SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Isemid 4 mg chewable tablets for dogs (> 23-60 kg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each chewable tablet contains:

Active substance:
Torasemide 4 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oblong brown scored chewable tablets. The chewable 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 4.5 and 4.9 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.

Special precautions for the protection of the environment
Not applicable.

Other precautions
Not applicable.

4.6 Adverse reactions (frequency and seriousness)

Very common (>1 animal / 10 animals treated):	Renal insufficiency Elevated renal Parameters Electrolyte disorder[1] Haemoconcentration.
Common (1 to 10 animals / 100 animals treated):	Vomiting, Diarrhoea[2] Polyuria, Urinary incontinence[2] Anorexia, Dehydration, Weight loss, Lethargy, Polydipsia.[2]

[1] Chloride, sodium, potassium, phosphorus, magnesium and calcium levels
[2] These signs are episodic.

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.

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 its local representative or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

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 Amount(s) 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)
	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

Pharmacotherapeutic group: Cardiovascular system, high-ceiling diuretics, plain sulfonamides

ATCvet 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.

5.3 Environmental properties

Not applicable.

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

Medicines should not be disposed of via wastewater.
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 Animal Health Ltd.
Explorer House
Mercury Park
Wycombe Lane
Wooburn Green
High Wycombe
Buckinghamshire
HP10 0HH
United Kingdom

8. MARKETING AUTHORISATION NUMBER

Vm 15052/5010

9. DATE OF FIRST AUTHORISATION

09 January 2019

10. DATE OF REVISION OF THE TEXT

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable

11. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCT

Veterinary medicinal product subject to prescription
Find more product information by searching for the 'Product Information Database' or 'PID' on www.gov.uk.

Gavin Hall
Approved 07 October 2024