

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 chewable tablets

Toraseamide 1 mg

Isemid 2 mg chewable tablets

Toraseamide 2 mg

Isemid 4 mg chewable tablets

Toraseamide 4 mg

Excipients:

Qualitative composition of excipients and other constituents
Lactose monohydrate
Cellulose microcrystalline
Povidone (K30)
Pork liver powder flavour
Compressible sugar
Crospovidone (type B)
Magnesium stearate

Oblong brown scored chewable tablets.

The chewable tablet can be divided into halves.

3. CLINICAL INFORMATION

3.1 Target species

Dogs.

3.2 Indications for use for each target species

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

3.3 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.

3.4 Special warnings

The initial/maintenance dose may be temporarily increased when pulmonary oedema becomes more severe, i.e. reaching alveolar oedema state (see section 3.9).

3.5 Special precautions for use

Special precautions for safe use in the target species:

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 3.3 and 3.6 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 the veterinary medicinal product 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 veterinary medicinal 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 chewable tablets are flavoured.

Keep the chewable tablets out of the reach of animals in order to avoid any accidental ingestion.

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 immediately and show the package leaflet or the label to the physician.

Wash hands after use.

Special precaution for the protection of the environment:

Not applicable.

3.6 Adverse events

Dogs:

Very common (>1 animal / 10 animals treated):	Renal insufficiency Elevated renal parameters Electrolyte disorder ¹ Haemoconcentration.
Common (1 to 10 animals / 100 animals treated):	Digestive tract disorders ² (e.g. vomiting, diarrhoea) Polyuria, Urinary incontinence Anorexia, Dehydration, Weight loss, Lethargy, Polydipsia.
Undetermined frequency (cannot be estimated from the available data)	Dry mucous membrane (oral) ³ , Alkaline urine ³ , Decreased urine concentration ³ , Increases in glucose and aldosterone serum concentrations ³ (reversible).

¹ Alterations in chloride, sodium, potassium, phosphorus, magnesium and calcium levels

² These signs are episodic.

³ Effects consistent with the pharmacological activity of torasemide observed in healthy dogs at the recommended dose.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy and lactation in dogs.

The use is not recommended during pregnancy, lactation and in breeding animals.

Laboratory studies in rats and rabbits have shown evidence of foetotoxic effects at maternotoxic doses.

3.8 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.

3.9 Administration routes and dosage

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

3.10 Symptoms of overdose (and where applicable, emergency procedures and 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 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.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

Not applicable.

3.12 Withdrawal periods

Not applicable.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QC03CA04

4.2 Pharmacodynamics

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

The primary site of action of torsemide is the thick ascending limb of the loop of Henle, where it interacts with the $\text{Na}^+ \text{-K}^+ \text{-2Cl}^-$ cotransporter localised in the luminal membrane (urine side) and blocks the active reabsorption of sodium and chloride. Therefore, diuretic activity of torsemide correlates better with the rate of torsemide 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.

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

4.3 Pharmacokinetics

In dogs, following a single intravenous dose of 0.2 mg torsemide/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 torsemide/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 mcg/L vs 2221 mcg/L, respectively). Furthermore, the diuretic effect of torasemide is approximately the same in fed and fasted conditions. Consequently, the veterinary 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.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

Not applicable.

5.2 Shelf life

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

5.3 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.

5.4 Nature and composition of immediate packaging

Blister pack of polyamide/aluminium/PVC thermo-sealed by an aluminium foil.

Pack sizes:

Cardboard box containing 30 or 90 chewable tablets.

Each blister pack contains 10 tablets.

Not all pack sizes may be marketed.

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

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Ceva Santé Animale

7. MARKETING AUTHORISATION NUMBER(S)

EU/2/18/232/001 – 006

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: 9/01/2019

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

{DD/MM/YYYY}

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (<https://medicines.health.europa.eu/veterinary>)

ANNEX II

OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

None

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

Isemid 2 mg chewable tablets

Isemid 4 mg chewable tablets

2. STATEMENT OF ACTIVE SUBSTANCES

Each chewable tablet contains:

Torsemide 1 mg

Torsemide 2 mg

Torsemide 4 mg

3. PACKAGE SIZE

30 chewable tablets

90 chewable tablets

4. TARGET SPECIES

Dogs

5. INDICATION(S)

6. ROUTES OF ADMINISTRATION

Oral use.

7. WITHDRAWAL PERIODS

8. EXPIRY DATE

Exp. {mm/yyyy}

9. SPECIAL STORAGE PRECAUTIONS

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

10. THE WORDS “READ THE PACKAGE LEAFLET BEFORE USE”

Read the package leaflet before use.

11. THE WORDS “FOR ANIMAL TREATMENT ONLY”

For animal treatment only.

12. THE WORDS “KEEP OUT OF THE SIGHT AND REACH OF CHILDREN”

Keep out of the sight and reach of children.

13. NAME OF THE MARKETING AUTHORISATION HOLDER

Ceva Santé Animale



14. MARKETING AUTHORISATION NUMBERS

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)

15. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
BLISTER

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Isemid



2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

Torsemide 1 mg
Torsemide 2 mg
Torsemide 4 mg

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

B. PACKAGE LEAFLET

PACKAGE LEAFLET

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. Composition

Each chewable tablet contains:

Active substance:

Isemid 1 mg chewable tablets

Torsemide 1 mg

Isemid 2 mg chewable tablets

Torsemide 2 mg

Isemid 4 mg chewable tablets

Torsemide 4 mg

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

3. Target species

Dogs.

4. Indications for use

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 cases of hypersensitivity to the active substance or to any of the excipients.

6. Special warnings

Special warnings:

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, routes and method of administration”).

Special precautions for safe use in the target species:

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 the veterinary medicinal product 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 veterinary medicinal 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 chewable tablets are flavoured.

Keep the chewable tablets out of the reach of animals in order to avoid any accidental ingestion.

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 immediately and show the package leaflet or the label to the physician.

Wash hands after use.

Pregnancy and lactation:

The safety of the veterinary medicinal product has not been established during pregnancy and lactation in dogs.

The use is not recommended during pregnancy, lactation and in breeding animals.

Laboratory studies in rats and rabbits have shown evidence of foetotoxic effects at maternotoxic doses.

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:

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 subcapsular cysts) were noted in addition to the effects observed after the administration of the recommended dose (see section "Adverse events"). 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.

7. Adverse events

Dogs:

Very common (>1 animal / 10 animals treated):
Renal insufficiency, Elevated renal parameters, Electrolyte disorder ¹ , Haemoconcentration
Common (1 to 10 animals / 100 animals treated):
Digestive tract disorder ² (e.g. vomiting, diarrhoea), Polyuria, Urinary incontinence, Anorexia, Dehydration, Weight loss, Lethargy, Polydipsia.
Undetermined frequency (cannot be estimated from the available data):
Dry mucous membrane (oral) ³ , Alkaline urine ³ , Decreased urine concentration ³ , Increases in glucose and aldosterone serum concentrations ³ (reversible).

¹ Alteration in chloride, sodium, potassium, phosphorus, magnesium and calcium levels

² These signs are episodic.

³ Effects consistent with the pharmacological activity of torasemide observed in healthy dogs at the recommended dose.

Reporting adverse events is important. It allows continuous safety monitoring of a product. 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 contact, in the first instance, your veterinarian. You can also report any adverse events to the marketing authorisation holder using the contact details at the end of this leaflet, or via your national reporting system: {national system details}.

8. Dosage for each species, routes 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 chewable 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 chewable tablet is not spontaneously taken by the dog, it can also be given with food or directly into the mouth.

10. Withdrawal periods

Not applicable.

11. Special storage precautions

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.

12. Special precautions for disposal

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any applicable national collection systems. These measures should help to protect the environment.

Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required.

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

14. Marketing authorisation numbers and pack sizes

EU/2/18/232/001-006

Pack sizes:

Cardboard box containing 30 or 90 chewable tablets.

Each blister pack contains 10 tablets.

Not all pack sizes may be marketed.

15. Date on which the package leaflet was last revised

{MM/YYYY}

Detailed information on this veterinary medicinal product is available in the Union Product Database (<https://medicines.health.europa.eu/veterinary>).

16. Contact details

Marketing authorisation holder and contact details to report suspected adverse reactions:

Ceva Santé Animale
10, av. de La Ballastière
33500 Libourne
France
Tel: +800 35 22 11 51
E-mail: pharmacovigilance@ceva.com

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

17. Other information

Pharmacodynamics

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

The primary site of action of torsemide 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 torsemide correlates better with the rate of torsemide 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.

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

Pharmacokinetics

In dogs, following a single intravenous dose of 0.2 mg torsemide/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 torsemide/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 torsemide AUC_{0-∞} by 37% and slightly delayed T_{max} but in fasted and fed conditions the maximal concentrations (C_{max}) are approximately the same (2015 mcg/L vs 2221 mcg/L, respectively). Furthermore, the diuretic effect of torsemide is approximately the same in fed or fasted conditions. Consequently, the veterinary 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.