ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Isemid 1 mg chewable tablets for dogs (2.5-11.5 kg)
Isemid 2 mg chewable tablets for dogs (> 11.5-23 kg)
Isemid 4 mg chewable tablets for dogs (> 23-60 kg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each chewable tablet contains:

Active substance:

Isemid 1 mg	1 mg of torasemide
Isemid 2 mg	2 mg of torasemide
Isemid 4 mg	4 mg of torasemide

Excipients:
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Chewable tablet.
Oblong brown scored tablets. The tablet can be divided into halves.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs.

4.2 Indications for use, specifying the target species

For treatment of clinical signs related to congestive heart failure in dogs, including pulmonary oedema.

4.3 Contraindications

Do not use in cases of renal failure.
Do not use in cases of dehydration, hypovolaemia or hypotension.
Do not use concomitantly with other loop diuretics.
Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings for each target species

The initial/maintenance dose may be temporarily increased when pulmonary oedema becomes more severe, i.e. reaching alveolar oedema state (see section 4.9).

4.5 Special precautions for use

Special precautions for use in animals
In dogs presenting with acute pulmonary oedema requiring emergency treatment, the use of injectable medicinal products should be considered first before commencing oral diuretic therapy.

Renal function (measurement of blood urea and creatinine as well as urine protein: creatinine (UPC) ratio), hydration status and serum electrolytes status should be monitored prior to and during treatment

at very regular intervals according to the benefit-risk assessment performed by the responsible veterinarian (see sections 4.3 and 4.6 of the SPC). The diuretic response to torasemide may increase over time upon repeated dosing, particularly at doses greater than 0.2 mg/kg/day; therefore more frequent monitoring should be considered.

Torasemide should be used with caution in cases of diabetes mellitus. Monitoring of glycaemia in diabetic animals is recommended prior to and during treatment. In dogs with pre-existing electrolyte and/or water imbalance, this should be corrected prior to treatment with torasemide.

As torasemide increases thirst, dogs should have free access to fresh water.
In case of loss of appetite and/or vomiting and/or lethargy or in case of treatment adjustment, renal function (blood urea and creatinine as well as urine protein:creatinine (UPC) ratio) should be assessed.

In a clinical field trial, the efficacy of Isemid was demonstrated when it was used as a first line treatment. Transferring treatment from an alternative loop diuretic to this veterinary medicinal product has not been evaluated and such a change should only be implemented based on a benefit-risk assessment performed by the responsible veterinarian.

The safety and efficacy of the product has not been assessed for dogs weighing less than 2.5 kg. For these animals use only according to the benefit/risk assessment by the responsible veterinarian.

The tablets are flavoured.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
This veterinary medicinal product may cause increased urination, thirst and/or gastrointestinal disturbances and/or hypotension and/or dehydration if ingested. Any part-used tablets should be returned to the blister pack and then to the original carton to help prevent access by children. In case of accidental ingestion, particularly by a child, seek medical advice immediately and show the package leaflet or the label to the physician.

This veterinary medicinal product may cause hypersensitivity (allergic) reactions in persons that are sensitized to torasemide. People with known hypersensitivity to torasemide, to sulfonamides or to any of the excipients should avoid contact with the veterinary medicinal product. If symptoms of allergy occur, seek medical advice and show the product packaging to the physician.

Wash hands after use.

4.6 Adverse reactions (frequency and seriousness)

In a clinical field study, renal insufficiency, an increase in renal blood parameters, haemoconcentration and alterations in electrolyte levels (chloride, sodium, potassium, phosphorus, magnesium, calcium) were very commonly observed.

The following clinical signs were observed commonly: episodic gastrointestinal signs such as vomiting and diarrhoea, dehydration, polyuria, polydipsia, urinary incontinence, anorexia, weight loss and lethargy.

Other effects consistent with the pharmacological activity of torasemide were observed in pre-clinical studies in healthy dogs at the recommended dose, i.e. dry mucosa of the oral cavity, reversible increases in glucose and aldosterone serum concentrations, decrease in urine specific gravity and increase in urine pH.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)

- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports)

4.7 Use during pregnancy, lactation or lay

Laboratory studies in rats and rabbits have shown foetotoxicity at maternotoxic doses. As the safety of the product has not been established in the target species, the use of the product is not recommended during pregnancy, lactation and breeding animals.

4.8 Interaction with other medicinal products and other forms of interaction

Co-administration of loop diuretics and NSAIDs can result in a decreased natriuretic response.

Concomitant use with NSAIDs, aminoglycosides or cephalosporins may increase the risk of nephrotoxicity and/or ototoxicity of those medicinal products.
Torasemide may antagonise the action of oral hypoglycaemic agents.
Torasemide may increase the risk of sulfonamide allergy.

In cases of co-administration with corticosteroids, the effects of loss of potassium may be potentiated.
In cases of co-administration with amphotericin B, increased potential for nephrotoxicity and intensification of electrolyte imbalance can be observed.

No pharmacokinetic interactions have been reported following co-administration of torasemide with digoxin; however hypokalaemia can enhance digoxin-induced arrhythmias.

Torasemide can reduce the renal excretion of salicylates, leading to an increased risk of toxicity.

Care should be exercised when administering torasemide with other highly plasma protein bound drugs. Since protein binding facilitates the renal secretion of torasemide, a decrease in binding due to displacement by another drug may be a cause of diuretic resistance.

Concomitant administration of torasemide with other substances metabolised by cytochrome P450 families 3A4 (e.g.: enalapril, buprenorphine, doxycycline, cyclosporine) and 2E1 (isoflurane, sevoflurane, theophylline) may decrease their clearance from the systemic circulation.
The effect of antihypertensive veterinary medicinal products, especially angiotensin converting enzyme (ACE)-inhibitors, may be potentiated when co-administered with torasemide.

4.9 Amounts to be administered and administration route

Oral use.

The recommended initial/maintenance dose is 0.13 to 0.25 mg torasemide/kg bodyweight/day, once daily.
In case of moderate or severe pulmonary oedema, this dose can be increased if necessary up to a maximum dose of 0.4 mg/kg bodyweight/day once daily.

Doses of 0.26 mg/kg and higher should only be administered for a maximum period of 5 days. After this period, the dose should be reduced to the maintenance dose and the dog should be evaluated by the veterinarian in a few days.
The following table shows the dose adjustment scheme within the recommended dose range of 0.13 to 0.4 mg/kg/day:

Dog Bodyweight (kg)	Number and strength of Isemid tablets to be administered	
	Initial/Maintenance dose (0.13 to 0.25 mg/kg/day)	**Temporary high dose** (0.26 to 0.40 mg/kg/day)
	1 mg	
2.5 to 4	½	1
> 4 to 6	1	1 + ½
> 6 to 8	From 1 to 1 + ½	From 2 to 2 + ½
> 8 to 11.5	From 1 + ½ to 2	From 2 + ½ to 3
	2 mg	
> 11.5 to 15	From 1 to 1 + ½	2
> 15 to 23	From 1 + ½ to 2	From 2 + ½ to 3
	4 mg	
> 23 to 30	From 1 to 1 + ½	2
> 30 to 40	From 1 + ½ to 2	From 2 + ½ to 3
> 40 to 60	From 2 to 2 + ½	From 3 to 4

The dose should be adjusted to maintain patient comfort with attention to renal function and electrolytes status. Once signs of congestive heart failure have been controlled and the patient is stable, it should be continued at the lowest effective dose, if long term diuretic therapy with this product is required.

If the tablet is not spontaneously taken by the dog, it can also be given with food or directly into the mouth.

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

After administration to healthy dogs of 3 times and 5 times the maximum dose for 5 consecutive days followed by 177 daily administrations of 3 times and 5 times the highest therapeutic recommended dose for maintenance, histopathological changes in the kidneys (interstitial inflammation, dilatation of renal tubules and subscapular cysts) were noted in addition to the effects observed after the administration of the recommended dose (see section 4.6). The renal lesions were still present at 28 days after the end of treatment. Microscopic characteristics of the lesions suggest an ongoing repair process. These lesions may most likely be considered as a result of the pharmacodynamic effect (diuresis) and were not associated with evidence of glomerulosclerosis or interstitial fibrosis. Transient dose response alterations in the adrenal glands, consisting of minimal to moderate reactive hypertrophy/hyperplasia, presumably related to high production of aldosterone, were observed in the dogs treated with up to 5 times the highest therapeutic recommended dose. An increase in albumin serum concentration was observed. ECG alterations without any clinical signs (increase in P wave and/or QT interval) were observed in some animals after the administration of 5 times the highest recommended dose. The causative role of changes in plasma electrolyte values cannot be excluded.

After administration of 3 and 5 times the highest therapeutic recommended dose to healthy dogs, a decrease of appetite was observed which led to a weight loss in some cases.

In case of overdose, treatment would be at the discretion of the responsible veterinarian, based on the presenting signs.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Cardiovascular system, high-ceiling diuretics, plain sulfonamides
ATC vet code: QC03CA04

5.1 Pharmacodynamic properties

Torasemide belongs to the pyridine-3-sulfonylurea class of loop diuretics, also called high-ceiling diuretics. Torasemide has a chemical structure between those of loop diuretics (such as furosemide) and Cl^- channel blockers.
The primary site of action of torasemide is the thick ascending limb of the loop of Henle, where it interacts with the Na^+-K^+-$2Cl^-$ cotransporter localised in the luminal membrane (urine side) and blocks the active reabsorption of sodium and chloride. Therefore, diuretic activity of torasemide correlates better with the rate of torasemide excretion in the urine than with the concentration in the blood.
Since the ascending limb of the loop of Henle is impermeable to water, the inhibition of Na^+ and Cl^- movement from the lumen to the interstitial space increases the concentration of ions in the lumen and produces a hypertonic medullary interstitium. Consequently, water reabsorption from the collecting duct is inhibited and the volume of water on the luminal side is increased.
Torasemide causes a significant, dose-dependent increase in urine flow and the urinary excretion of sodium and potassium. Torasemide has a more potent, longer-acting diuretic activity than furosemide.

5.2 Pharmacokinetic particulars

In dogs, following a single intravenous dose of 0.2 mg torasemide/kg bodyweight, the mean total clearance was 22.1 mL/h/kg, with a mean volume of distribution of 166 mL/kg and a mean terminal half-life of about 6 hours. After oral administration of 0.2 mg torasemide/kg bodyweight, the absolute bioavailability is about 99% based on plasma concentration-time data and 93% based on urine concentration-time data.
Feeding significantly increased torasemide $AUC_{0-\infty}$ by 37% and slightly delayed T_{max}, but in fasted and fed conditions the maximal concentrations (C_{max}) are approximately the same (2015 µg/L vs 2221 µg/L, respectively). Furthermore, the diuretic effect of torasemide is approximately the same in fed and fasted conditions. Consequently, the medicinal product can be administered with or without food.

In dogs, the plasma protein binding is > 98%.
A large proportion of the dose (about 60%) is excreted in the urine as unchanged parent substance. The proportion of torasemide excreted in the urine is approximately the same in fasted or fed conditions (61% vs. 59% respectively).
Two metabolites (a dealkylated and a hydroxylated metabolite) have been identified in urine. The parent substance is metabolised by the hepatic cytochrome P450 families 3A4 and 2E1, and to a lesser extent by 2C9.
No accumulation of torasemide is observed after repeated once daily oral administration for 10 days, whatever the dose administered (ranging from 0.1 to 0.4 mg/kg) even if a slight supra dose proportionality is observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Cellulose microcrystalline
Povidone (K30)
Pork liver powder flavour
Compressible sugar
Crospovidone (type B)
Magnesium stearate

6.2 Major incompatibilities

Not applicable.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 4 years.

6.4. Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.
Remaining tablet parts should be stored in the blister and be given at the next administration.
Keep the tablets out of the reach of animals in order to avoid any accidental ingestion.

6.5 Nature and composition of immediate packaging

Blister pack of polyamide/aluminium/PVC, thermo-sealed by an aluminium foil (each blister contains 10 tablets) and packaged in a cardboard box.

All strengths are available in the following pack sizes:
Pack sizes of 30 or 90 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 product 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/2/18/232/001 – 006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: <{DD/MM/YYYY}>.

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. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. STATEMENT OF THE MRLs

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Ceva Santé Animale
ZI Très le Bois
22600 Loudéac
France

Ceva Santé Animale
Boulevard de la Communication,
Zone autoroutière
53950 Louverne
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Veterinary medicinal product subject to prescription.

C. STATEMENT OF THE MRLs

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Cardboard box (30 tablets)
Cardboard box (90 tablets)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Isemid 1 mg chewable tablets for dogs (2.5-11.5 kg)
Isemid 2 mg chewable tablets for dogs (> 11.5-23 kg)
Isemid 4 mg chewable tablets for dogs (> 23-60 kg)

torasemide

2. STATEMENT OF ACTIVE SUBSTANCES

Each chewable tablet contains:
1 mg of torasemide
2 mg of torasemide
4 mg of torasemide

3. PHARMACEUTICAL FORM

Chewable tablet

4. PACKAGE SIZE

30 chewable tablets
90 chewable tablets

5. TARGET SPECIES

Dogs

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

8. WITHDRAWAL PERIOD(S)

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}

11. SPECIAL STORAGE CONDITIONS

Remaining tablet parts should be stored in the blister and be given at the next administration.
Store out of reach of animals.

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/2/18/232/001 (30 tablets 1 mg)
EU/2/18/232/002 (90 tablets 1 mg)
EU/2/18/232/003 (30 tablets 2 mg)
EU/2/18/232/004 (90 tablets 2 mg)
EU/2/18/232/005 (30 tablets 4 mg)
EU/2/18/232/006 (90 tablets 4 mg)

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Isemid 1 mg chewable tablets
Isemid 2 mg chewable tablets
Isemid 4 mg chewable tablets

torasemide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET
Isemid 1 mg chewable tablets for dogs (2.5-11.5 kg)
Isemid 2 mg chewable tablets for dogs (> 11.5-23 kg)
Isemid 4 mg chewable tablets for dogs (> 23-60 kg)

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

Manufacturer responsible for batch release:
Ceva Santé Animale
ZI Très le Bois
22600 Loudéac
France

Ceva Santé Animale
Boulevard de la Communication,
Zone autoroutière
53950 Louverne
France

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Isemid 1 mg chewable tablets for dogs (2.5-11.5 kg)
Isemid 2 mg chewable tablets for dogs (> 11.5-23 kg)
Isemid 4 mg chewable tablets for dogs (> 23-60 kg)
torasemide

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

Each chewable tablet contains:

Active substance:

Isemid 1 mg	1 mg of torasemide
Isemid 2 mg	2 mg of torasemide
Isemid 4 mg	4 mg of torasemide

The tablets are brown coloured, oblong shaped, chewable and can be divided into halves.

4. INDICATION(S)

For treatment of clinical signs related to congestive heart failure in dogs, including pulmonary oedema.

5. CONTRAINDICATIONS

Do not use in cases of renal failure.
Do not use in cases of dehydration, hypovolaemia or hypotension.
Do not use concomitantly with other loop diuretics.
Do not use in cased of hypersensitivity to the active substance or to any of the excipients.

6. ADVERSE REACTIONS

In a clinical field study, renal insufficiency, a transient increase in renal blood parameters, haemoconcentration and alterations in electrolyte levels (chloride, sodium, potassium, phosphorus, magnesium, calcium) were very commonly observed.

The following clinical signs were observed commonly: episodic gastrointestinal signs such as vomiting and diarrhoea, dehydration, polyuria, polydipsia, urinary incontinence, anorexia, weight loss and lethargy.

Other effects consistent with the pharmacological activity of torasemide were observed in pre-clinical studies in healthy dogs at the recommended dose, i.e. dry mucosa of the oral cavity, reversible increases in glucose and aldosterone serum concentrations, decrease in urine specific gravity and increase in urine pH were observed in pre-clinical studies in healthy dogs at the recommended dose.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports)

If you notice any side effects, even those not already listed in this package leaflet or you think that the medicine has not worked, please inform your veterinary surgeon.

7. TARGET SPECIES

Dogs.

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

Oral use.

The recommended initial/maintenance dose is 0.13 to 0.25 mg torasemide/kg bodyweight/day, once daily.
In case of moderate or severe pulmonary oedema, this dose can be increased if necessary up to a maximum dose of 0.4 mg/kg bodyweight/day once daily.

Doses of 0.26 mg/kg and higher should only be administered for a maximum period of 5 days. After this period, the dose should be reduced to the maintenance dose and the dog should be evaluated by the veterinarian in a few days.
The following table shows the dose adjustment scheme within the recommended dose range of 0.13 to 0.4 mg/kg/day:

Dog Bodyweight (kg)	Number and strength of Isemid tablets to be administered	
	Initial/Maintenance dose (0.13 to 0.25 mg/kg/day)	**Temporary high dose** (0.26 to 0.40 mg/kg/day)
	1 mg	
2.5 to 4	½	1
> 4 to 6	1	1 + ½
> 6 to 8	From 1 to 1 + ½	From 2 to 2 + ½
> 8 to 11.5	From 1 + ½ to 2	From 2 + ½ to 3
	2 mg	
> 11.5 to 15	From 1 to 1 + ½	2
> 15 to 23	From 1 + ½ to 2	From 2 + ½ to 3
	4 mg	
> 23 to 30	From 1 to 1 + ½	2
> 30 to 40	From 1 + ½ to 2	From 2 + ½ to 3
> 40 to 60	From 2 to 2 + ½	From 3 to 4

The dose should be adjusted to maintain patient comfort with attention to renal function and electrolytes status. Once signs of congestive heart failure have been controlled and the patient is stable, it should be continued at the lowest effective dose if long term diuretic therapy with this product is required.

9. ADVICE ON CORRECT ADMINISTRATION

If the tablet is not spontaneously taken by the dog, it can also be given with food or directly into the mouth.

10. WITHDRAWAL PERIOD(S)

Not applicable.

11. SPECIAL STORAGE CONDITIONS

Keep out of the sight and reach of children.

This veterinary medicinal product does not require any special storage conditions.

Do not use this veterinary medicinal product after the expiry date which is stated on the carton or blister pack after "EXP". The expiry date refers to the last day of that month.

Remaining tablet parts should be stored in the blister and be given at the next administration.
Keep the tablets out of the reach of animals in order to avoid any accidental ingestion.

12. SPECIAL WARNING(S)

Special warnings for each target species:
The initial/maintenance dose may be temporarily increased when pulmonary oedema becomes more severe, *i.e.* reaching alveolar oedema state (see section "Dosage for each species, route(s) and method of administration").

Special precautions for use in animals:
In dogs with acute pulmonary oedema requiring emergency treatment, the use of injectable medicinal products should be considered first before commencing oral diuretic therapy.

Renal function (measurement of blood urea and creatinine as well as urine protein: creatinine (UPC) ratio), hydration status and serum electrolytes status should be monitored prior to and during treatment at very regular intervals according to the benefit-risk assessment performed by the responsible veterinarian (see sections "Contraindications" and "Adverse reactions"). The diuretic response to torasemide may increase over time upon repeated dosing, particularly at doses greater than 0.2 mg/kg/day; therefore more frequent monitoring should be considered.
Torasemide should be used with caution in cases of diabetes mellitus. Monitoring of glycaemia in diabetic animals is recommended prior to and during treatment. In dogs with pre-existing electrolyte and/or water imbalance, this should be corrected prior to treatment with torasemide.

As torasemide increases thirst, dogs should have free access to fresh water.
In case of loss of appetite and/or vomiting and/or lethargy or in case of treatment adjustment, renal function (blood urea and creatinine as well as urine protein:creatinine (UPC) ratio) should be assessed.

In a clinical field trial, the efficacy of Isemid was demonstrated when it was used as a first line treatment. Transferring treatment from an alternative loop diuretic to this veterinary medicinal product has not been evaluated and such a change should only be implemented based on a benefit-risk assessment performed by the responsible veterinarian.

The safety and efficacy of the product has not been assessed for dogs weighing less than 2.5 kg. For these animals use only according to the benefit/risk assessment by the responsible veterinarian.

The tablets are flavoured.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
This veterinary medicinal product may cause increased urination, thirst and/or gastrointestinal disturbances and/or hypotension and/or dehydration if ingested. Any part-used tablets should be returned to the blister pack and then to the original carton to help prevent access by children.
In case of accidental ingestion, particularly by a child, seek medical advice immediately and show the package leaflet or the label to the physician.

This veterinary medicinal product may cause hypersensitivity (allergic) reactions in persons that are sensitized to torasemide. People with known hypersensitivity to torasemide, to sulfonamides or to any of the excipients should avoid contact with the veterinary medicinal product. If symptoms of allergy occur, seek medical advice and show the product packaging to the physician.
Wash hands after use.

Pregnancy and lactation:
Laboratory studies in rats and rabbits have shown foetotoxicity at maternotoxic doses. As the safety of the product has not been established in the target species, the use of the product is not recommended during pregnancy, lactation and breeding animals.

Interaction with other medicinal products and other forms of interaction:
Co-administration of loop diuretics and NSAIDs can result in a decreased natriuretic response.
Concomitant use with NSAIDs, aminoglycosides or cephalosporins may increase the risk of nephrotoxicity and/or ototoxicity of those medicinal products.
Torasemide may antagonise the action of oral hypoglycaemic agents.
Torasemide may increase the risk of sulfonamide allergy.

In cases of co-administration with corticosteroids, the effects of loss of potassium may be potentiated.
In cases of co-administration with amphotericin B, increased potential for nephrotoxicity and intensification of electrolyte imbalance can be observed.

No pharmacokinetic interactions have been reported following co-administration of torasemide with digoxin; however hypokalaemia can enhance digoxin-induced arrhythmias.
Torasemide can reduce the renal excretion of salicylates, leading to an increased risk of toxicity.
Care should be exercised when administering torasemide with other highly plasma protein bound drugs. Since protein binding facilitates the renal secretion of torasemide, a decrease in binding due to displacement by another drug may be a cause of diuretic resistance.
Concomitant administration of torasemide with other substances metabolised by cytochrome P450 families 3A4 (e.g.: enalapril, buprenorphine, doxycycline, cyclosporine) and 2E1 (isoflurane, sevoflurane, theophylline) may decrease their clearance from the systemic circulation.
The effect of antihypertensive veterinary medicinal products, especially angiotensin converting enzyme (ACE)-inhibitors, may be potentiated when co-administered with torasemide.

Overdose (symptoms, emergency procedures, antidotes):
After administration to healthy dogs of 3 times and 5 times the maximum dose for 5 consecutive days followed by 177 daily administrations of 3 times and 5 times the highest therapeutic recommended dose for maintenance, histopathological changes in the kidneys (interstitial inflammation, dilatation of renal tubules and subscapular cysts) were noted in addition to the effects observed after the administration of the recommended dose (see section "Adverse reactions"). The renal lesions were still present at 28 days after the end of treatment. Microscopic characteristics of the lesions suggest an ongoing repair process. These lesions may most likely be considered as a result of the pharmacodynamic effect (diuresis) and were not associated with evidence of glomerulosclerosis or interstitial fibrosis. Transient dose response alterations in the adrenal glands, consisting of minimal to moderate reactive hypertrophy/hyperplasia, presumably related to high production of aldosterone, were observed in the dogs treated with up to 5 times the highest therapeutic recommended dose. An increase in albumin serum concentration was observed. ECG alterations without any clinical signs (increase in P wave and/or QT interval) were observed in some animals after the administration of 5 times the highest recommended dose. The causative role of changes in plasma electrolyte values cannot be excluded. After administration of 3 and 5 times the highest therapeutic recommended dose to healthy dogs, a decrease of appetite was observed which led to a weight loss in some cases.

In case of overdose, treatment would be at the discretion of the responsible veterinarian, based on the presenting signs.

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

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

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

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

15. OTHER INFORMATION

Pack sizes
Each blister contains 10 tablets and is packed in a cardboard box.
All strengths are available in pack sizes of 30 or 90 tablets.
Not all pack sizes may be marketed.

Pharmacodynamic properties

Torasemide belongs to the pyridine-3-sulfonylurea class of loop diuretics, also called high-ceiling diuretics. Torasemide has a chemical structure between those of loop diuretics (such as furosemide) and Cl^- channel blockers.

The primary site of action of torasemide is the thick ascending limb of the loop of Henle, where it interacts with the Na^+-K^+-$2Cl^-$ cotransporter localised in the luminal membrane (urine side) and blocks the active reabsorption of sodium and chloride. Therefore diuretic activity of torasemide correlates better with the rate of torasemide excretion in the urine than with the concentration in the blood. Since the ascending limb of the loop of Henle is impermeable to water, the inhibition of Na^+ and Cl^- movement from the lumen to the interstitial space increases the concentration of ions in the lumen and produces a hypertonic medullary interstitium. Consequently water reabsorption from the collecting duct is inhibited and the volume of water on the luminal side is increased.

Torasemide causes a significant, dose-dependent increase in urine flow and the urinary excretion of sodium and potassium. Torasemide has a more potent, longer-acting diuretic activity than furosemide.

Pharmacokinetic particulars

In dogs, following a single intravenous dose of 0.2 mg torasemide/kg bodyweight, the mean total clearance was 22.1 mL/h/kg, with a mean volume of distribution of 166 mL/kg and a mean terminal half-life of about 6 hours. After oral administration of 0.2 mg torasemide/kg bodyweight, the absolute bioavailability is about 99% based on plasma concentration-time data and 93% based on urine concentration-time data.

Feeding significantly increased torasemide $AUC_{0-\infty}$ by 37% and slightly delayed T_{max} but in fasted and fed conditions the maximal concentrations (C_{max}) are approximately the same (2015 µg/L vs 2221 µg/L, respectively). Furthermore, the diuretic effect of torasemide is approximately the same in fed or fasted conditions. Consequently, the medicinal product can be administered with or without food.

In dogs, the plasma protein binding is > 98%.

A large proportion of the dose (about 60%) is excreted in the urine as unchanged parent substance. The proportion of torasemide excreted in the urine is approximately the same in fasted or fed conditions (61% vs. 59% respectively).

Two metabolites (a dealkylated and a hydroxylated metabolite) have been identified in urine. The parent substance is metabolised by the hepatic cytochrome P450 families 3A4 and 2E1, and to a lesser extent by 2C9.

No accumulation of torasemide is observed after repeated once daily oral administration for 10 days, whatever the dose administered (ranging from 0.1 to 0.4 mg/kg) even if a slight supra dose proportionality is observed.