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
Torasemide 1 mg

Isemid 2 mg chewable tablets
Torasemide 2 mg

Isemid 4 mg chewable tablets
Torasemide 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

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.

4.3 Pharmacokinetics

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 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*)