Agency for Research on Cancer) review of spironolactone concluded that there is inadequate evidence for carcinogenicity in human and limited evidence in experimental animals, thus giving an overall evaluation that spironolactone is not classified as to its carcinogenicity to humans.
The carcinogenic potential of spironolactone would be most likely associated with hormonal disturbances (anti-androgenic activity) and secondary to induction of liver metabolising activity.
Effects on the thyroid were probably due to a compensatory reaction to lowered thyroid hormone levels.
Furthermore, spironolactone and the final formulation gave negative results in a relevant battery of mutagenic tests. Also, spironolactone has no structural analogy with known carcinogens. It can be concluded that the product should raise no carcinogenic concerns.

Other Studies

Spironolactone induced allergic reactions in human after oral administration or topical application. A warning in the case of hypersensitivity of the user is stated in the SPC. A contra-indication in the case of hypersensitivity to spironolactone of the dog is also stated. Spironolactone was classified as sensitizing to the skin in a well conducted skin sensitisation study in guinea pig.
The product was classified as slightly irritant for the skin and the eye of rabbit in well conducted studies on acute cutaneous and ocular irritation.

Observations in Humans

Spironolactone has been used as human medicine for several decades. It is used in the case of hyperaldosteronism and oedematous conditions linked to congestive heart failure. It is indicated in adults (25 mg once daily) and children (1 to 4 mg/kg/day in one or 2 daily administrations). Most of adverse effects are related to hormonal activities of spironolactone (gynecomastia and impotence in men, disturbances of menstrual cycles in women). Hypersensitive reactions may occur (cutaneous reactions, agranulocytosis) and hyperkalemia is also described.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

The applicant has provided a first phase environmental risk assessment in compliance with the relevant guideline.

The product is not expected to pose a risk for the environment when used as recommended.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacokinetics and pharmacodynamics properties of spironolactone in dog following oral administration of the product were documented by studies and by published papers.

A comparative dissolution was performed between the three strengths of the product. Under the tested conditions (3 pH and sodium lauryl sulfate), the spironolactone is similarly dissolved from the three products: more than 85% within 15 minutes.

A GLP kinetic study was performed in dogs following single oral and intravenous administration of spironolactone at 2 mg/kg bw. From these data, an absolute bioavailability of 83% was determined for the product.
A GLP kinetic study was performed in dogs following repeated oral administration of the product at the dose rate of spironolactone of 2 mg/kg bw. Some issues were raised on the protocol and the conclusion about the accumulation is limited. A slight accumulation was observed.
A non GLP study was performed to characterize the excretion balance of spironolactone in dog following a single oral administration at 2 mg/kg bw. The faecal route is the major route of elimination of spironolactone.
The elimination is rapid. The whole dose was eliminated over 48 hours.
An *in vitro* study was performed to characterize the protein binding of spironolactone in dog plasma. On the tested concentrations 1 to 200 ng/mL, the protein binding of the total radioactivity is about 90% and is not concentration dependent.

A dose determination was provided. The dose rate of 2 mg/kg bw was established by using an experimental model of induced hyperaldosteronism (Hoffman model) taking in account the ratio of urinary concentration Na/K. No differences were observed between the product and PRILACTONE of CEVA, the comparator.

Tolerance in the Target Species of Animals

The applicant provided a well conducted GLP tolerance study. It was conducted in accordance with VICH GL43 (Target animal safety or VMP) recommendations.
The product was daily orally administered to healthy Beagle dogs of both sexes at the recommended dose, 3X and 5X the recommended dose for 13 weeks with a 4 weeks recovery period for control and high dosed animals.
Target organs were prostate and liver only in male dogs. Progesterone levels were also affected in male dogs.

A dose related decrease in the volume and the weight of the prostate was noted. These findings were associated with a macroscopic atrophy of the prostate and with a minimal to moderate diffuse acinar atrophy.
Serum progesterone levels were increased in treated males.
These findings are in accordance with the anti-androgenic (or estrogenic) activity of spironolactone.
A moderate increase was observed in the liver weight of treated males, but without any associated histopathological changes.
All these findings were not associated with clinical signs and were reversible when the treatment was withdrawn.
The safety of the product has not been assessed in pregnant and lactating bitches and in dogs used for, or intended for breeding. Because of reprotoxicity of spironolactone, the use of the product is contra-indicated in these animals.
Palatabilities of the tested product tablets and the comparator tablets are similar.

IV.B Clinical Studies

The applicant provided one dose determination study (see pharmacological part) and one clinical field study.

The selected dose rate, 2 mg/kg of bodyweight was confirmed in the field trial. The field trial was multicentric, positive controlled, blinded, randomized GCP-compliant study conducted with the final formulation of the tested product. 259 dogs with degenerative valvular disease, presence of clinical signs of heart failure (NYHA class > 1) and receiving an ACEI (for at least 1 month) and/or pimobendane (for at least 1 week) were enrolled. There were 125 males and 101 females of all breeds, mean age of 11.18 ± 3.03 years. The efficacy of the product was demonstrated by testing the non-inferiority of the investigational product to the comparator, PRILACTONE of CEVA, on the survival in dogs with congestive heart failure due to mitral valve regurgitation.

V. OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.