

**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.

Torsemide may antagonise the action of oral hypoglycaemic agents.

Torsemide 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 torsemide with digoxin; however hypokalaemia can enhance digoxin-induced arrhythmias.

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

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

Concomitant administration of torsemide 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 torsemide.

#### **4.9 Amounts to be administered and administration route**

Oral use.

The recommended initial/maintenance dose is 0.13 to 0.25 mg torsemide/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:

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

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

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

Toraseamide causes a significant, dose-dependent increase in urine flow and the urinary excretion of sodium and potassium. Toraseamide 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 toraseamide/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 toraseamide/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 toraseamide  $\text{AUC}_{0-\infty}$  by 37% and slightly delayed  $T_{\text{max}}$ , but in fasted and fed conditions the maximal concentrations ( $C_{\text{max}}$ ) are approximately the same (2015  $\mu\text{g/L}$  vs 2221  $\mu\text{g/L}$ , respectively). Furthermore, the diuretic effect of toraseamide 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 toraseamide 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 toraseamide 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: 09/01/2019

## **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 (&gt; 11.5-23 kg)

Isemid 4 mg chewable tablets for dogs (&gt; 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 cases 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)
	<b>1 mg</b>	
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
	<b>2 mg</b>	
> 11.5 to 15	From 1 to 1 + ½	2
> 15 to 23	From 1 + ½ to 2	From 2 + ½ to 3
	<b>4 mg</b>	
> 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 subcapsular 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

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  $\text{Cl}^-$  channel blockers.

The primary site of action of torsemide is the thick ascending limb of the loop of Henle, where it interacts with the  $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$  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  $\text{Na}^+$  and  $\text{Cl}^-$  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.

### Pharmacokinetic particulars

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  $\text{AUC}_{0-\infty}$  by 37% and slightly delayed  $T_{\text{max}}$  but in fasted and fed conditions the maximal concentrations ( $C_{\text{max}}$ ) are approximately the same (2015  $\mu\text{g/L}$  vs 2221  $\mu\text{g/L}$ , respectively). Furthermore, the diuretic effect of torsemide 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 torsemide 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 torsemide 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.