**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

UpCard 0.75 mg tablets for dogs
UpCard 3 mg tablets for dogs
UpCard 7.5 mg tablets for dogs
UpCard 18 mg tablets for dogs

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

**Active substance:**

| | |
|---|---|
| UpCard 0.75 mg | 0.75 mg of torasemide |
| UpCard 3 mg | 3 mg of torasemide |
| UpCard 7.5 mg | 7.5 mg of torasemide |
| UpCard 18 mg | 18 mg of torasemide |

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablets.

UpCard 0.75 mg tablets: oblong white to off-white tablets with 1 break-line on each side. The tablets can be divided into equal halves.

UpCard 3 mg, 7.5 mg and 18 mg tablets: oblong white to off-white tablets with 3 break-lines on each side. The tablets can be divided into equal quarters.

## 4. CLINICAL PARTICULARS

### 4.1 Target species

Dogs.

### 4.2 Indications for use, specifying the target species

For treatment of clinical signs, including oedema and effusion, related to congestive heart failure.

### 4.3 Contraindications

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

### 4.4 Special warnings for each target species

None.

## 4.5 Special precautions for use

Special precautions for use in animals
In dogs presenting in acute crisis with pulmonary oedema, pleural effusion and/or ascites requiring emergency treatment, the use of injectable drugs should be considered first before commencing oral diuretic therapy.

Renal function, hydration status and serum electrolytes status should be monitored:
- At treatment initiation
- from 24 hours to 48 hours after treatment initiation
- from 24 hours to 48 hours after dose change
- In case of adverse events.

While the animal is on treatment, these parameters should be monitored at very regular intervals according to the benefit-risk assessment performed by the responsible veterinarian.

Torasemide should be used with caution in cases of diabetes mellitus, and in dogs with previously prescribed high doses of an alternative loop diuretic. In dogs with pre-existing electrolyte and/or water imbalance, this should be corrected prior to treatment with torasemide.

Torasemide treatment should not be initiated in dogs already clinically stable on an alternative diuretic for treatment of the signs of congestive heart failure, except where this has been justified taking into account the risk of de-stabilising the clinical condition and of adverse reactions as indicated in section 4.6.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
People with known hypersensitivity to torasemide or other sulphonamides should administer the veterinary medicinal product with caution.

This product may cause increased urination and/or gastrointestinal disturbances if ingested.

Keep tablets in the blister packs until required, and keep the blisters in the outer carton.

In case of accidental ingestion, particularly in the case of children, seek medical advice immediately and show the package leaflet or the label to the physician.

## 4.6 Adverse reactions (frequency and seriousness)

Increase in renal blood parameters and renal insufficiency are very commonly observed during treatment.

As a result of the diuretic action of torasemide, haemoconcentration and, very commonly, polyuria and/or polydipsia are observed.

In cases of prolonged treatment, electrolyte deficiency (including hypokalaemia, hypochloraemia, hypomagnesaemia) and dehydration may occur.

Gastrointestinal signs which include emesis, reduced or absent faeces and, in rare cases, soft faeces may be observed. Occurrence of soft faeces is transient, mild, and does not necessitate the withdrawal of the treatment.

Erythema of the inner pinnae may be observed.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals displaying adverse reaction(s) during the course of one treatment)

- common (more than 1 but less than 10 animals in 100 animals)
- uncommon (more than 1 but less than 10 animals in 1,000 animals)
- rare (more than 1 but less than 10 animals in 10,000 animals)
- very rare (less than 1 animal in 10,000 animals, including isolated reports).

## 4.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy or lactation. The use of UpCard is not recommended during pregnancy, lactation and in 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 veterinary medicinal products affecting electrolyte balance (corticosteroids, amphotericin B, cardiac glycosides, other diuretics) requires careful monitoring.

Concurrent use of drugs that increase the risk of renal injury or renal insufficiency should be avoided.

Concomitant use with aminoglycosides or cephalosporins may increase the risk of nephrotoxicity and ototoxicity.

Torasemide may increase the risk of sulfonamide allergy.

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 drugs 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 drugs, especially angiotensin converting enzyme (ACE)-inhibitors, may be potentiated when co-administered with torasemide.

When used in combination with cardiac treatments (e.g. ACE-inhibitors, digoxin), the dose regimen may need to be modified depending upon the animal’s response to therapy.

## 4.9 Amounts to be administered and administration route

Oral use.

UpCard tablets can be administered with or without food.

The recommended dose of torasemide is 0.1 to 0.6 mg per kg bodyweight, once daily. The majority of dogs are stabilised at a dose of torasemide less than or equal to 0.3 mg per kg bodyweight, once daily. The dosage should be titrated to maintain patient comfort with attention to renal function and electrolytes status. If the level of diuresis requires alteration, the dose may be increased or decreased within the recommended dose range by increments of 0.1 mg/kg bodyweight. Once signs of congestive heart failure have been controlled and the patient is stable, if long term diuretic therapy with this product is required it should be continued at the lowest effective dose.

Frequent re-examinations of the dog will enhance the establishment of an appropriate diuretic dose.

The daily schedule of administration can be timed to control the period of micturition according to need.

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

Doses greater than 0.8 mg/kg/day have not been evaluated in the target animal safety or controlled clinical studies. However, it is anticipated that overdose increases the risk of dehydration, electrolyte imbalance, renal insufficiency, anorexia, weight loss and cardiovascular collapse.
Treatment should be symptomatic.

### 4.11 Withdrawal period(s)

Not applicable.

## 5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Cardiovascular system, high-ceiling diuretics, plain sulfonamides.
ATCvet code: QC03CA04.

### 5.1 Pharmacodynamic properties

Torasemide is a loop diuretic of the pyridyl sulfonylurea class. Torasemide is secreted into the tubule lumen via the probenecid-sensitive organic acid transport system. The main site of action is the medullary portion of the ascending limb of the loop of Henle. Loop diuretics mainly inhibit the $Na^+/2Cl^-/K^+$ carrier from the luminal side of the cell.

Inhibition of sodium and chloride ion reabsorption not only results in saluresis but also a decrease in interstitial osmolarity within the renal medulla. This in turn decreases free water reabsorption resulting in increased water excretion/urine production.

In healthy dogs and after once daily administration for 5 days, the mean percentage of increase in excreted urine over 24 hours ranged between 33% and 50% at 0.15 mg/kg, between 181% and 328% at 0.4 mg/kg and between 264% and 418% at 0.75 mg/kg.

Based on a pharmacodynamics modelling study conducted in healthy dogs at doses of 0.1 and 0.6 mg torasemide/kg, a single dose of torasemide had approximately 20 times the diuretic effect of a single dose of furosemide. Refer to section 4.5.

### 5.2 Pharmacokinetic particulars

In dogs, after a single intravenous dose at 0.1 mg/kg, the total body clearance was 0.017 L/h·kg, the volume of distribution was 0.14 L/kg and the terminal half-life was 7.0 hours. After a single oral dose of 0.1 mg/kg, the oral absolute bioavailability corresponded to about 90%. The oral absorption was fast with mean $T_{max}$ at 0.93 hours after administration of 0.1 mg/kg. The maximum plasma concentrations $C_{max}$ corresponded to 1.1 µg/mL after a single oral dose of 0.1 mg/kg and to 19 µg/mL after a single oral dose of 1.6 mg/kg. The $AUC_{inf}$ corresponded to 6.3 µg·h/mL after a single oral dose of 0.1mg/kg and to 153.6 µg·h/mL after a single oral dose of 1.6 mg/kg. The plasma protein binding was > 98%. A large proportion of the dose (between 61% and 70%) is excreted in the urine as unchanged parent drug. Two metabolites (a dealkylated and a hydroxylated metabolite) were also identified in urine. The parent drug is metabolised by the hepatic cytochrome P450 families 3A4 and 2E1, and to a lesser extent by 2C9. Dose proportionality for $C_{max}$ and $AUC_{inf}$ was demonstrated between 0.2 and 1.6 mg/kg.

Feeding significantly increased torasemide $AUC_{last}$ by 36% on average and slightly delayed $T_{max}$ but no significant impact on $C_{max}$ was detected. After repeated administration to dogs at 0.2 mg/kg daily for 14 days, no plasma accumulation of torasemide was detected.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Lactose monohydrate
Povidone
Sodium laurilsulfate
Crospovidone
Microcrystalline cellulose
Sodium stearyl fumarate
Bacon flavour

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Any remaining tablet part should be discarded after 7 days.

### 6.4. Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.
Any part tablet should be stored in the blister pack or in a closed container for a maximum of 7 days.

### 6.5 Nature and composition of immediate packaging

Polychlorotrifluoroethylene-PVC/aluminium blister pack (each blister pack contains 10 tablets) and is packaged in an outer cardboard box.

All strengths are available in the following pack sizes:
Pack sizes of 30 or 100 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

Vétoquinol SA
Magny-Vernois
70200 Lure
FRANCE

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/2/15/184/001–008

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31/07/2015

## 10 DATE OF REVISION OF THE TEXT

{DD/MM/YYYY}

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. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. STATEMENT OF THE MRLs**

## A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Vétoquinol SA
Magny-Vernois
70200 Lure
FRANCE

## 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**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

UpCard 0.75 mg tablets for dogs
UpCard 3 mg tablets for dogs
UpCard 7.5 mg tablets for dogs
UpCard 18 mg tablets for dogs
torasemide

## 2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

0.75 mg torasemide
3 mg torasemide
7.5 mg torasemide
18 mg torasemide

## 3. PHARMACEUTICAL FORM

Tablets

## 4. PACKAGE SIZE

30 tablets
100 tablets

## 5. TARGET SPECIES

Dogs

## 6. INDICATION(S)

## 7. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

## 8. WITHDRAWAL PERIOD

Not applicable.

## 9. SPECIAL WARNING(S), IF NECESSARY

## 10. EXPIRY DATE

EXP {month/year}

## 11. SPECIAL STORAGE CONDITIONS

## 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

Vétoquinol SA
Magny-Vernois
70200 Lure
FRANCE
+33 3 84 62 55 55
+33 3 84 62 55 29

## 16. MARKETING AUTHORISATION NUMBER(S)

EU/2/15/184/001 30 tablets of 0.75 mg
EU/2/15/184/002 100 tablets of 0.75 mg
EU/2/15/184/003 30 tablets of 3 mg
EU/2/15/184/004 100 tablets of 3 mg
EU/2/15/184/005 30 tablets of 7.5 mg
EU/2/15/184/006 100 tablets of 7.5 mg
EU/2/15/184/007 30 tablets of 18 mg
EU/2/15/184/008 100 tablets of 18 mg

## 17. MANUFACTURER'S BATCH NUMBER

Lot {number}

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**Blister pack**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

UpCard 0.75 mg tablets for dogs
UpCard 3 mg tablets for dogs
UpCard 7.5 mg tablets for dogs
UpCard 18 mg tablets for dogs
torasemide

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Vétoquinol SA

## 3. EXPIRY DATE

EXP {month/year}

## 4. BATCH NUMBER

Lot{number}

## 5. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

**B. PACKAGE LEAFLET**

**PACKAGE LEAFLET FOR:**
**UpCard 0.75 mg tablets for dogs**
**UpCard 3 mg tablets for dogs**
**UpCard 7.5 mg tablets for dogs**
**UpCard 18 mg tablets for dogs**

## 1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder and manufacturer responsible for batch release:
Vétoquinol SA
Magny-Vernois
70200 Lure
FRANCE

## 2. NAME OF THE VETERINARY MEDICINAL PRODUCT

UpCard 0.75 mg tablets for dogs
UpCard 3 mg tablets for dogs
UpCard 7.5 mg tablets for dogs
UpCard 18 mg tablets for dogs

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

Each tablet contains:

| | |
|---|---|
| UpCard 0.75 mg tablets for dogs | 0.75 mg of torasemide |
| UpCard 3 mg tablets for dogs | 3 mg of torasemide |
| UpCard 7.5 mg tablets for dogs | 7.5 mg of torasemide |
| UpCard 18 mg tablets for dogs | 18 mg of torasemide |

UpCard 0.75 mg tablets are oblong white to off-white tablets with 1 break-line on each side. The tablets can be divided into equal halves.
UpCard 3 mg, 7.5 mg and 18 mg tablets are oblong white to off-white tablets with 3 break-lines on each side. The tablets can be divided into equal quarters.

## 4. INDICATION(S)

For treatment of clinical signs, including oedema and effusion, related to congestive heart failure.

## 5. CONTRAINDICATIONS

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

## 6. ADVERSE REACTIONS

Increase in renal blood parameters and renal insufficiency are very commonly observed during treatment.
As a result of the diuretic action of torasemide, haemoconcentration and, very commonly, polyuria and/or polydipsia are observed.
In case of prolonged treatment, electrolyte deficiency (including hypokalaemia, hypochloraemia, hypomagnesaemia) and dehydration may occur.
Gastrointestinal signs which include emesis, reduced or absent faeces and, in rare cases, soft faeces may be observed. Occurrence of soft faeces is transient, mild, and does not necessitate the withdrawal of the treatment.
Erythema of the inner pinnae may be observed.

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

If you notice any serious effects or other effects not mentioned in this package leaflet, please inform your veterinary surgeon.

## 7. TARGET SPECIES

Dogs

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

Oral use.

The recommended dose of torasemide is 0.1 to 0.6 mg per kg bodyweight, once daily. The dosage should be titrated to maintain patient comfort with attention to renal function and electrolytes status. If the level of diuresis requires alteration, the dose may be increased or decreased within the recommended dose range by increments of 0.1 mg/kg bodyweight. Once signs of congestive heart failure have been controlled and the patient is stable, if long term diuretic therapy with this product is required it should be continued at the lowest effective dose.

Frequent re-examination of the dog will enhance the establishment of an appropriate diuretic dose. The daily schedule of administration can be timed to control the period of micturition according to need.

## 9. ADVICE ON CORRECT ADMINISTRATION

UpCard tablets can be administered with or without food.

## 10. WITHDRAWAL PERIOD

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.
Any part tablet should be stored in the blister pack or in a closed container for a maximum of 7 days.
Do not use this veterinary medicinal product after the expiry date which is stated on the carton.

## 12. SPECIAL WARNING(S)

Special precautions for use in animals:
In dogs presenting in acute crisis with pulmonary oedema, pleural effusion and/or ascites requiring emergency treatment, the use of injectable drugs should be considered first before commencing oral diuretic therapy.
Renal function, hydration status and serum electrolytes status should be monitored:
- At treatment initiation
- 24 hours to 48 hours after treatment initiation
- 24 hours to 48 hours after dose change
- In case of adverse events.

While the animal is on treatment, these parameters should be monitored at very regular intervals according to the benefit-risk assessment performed by the responsible veterinarian.
Torasemide should be used with caution in cases of diabetes mellitus, and in dogs with previously prescribed high doses of an alternative loop diuretic. In dogs with pre-existing electrolyte and/or water imbalance, this should be corrected prior to treatment with torasemide.
Torasemide treatment should not be initiated in dogs already clinically stable on an alternative diuretic for treatment of the signs of congestive heart failure, except where this has been justified taking into account the risk of de-stabilising the clinical condition and of adverse reactions as indicated in section 6.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
People with known hypersensitivity to torasemide or other sulphonamides should administer the veterinary medicinal product with caution.
This product may cause increased urination and/or gastrointestinal disturbances if ingested.
Keep tablets in the blister packs until required, and keep the blisters in the outer carton.
In case of accidental ingestion, particularly in the case of children, seek medical advice immediately and show the package leaflet or the label to the physician.

Pregnancy and lactation:
The safety of the veterinary medicinal product has not been established during pregnancy or lactation.
The use of UpCard is not recommended during pregnancy, lactation and in breeding animals.

Interaction with other medicinal products and other forms of interaction:
Co-administration of loop diuretics and non-steroidal anti-inflammatory drugs can result in a decreased natriuretic response.
Concomitant use with veterinary medicinal products affecting electrolyte balance (corticosteroids, amphotericin B, cardiac glycosides, other diuretics) requires careful monitoring.
Concurrent use of drugs that increase the risk of renal injury or renal insufficiency should be avoided.
Concomitant use with aminoglycosides or cephalosporins may increase the risk of nephrotoxicity and ototoxicity.
Torasemide may increase the risk of sulfonamide allergy.
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 drugs 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 drugs, especially angiotensin converting enzyme (ACE)-inhibitors, may be potentiated when co-administered with torasemide.
When used in combination with cardiac treatments (e.g. ACE-inhibitors, digoxin), the dose regimen may need to be modified depending upon the animal's response to therapy.

Overdose (symptoms, emergency procedures, antidotes):
Doses greater than 0.8 mg/kg/day have not been evaluated in the target animal safety or controlled clinical studies. However, it is anticipated that overdose increases the risk of dehydration, electrolyte imbalance, renal insufficiency, anorexia, weight loss and cardiovascular collapse.
Treatment should be symptomatic.

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

Medicines should not be disposed of via wastewater or household waste.
Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.

## 14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

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

## 15. OTHER INFORMATION

UpCard tablets are supplied in blister packs with 10 tablets per blister pack. Pack sizes are of 30 or 100 tablets.
Not all pack sizes may be marketed.

Based on a pharmacodynamics modelling study conducted in healthy dogs at doses of 0.1 and 0.6 mg torasemide/kg, a single dose of torasemide had approximately 20 times the diuretic effect of a single dose of furosemide.