ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Spironolactone Ceva 10 mg tablets for dogs
Spironolactone Ceva 40 mg tablets for dogs
Spironolactone Ceva 80 mg tablets for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Spironolactone Ceva 10 mg contains 10 mg spironolactone
Spironolactone Ceva 40 mg contains 40 mg spironolactone
Spironolactone Ceva 80 mg contains 80 mg spironolactone

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Spironolactone Ceva 10 mg : Brown bisected oval tablet of 10 mm length.
Spironolactone Ceva 40 mg : Brown bisected oval tablet of 17 mm length
Spironolactone Ceva 80 mg : Brown quadrisected oval tablet of 20 mm length

4. CLINICAL PARTICULARS

4.1 Target species

Dogs.

4.2 Indications for use, specifying the target species

For use in combination with standard therapy (including diuretic support, where necessary) for the treatment of congestive heart failure caused by valvular regurgitation in dogs.

4.3 Contraindications

Do not use in dogs suffering from hypoadrenocorticism, hyperkalaemia or hyponatraemia.
Do not use in conjunction with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in dogs with renal insufficiency (kidney impairment/dysfunction).
Do not use during pregnancy or lactation.
Do not use in animals used for, or intended for use in breeding.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals

Kidney function and serum potassium levels should be evaluated before initiating combined treatment with spironolactone and Angiotensin Converting Enzyme (ACE) inhibitors. Unlike in humans, an increased incidence of hyperkalaemia was not observed in clinical trials performed in dogs with this

combination. However, in dogs with renal impairment regular monitoring of renal function and serum potassium levels is recommended as there may be an increased risk of hyperkalaemia.
Dogs treated concomitantly with spironolactone and NSAIDs should be correctly hydrated.
Monitoring of their renal function and plasma potassium levels is recommended before initiation and during treatment with combined therapy (see section 4.3).
As spironolactone has an antiandrogenic effect, it is not recommended to administer the veterinary medicinal product to growing dogs.
As spironolactone undergoes extensive hepatic biotransformation, care should be taken when using the veterinary medicinal product to treat dogs with hepatic dysfunction.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

May cause skin sensitisation: people with known hypersensitivity to spironolactone should avoid contact with the veterinary medicinal product. Wash hands after use.
In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

4.6 Adverse reactions (frequency and seriousness)

A reversible prostatic atrophy is often observed in entire male dogs.

4.7 Use during pregnancy, lactation or lay

Do not use during pregnancy and lactation, laboratory studies in species (rat, mouse, rabbit and monkey) have shown evidence of developmental toxicity.

4.8 Interaction with other medicinal products and other forms of interaction

Furosemide and pimobendan have been used together with Spironolactone Ceva in dogs with heart failure without any clinical evidence of adverse reactions.
Spironolactone decreases digoxin elimination and hence raises digoxin plasma concentration. As the therapeutic index for digoxin is very narrow, it is advisable to monitor closely dogs receiving both digoxin and spironolactone.
The administration of either deoxycorticosterone or NSAIDs with spironolactone may lead to a moderate reduction of the natriuretic effects (reduction of urinary sodium excretion) of spironolactone.
Concomitant administration of spironolactone with ACE-inhibitors and other potassium-sparing drugs (as angiotensin receptor blockers, β-blockers, calcium channels blockers…etc) may potentially lead to hyperkalaemia (see section 4.5).
Spironolactone may cause both induction and inhibition of cytochrome P450 enzymes and could therefore affect the metabolism of other drugs utilizing these metabolic pathways.

4.9 Amounts to be administered and administration route

Oral use.

Administer 2 mg/kg of body weight of spironolactone once daily. The veterinary medicinal product should be administered with food. The tablet can either be mixed with a small amount of food offered prior to the main meal, or administered directly into the mouth after feeding.
The tablets contain beef flavouring to improve palatability, and a study conducted in healthy dogs showed that they were voluntarily and fully consumed 75% of the time.

	Number of tablets		
BODYWEIGHT	**Spironolactone Ceva 10 mg**	**Spironolactone Ceva 40 mg**	**Spironolactone Ceva 80 mg**
1 to 2.5 kg	**½**		
2.5 to 5 kg	**1**		
5 to 10 kg	**2**		
10 to 15 kg	**3**		
15 to 20 kg		**1**	
20 to 30 kg		**1 + ½**	
30 to 40 kg			**1**
40 to 50 kg			**1 + ¼**
50 to 60 kg			**1 + ½**

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

After administration of up to 10 times the recommended dose (20 mg/kg) to healthy dogs, dose-dependent adverse effects were noted (see section 4.6).
In case of an accidental massive ingestion by a dog, there is no specific antidote or treatment. It is therefore recommended to induce vomiting, gastric lavage (depending on risk assessment) and monitor electrolytes. Symptomatic treatment, e.g., fluid therapy, should be provided.

4.11 Withdrawal period

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Aldosterone antagonist.
ATCvet code: QC03DA01.

5.1 Pharmacodynamic properties

Spironolactone and its active metabolites (including 7α-thiomethyl-spironolactone and canrenone) act as specific antagonists of aldosterone, and exert their effects by binding competitively to the mineralocorticoid receptor located in the kidneys, heart and blood vessels.
Spironolactone is a natriuretic drug (historically described as a soft diuretic). In the kidney, spironolactone inhibits the aldosterone-induced sodium retention leading to increase in sodium and subsequently water excretion, and potassium retention.
The renal effects of spironolactone and its metabolites lead to a decrease in extracellular volume and consequently in a decrease of cardiac preload and left atrial pressure. The result is an improvement in heart function.
In the cardiovascular system, spironolactone prevents the detrimental effects of aldosterone. Although the precise mechanism of action is not yet clearly defined, aldosterone promotes myocardial fibrosis, myocardial and vascular remodelling and endothelial dysfunction.
In experimental models in dogs, it was shown that long term therapy with an aldosterone antagonist prevents progressive left ventricle dysfunction and attenuates left ventricle remodelling in dogs with chronic heart failure.

In a clinical study investigating the survival time in dogs with congestive heart failure, there was a 65% reduction in the relative risk of mortality at 15 months in dogs treated with spironolactone in combination with standard therapy compared to dogs treated with standard therapy alone. (Mortality was classified as death or euthanasia due to heart failure).
When used in combination with ACE-inhibitors, spironolactone may counteract the effects of "aldosterone escape".
A slight increase in aldosterone blood levels may be observed in animals on treatment. This is thought to be due to activation of feedback mechanisms without adverse clinical consequence. There may be a dose related hypertrophy of the adrenal zona glomerulosa at high dose rates.

5.2 Pharmacokinetic particulars

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

Absorption
After oral administration of spironolactone to dogs, it was demonstrated that the three metabolites achieved levels from 32 % to 49 % of the administered dose. Food increases the bioavailability from 80 % to 90 %. Following oral administration of 2 to 4 mg/kg, absorption increases linearly over the range. After multiple oral doses of 2 mg spironolactone/ kg for 10 consecutive days, no accumulation is observed. Mean C_{max} of 382 µg/l and 94 µg/l are achieved for the primary metabolites, 7α-thiomethyl-spironolactone and canrenone, after 2 and 4 hours, respectively. Steady-state conditions are reached by day 2.

Distribution
The mean volumes of distribution (Vss) of 7α-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.

Metabolism
Spironolactone is rapidly and completely metabolised by the liver into its active metabolites, 7α-thiomethyl-spironolactone and canrenone, which are the primary metabolites in the dog.

Elimination
Spironolactone is mainly excreted via its metabolites. Plasma clearance of canrenone is 1.45±0.39 l/h/kg and 7α-thiomethyl-spironolactone is 0.89±0.44 l/h/kg. After oral administration of radiolabelled spironolactone to the dog, 70 % of the dose is recovered in faeces and 20 % in the urine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Cellulose, microcrystalline
Crospovidone
Povidone K30
Artificial beef flavour
Compressible sugar
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years
2 months after first opening the bottle.

6.4. Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.
Partially used tablets should be stored in the original bottle.

6.5 Nature and composition of immediate packaging

White HDPE bottle containing 30 tablets with a white polypropylene child-resistant tamper-evident screw cap fitted with a desiccant insert, packaged in a cardboard box.

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Ceva Santé Animale
10, av. de La Ballastière
33500 Libourne
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/2/07/074/007-009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 June 2007
Date of last renewal: 22 May 2012

10 DATE OF REVISION OF THE TEXT

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Spironolactone Ceva 10 mg tablets for dogs
Spironolactone Ceva 40 mg tablets for dogs
Spironolactone Ceva 80 mg tablets for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Spironolactone Ceva 10 mg contains 10 mg spironolactone
Spironolactone Ceva 40 mg contains 40 mg spironolactone
Spironolactone Ceva 80 mg contains 80 mg spironolactone

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Spironolactone Ceva 10 mg: White, with a slight brownish mottling, bisected oval tablet of 10 mm length.
Spironolactone Ceva 40 mg: White, with a slight brownish mottling, oval tablet of 17 mm length with three parallel break-lines.
Spironolactone Ceva 80 mg: White, with a slight brownish mottling, oval tablet of 20 mm length with three parallel break-lines.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs.

4.2 Indications for use, specifying the target species

For use in combination with standard therapy (including diuretic support, where necessary) for the treatment of congestive heart failure caused by valvular regurgitation in dogs.

4.3 Contraindications

Do not use in dogs suffering from hypoadrenocorticism, hyperkalaemia or hyponatraemia.
Do not use in conjunction with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in dogs with renal insufficiency (kidney impairment/dysfunction).
Do not use during pregnancy or lactation.
Do not use in animals used for, or intended for use in breeding.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals

Kidney function and serum potassium levels should be evaluated before initiating combined treatment with spironolactone and Angiotensin Converting Enzyme (ACE) inhibitors. Unlike in humans, an increased incidence of hyperkalaemia was not observed in clinical trials performed in dogs with this combination. However, in dogs with renal impairment regular monitoring of renal function and serum potassium levels is recommended as there may be an increased risk of hyperkalaemia.
Dogs treated concomitantly with spironolactone and NSAIDs should be correctly hydrated. Monitoring of their renal function and plasma potassium levels is recommended before initiation and during treatment with combined therapy (see section 4.3).
As spironolactone has an antiandrogenic effect, it is not recommended to administer the veterinary medicinal product to growing dogs.
As spironolactone undergoes extensive hepatic biotransformation, care should be taken when using the veterinary medicinal product to treat dogs with hepatic dysfunction.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

May cause skin sensitisation: people with known hypersensitivity to spironolactone should avoid contact with the veterinary medicinal product. Wash hands after use.
In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

4.6 Adverse reactions (frequency and seriousness)

A reversible prostatic atrophy is often observed in entire male dogs.

4.7 Use during pregnancy, lactation or lay

Do not use during pregnancy and lactation. Laboratory studies in species (rat, mouse, rabbit and monkey) have shown evidence of developmental toxicity.

4.8 Interaction with other medicinal products and other forms of interaction

Furosemide and pimobendan have been used together with Spironolactone Ceva in dogs with heart failure without any clinical evidence of adverse reactions.
Spironolactone decreases digoxin elimination and hence raises digoxin plasma concentration. As the therapeutic index for digoxin is very narrow, it is advisable to monitor closely dogs receiving both digoxin and spironolactone.
The administration of either deoxycorticosterone or NSAIDs with spironolactone may lead to a moderate reduction of the natriuretic effects (reduction of urinary sodium excretion) of spironolactone.
Concomitant administration of spironolactone with ACE-inhibitors and other potassium-sparing drugs (as angiotensin receptor blockers, ß-blockers, calcium channels blockers…etc) may potentially lead to hyperkalaemia (see section 4.5).
Spironolactone may cause both induction and inhibition of cytochrome P450 enzymes and could therefore affect the metabolism of other drugs utilizing these metabolic pathways.

4.9 Amounts to be administered and administration route

Oral use.

Administer 2 mg/kg of body weight of spironolactone once daily. The veterinary medicinal product should be administered with food. The tablet can either be mixed with a small amount of food offered prior to the main meal, or administered directly into the mouth after feeding.

	Number of # tablets		
BODYWEIGHT	**Spironolactone Ceva 10 mg**	**Spironolactone Ceva 40 mg**	**Spironolactone Ceva 80 mg**
1 to 2.5 kg	½		
2.5 to 5 kg	**1**		
5 to 10 kg	**2**		
10 to 15 kg	**3**		
15 to 20 kg		**1**	
20 to 30 kg		**1 + ½**	
30 to 40 kg			**1**
40 to 50 kg			**1 + ¼**
50 to 60 kg			**1 + ½**

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

After administration of up to 10 times the recommended dose (20 mg/kg) to healthy dogs, dose-dependent adverse effects were noted (see section 4.6).
In case of an accidental massive ingestion by a dog, there is no specific antidote or treatment. It is therefore recommended to induce vomiting, gastric lavage (depending on risk assessment) and monitor electrolytes. Symptomatic treatment, e.g., fluid therapy, should be provided.

4.11 Withdrawal period

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Aldosterone antagonist.
ATCvet code: QC03DA01.

5.1 Pharmacodynamic properties

Spironolactone and its active metabolites (including 7α-thiomethyl-spironolactone and canrenone) act as specific antagonists of aldosterone, and exert their effects by binding competitively to the mineralocorticoid receptor located in the kidneys, heart and blood vessels.
Spironolactone is a natriuretic drug (historically described as a soft diuretic). In the kidney, spironolactone inhibits the aldosterone-induced sodium retention leading to increase in sodium and subsequently water excretion, and potassium retention.
The renal effects of spironolactone and its metabolites lead to a decrease in extracellular volume and consequently in a decrease of cardiac preload and left atrial pressure. The result is an improvement in heart function.
In the cardiovascular system, spironolactone prevents the detrimental effects of aldosterone. Although the precise mechanism of action is not yet clearly defined, aldosterone promotes myocardial fibrosis, myocardial and vascular remodelling and endothelial dysfunction.
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In a clinical study investigating the survival time in dogs with congestive heart failure, there was a 65% reduction in the relative risk of mortality at 15 months in dogs treated with spironolactone in combination with standard therapy compared to dogs treated with standard therapy alone. (Mortality was classified as death or euthanasia due to heart failure).
When used in combination with ACE-inhibitors, spironolactone may counteract the effects of "aldosterone escape".
A slight increase in aldosterone blood levels may be observed in animals on treatment. This is thought to be due to activation of feedback mechanisms without adverse clinical consequence. There may be a dose related hypertrophy of the adrenal zona glomerulosa at high dose rates.

5.2 Pharmacokinetic particulars

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

Absorption
After oral administration of spironolactone to dogs, it was demonstrated that the three metabolites achieved levels from 32 % to 49 % of the administered dose. Food increases the bioavailability from 80 % to 90 %. Following oral administration of 2 to 4 mg/kg, absorption increases linearly over the range. After multiple oral doses of 2 mg spironolactone/ kg for 10 consecutive days, no accumulation is observed. Mean C_{max} of 382 µg/l and 94 µg/l are achieved for the primary metabolites, 7α-thiomethyl-spironolactone and canrenone, after 2 and 4 hours, respectively. Steady-state conditions are reached by day 2.

Distribution
The mean volumes of distribution (Vss) of 7α-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.

Metabolism
Spironolactone is rapidly and completely metabolised by the liver into its active metabolites, 7α-thiomethyl-spironolactone and canrenone, which are the primary metabolites in the dog.

Elimination
Spironolactone is mainly excreted via its metabolites. Plasma clearance of canrenone is 1.45±0.39 l/h/kg and 7α-thiomethyl-spironolactone is 0.89±0.44 l/h/kg. After oral administration of radiolabelled spironolactone to the dog, 70 % of the dose is recovered in faeces and 20 % in the urine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Beef flavouring
Mannitol
Sodium laurilsulfate
Microcrystalline cellulose
Povidone
Sorbitol
Talc
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years
Partially used tablets to be used within 7 days.

6.4. Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.
Partially used tablets should be stored in the original blister.

6.5 Nature and composition of immediate packaging

Polyamide/aluminium/polyvinyl chloride//aluminium blisters containing 10 tablets.

Pack sizes
Cardboard box containing 3 or 18 blisters of 10 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Ceva Santé Animale
10, av. de La Ballastière
33500 Libourne
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/2/07/074/001-006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 June 2007
Date of last renewal: 22 May 2012

10 DATE OF REVISION OF THE TEXT

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. STATEMENT OF THE MRLs

D. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Ceva Santé Animale
Z.I. Très le Bois
22600 Loudéac
France

Catalent Germany
Schorndorf GmbH
Steinbeistrasse 2
D-73614 Schorndorf
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Veterinary medicinal product subject to prescription.

C. STATEMENT OF THE MRLs

Not applicable.

D. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Ceva Santé Animale ensures that the system of pharmacovigilance, as described in Part I of the marketing authorisation application, is in place and functioning before and whilst the veterinary medicinal product is on the market.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Cardboard box of 1 bottle of 30 tablets

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Spironolactone Ceva 10 mg tablets for dogs
Spironolactone Ceva 40 mg tablets for dogs
Spironolactone Ceva 80 mg tablets for dogs

Spironolactone.

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Spironolactone 10 mg
Spironolactone 40 mg
Spironolactone 80 mg

3. PHARMACEUTICAL FORM

Tablet

4. PACKAGE SIZE

30 tablets

5. TARGET SPECIES

Dogs

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP: {month/year}
Use within 2 months after first opening the bottle.

11. SPECIAL STORAGE CONDITIONS

Store partially used tablets in the original bottle.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read package leaflet.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, if applicable

For animal treatment only – to be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ceva Santé Animale
10, av. de La Ballastière
33500 Libourne
France

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/07/074/007
EU/2/07/074/008
EU/2/07/074/009

17. MANUFACTURER'S BATCH NUMBER

Lot: {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Cardboard box - 10 mg tablets, 40 mg tablets and 80 mg tablets

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Spironolactone Ceva 10 mg tablets for dogs
Spironolactone Ceva 40 mg tablets for dogs
Spironolactone Ceva 80 mg tablets for dogs
Spironolactone.

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Spironolactone 10 mg
Spironolactone 40 mg
Spironolactone 80 mg

3. PHARMACEUTICAL FORM

Tablet

4. PACKAGE SIZE

30 tablets
180 tablets

5. TARGET SPECIES

Dogs

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP: {month/year}
Partially used tablets to be used within 7 days.

11. SPECIAL STORAGE CONDITIONS

Store partially used tablets in the original blister.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read package leaflet.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, if applicable

For animal treatment only – to be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ceva Santé Animale
10, av. de La Ballastière
33500 Libourne
France

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/07/074/001 (3 blisters of 10 tablets)
EU/2/07/074/002 (18 blisters of 10 tablets)

EU/2/07/074/003 (3 blisters of 10 tablets)
EU/2/07/074/004 (18 blisters of 10 tablets)

EU/2/07/074/005 (3 blisters of 10 tablets)
EU/2/07/074/006 (18 blisters of 10 tablets)

17. MANUFACTURER'S BATCH NUMBER

Lot: {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

Bottle of 30 tablets

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Spironolactone Ceva 10 mg tablets for dogs
Spironolactone Ceva 40 mg tablets for dogs
Spironolactone Ceva 80 mg tablets for dogs

spironolactone

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

spironolactone 10 mg
spironolactone 40 mg
spironolactone 80 mg

3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

30 tablets

4. ROUTE(S) OF ADMINISTRATION

5. WITHDRAWAL PERIOD

6. BATCH NUMBER

Lot {number}

7. EXPIRY DATE

EXP {month/year}

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister - 10 mg tablets, 40 mg tablets and 80 mg tablets

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Spironolactone Ceva 10 mg tablets for dogs
Spironolactone Ceva 40 mg tablets for dogs
Spironolactone Ceva 80 mg tablets for dogs

Spironolactone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

CEVA

3. EXPIRY DATE

EXP: {month/year}

4. BATCH NUMBER

Lot:

5. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET

Spironolactone Ceva 10 mg tablets for dogs
Spironolactone Ceva 40 mg tablets for dogs
Spironolactone Ceva 80 mg tablets for dogs

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder:

Ceva Santé Animale
10, av. de La Ballastière
33500 Libourne
France
Tel: + 33 (0) 5 57 55 40 40
Fax : + 33 (0) 5 57 55 41 98

Manufacturers for batch release:

Ceva Santé Animale
Z.I. Très le Bois
22600 Loudéac
France

Catalent Germany
Schorndorf GmbH
Steinbeistrasse 2
D-73614 Schorndorf
Germany

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Spironolactone Ceva 10 mg tablets for dogs
Spironolactone Ceva 40 mg tablets for dogs
Spironolactone Ceva 80 mg tablets for dogs

Spironolactone

3. STATEMENT OF THE ACTIVE SUBSTANCE AND OTHER INGREDIENT

Spironolactone Ceva 10 mg contains 10 mg spironolactone
Spironolactone Ceva 40 mg contains 40 mg spironolactone
Spironolactone Ceva 80 mg contains 80 mg spironolactone

4. INDICATION

Spironolactone Ceva tablets are used in combination with standard therapy (including diuretic support, where necessary) for the treatment of congestive heart failure caused by valvular regurgitation in dogs.

5. CONTRAINDICATIONS

Do not use in dogs suffering from hypoadrenocorticism, hyperkalaemia or hyponatraemia.
Do not use in conjunction with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in dogs with renal insufficiency (kidney impairment/dysfunction).
Do not use during pregnancy or lactation.
Do not use in animals used for, or intended for use in breeding.

6. ADVERSE REACTIONS

A reversible prostatic atrophy (reduction in size) is often observed in entire male dogs.

If you notice any serious effects or other effects not mentioned in this leaflet, please inform your veterinary surgeon.

7. TARGET SPECIES

Dogs.

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

Oral use.

Administer 2 mg/kg of body weight of spironolactone once daily.

	Number of tablets		
BODYWEIGHT	**Spironolactone Ceva 10 mg**	**Spironolactone Ceva 40 mg**	**Spironolactone Ceva 80 mg**
1 to 2.5 kg	**½**		
2.5 to 5 kg	**1**		
5 to 10 kg	**2**		
10 to 15 kg	**3**		
15 to 20 kg		**1**	
20 to 30 kg		**1 + ½**	
30 to 40 kg			**1**
40 to 50 kg			**1 + ¼**
50 to 60 kg			**1 + ½**

9. ADVICE ON CORRECT ADMINISTRATION

The veterinary medicinal product should be administered with food. The tablet can either be mixed with a small amount of food offered prior to the main meal, or administered directly into the mouth after feeding. The tablets contain beef flavouring to improve palatability, and a study conducted in healthy dogs showed that they were voluntarily and fully consumed 75% of the time.

10. WITHDRAWAL PERIOD

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
This veterinary medicinal product does not require any special storage conditions.
Use within 2 months after first opening the bottle.
Partially used tablets should be stored in the original bottle.
Do not use after the expiry date which is stated on the carton after EXP.

12. SPECIAL WARNING(S)

Special precautions for use in animals
Kidney function and serum potassium levels should be evaluated before initiating combined treatment with spironolactone and Angiotensin Converting Enzyme (ACE) inhibitors. Unlike in humans, an increased incidence of hyperkalaemia (raised blood potassium levels) was not observed in studies in dogs with this combination. However, in dogs with renal impairment regular monitoring of renal function and serum potassium levels is recommended as there may be an increased risk of hyperkalaemia.
Dogs treated concomitantly with spironolactone and NSAIDs should be correctly hydrated. Monitoring of their renal function and plasma potassium levels is recommended before initiation and during treatment with combined therapy (see section "Contraindications").
As spironolactone has an antiandrogenic effect (acts against male hormones), it is not recommended to administer the veterinary medicinal product to growing dogs.
As spironolactone undergoes extensive hepatic (liver) biotransformation, care should be taken when using the veterinary medicinal product in dogs with liver dysfunction.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
May cause skin sensitisation: people with known hypersensitivity to spironolactone should avoid contact with the veterinary medicinal product. Wash hands after use.
In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

Use during pregnancy, lactation or lay
Do not use during pregnancy and lactation, laboratory studies in species (rat, mouse, rabbit and monkey) have shown evidence of developmental toxicity.

Interactions
Furosemide and pimobendan have been used together with Spironolactone Ceva in dogs with heart failure without any clinical evidence of adverse reactions.
Spironolactone decreases digoxin elimination and hence raises digoxin plasma concentration. As the therapeutic index for digoxin is very narrow, it is advisable to monitor closely dogs receiving both digoxin and spironolactone.
The administration of either deoxycorticosterone or NSAIDs with spironolactone may lead to a moderate reduction of the natriuretic effects (reduction of urinary sodium excretion) of spironolactone.
Concomitant administration of spironolactone with ACE-inhibitors and other potassium-sparing drugs (as angiotensin receptor blockers, ß-blockers, calcium channels blockers, etc) may potentially lead to hyperkalaemia (see section "Special precautions for use in animals").
Spironolactone may cause both induction and inhibition of cytochrome P450 enzymes and could therefore affect the metabolism of other drugs utilizing these metabolic pathways.

Overdose
After administration of up to 10 times the recommended dose (20 mg/kg) to healthy dogs, dose-dependent adverse effects were noted (see section "Adverse Reactions").
In case of an accidental massive ingestion by the dog, there is no specific antidote or treatment. It is therefore recommended to induce vomiting, gastric lavage (depending on risk assessment) and monitor electrolytes. Symptomatic treatment, e.g., fluid therapy, should be provided.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

Detailed information on this product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu

15. OTHER INFORMATION

Pack size:
Bottle containing 30 tablets packed in a cardboard box.

Not all pack sizes may be marketed.

Pharmacodynamic properties
Spironolactone and its active metabolites (including 7α-thiomethyl-spironolactone and canrenone) act as specific antagonists of aldosterone, and exert their effects by binding competitively to the mineralocorticoid receptor located in the kidneys, heart and blood vessels.
Spironolactone is a natriuretic drug (historically described as a soft diuretic). In the kidney, spironolactone inhibits the aldosterone induced sodium retention leading to increase in sodium and subsequently water excretion, and potassium retention.
The renal effects of spironolactone and its metabolites lead to a decrease in extracellular volume and consequently in a decrease of cardiac preload and left atrial pressure. The result is an improvement in heart function.
In the cardiovascular system spironolactone prevents the detrimental effects of aldosterone. Although the precise mechanism of action is not yet clearly defined, aldosterone promotes myocardial fibrosis, myocardial and vascular remodelling and endothelial dysfunction.
In experimental models in dogs, it was shown that long term therapy with an aldosterone antagonist prevents progression left ventricle dysfunction and attenuates left ventricle remodelling in dogs with chronic heart failure.
In a clinical study investigating the survival time in dogs with congestive heart failure, there was a 65% reduction in the relative risk of mortality at 15 months in dogs treated with spironolactone in combination with standard therapy compared to dogs treated with standard therapy alone. (Mortality was classified as death or euthanasia due to heart failure).
When used in combination with ACE-inhibitors, spironolactone may counteract the effects of "aldosterone escape".
A slight increase in aldosterone blood levels may be observed in animals on treatment. This is thought to be due to activation of feedback mechanisms without adverse clinical consequence.
There may be a dose related hypertrophy of the adrenal zona glomerulosa at high dose rates.

PACKAGE LEAFLET FOR

Spironolactone Ceva 10 mg tablets for dogs
Spironolactone Ceva 40 mg tablets for dogs
Spironolactone Ceva 80 mg tablets for dogs

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder:

Ceva Santé Animale
10, av. de La Ballastière
33500 Libourne
France
Tel: + 33 (0) 5 57 55 40 40
Fax : + 33 (0) 5 57 55 41 98

Manufacturers for batch release:

Ceva Santé Animale
Z.I. Très le Bois
22600 Loudéac
France

Catalent Germany
Schorndorf GmbH
Steinbeistrasse 2
D-73614 Schorndorf
Germany

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Spironolactone Ceva 10 mg tablets for dogs
Spironolactone Ceva 40 mg tablets for dogs
Spironolactone Ceva 80 mg tablets for dogs

Spironolactone

3. STATEMENT OF THE ACTIVE SUBSTANCE AND OTHER INGREDIENT

Spironolactone Ceva 10 mg contains 10 mg spironolactone
Spironolactone Ceva 40 mg contains 40 mg spironolactone
Spironolactone Ceva 80 mg contains 80 mg spironolactone

4. INDICATION

Spironolactone Ceva tablets are used in combination with standard therapy (including diuretic support, where necessary) for the treatment of congestive heart failure caused by valvular regurgitation in dogs.

5. CONTRAINDICATIONS

Do not use in dogs suffering from hypoadrenocorticism, hyperkalaemia or hyponatraemia.
Do not use in conjunction with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in dogs with renal insufficiency (kidney impairment/dysfunction).
Do not use during pregnancy or lactation.
Do not use in animals used for, or intended for use in breeding.

6. ADVERSE REACTIONS

A reversible prostatic atrophy (reduction in size) is often observed in entire male dogs.

If you notice any serious effects or other effects not mentioned in this leaflet, please inform your veterinary surgeon.

7. TARGET SPECIES

Dogs.

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

Oral use.

Administer 2 mg/kg of body weight of spironolactone once daily.

	Number of # tablets		
BODYWEIGHT	**Spironolactone Ceva 10 mg**	**Spironolactone Ceva 40 mg**	**Spironolactone Ceva 80 mg**
1 to 2.5 kg	**½**		
2.5 to 5 kg	**1**		
5 to 10 kg	**2**		
10 to 15 kg	**3**		
15 to 20 kg		**1**	
20 to 30 kg		**1 + ½**	
30 to 40 kg			**1**
40 to 50 kg			**1 + ¼**
50 to 60 kg			**1 + ½**

9. ADVICE ON CORRECT ADMINISTRATION

The veterinary medicinal product should be administered with food. The tablet can either be mixed with a small amount of food offered prior to the main meal, or administered directly into the mouth after feeding.

10. WITHDRAWAL PERIOD

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
This veterinary medicinal product does not require any special storage conditions.
Partially used tablets should be stored in the original blister and used within 7 days.
Do not use after the expiry date which is stated on the carton and blister label after EXP.

12. SPECIAL WARNING(S)

Special precautions for use in animals
Kidney function and serum potassium levels should be evaluated before initiating combined treatment with spironolactone and Angiotensin Converting Enzyme (ACE) inhibitors. Unlike in humans, an increased incidence of hyperkalaemia (raised blood potassium levels) was not observed in studies in dogs with this combination. However, in dogs with renal impairment regular monitoring of renal function and serum potassium levels is recommended as there may be an increased risk of hyperkalaemia.
Dogs treated concomitantly with spironolactone and NSAIDs should be correctly hydrated.
Monitoring of their renal function and plasma potassium levels is recommended before initiation and during treatment with combined therapy (see section "Contraindications").
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May cause skin sensitisation: people with known hypersensitivity to spironolactone should avoid contact with the veterinary medicinal product. Wash hands after use.
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Use during pregnancy, lactation or lay
Do not use during pregnancy and lactation, laboratory studies in species (rat, mouse, rabbit and monkey) have shown evidence of developmental toxicity.

Interactions
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The administration of either deoxycorticosterone or NSAIDs with spironolactone may lead to a moderate reduction of the natriuretic effects (reduction of urinary sodium excretion) of spironolactone.
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Spironolactone may cause both induction and inhibition of cytochrome P450 enzymes and could therefore affect the metabolism of other drugs utilizing these metabolic pathways.

Overdose
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In case of an accidental massive ingestion by the dog, there is no specific antidote or treatment. It is therefore recommended to induce vomiting, gastric lavage (depending on risk assessment) and monitor electrolytes. Symptomatic treatment, e.g., fluid therapy, should be provided.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

Detailed information on this product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu

15. OTHER INFORMATION

Pack sizes:
Cardboard box containing 3 or 18 blisters of 10 tablets.

Not all pack sizes may be marketed.

Pharmacodynamic properties
Spironolactone and its active metabolites (including 7α-thiomethyl-spironolactone and canrenone) act as specific antagonists of aldosterone, and exert their effects by binding competitively to the mineralocorticoid receptor located in the kidneys, heart and blood vessels.
Spironolactone is a natriuretic drug (historically described as a soft diuretic). In the kidney, spironolactone inhibits the aldosterone-induced sodium retention leading to increase in sodium and subsequently water excretion, and potassium retention.
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In experimental models in dogs, it was shown that long term therapy with an aldosterone antagonist prevents progressive left ventricle dysfunction and attenuates left ventricle remodelling in dogs with chronic heart failure.
In a clinical study investigating the survival time in dogs with congestive heart failure, there was a 65% reduction in the relative risk of mortality at 15 months in dogs treated with spironolactone in combination with standard therapy compared to dogs treated with standard therapy alone. (Mortality was classified as death or euthanasia due to heart failure).
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