4 June 2015
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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for UpCard (EMEA/V/C/003836/0000)

International non-proprietary name: torasemide

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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Introduction

On 19 February 2014 Vétoquinol SA submitted an application for a marketing authorisation to the European Medicines Agency (The Agency) for UpCard, through the centralised procedure falling within the Article 3(2)a of Regulation (EC) No 726/2004 (new active substance).

The eligibility to the centralised procedure was agreed upon by the CVMP on 12 September 2013 as UpCard contains a new active substance which is not yet authorised as a veterinary medicinal product in the Community. The rapporteur appointed was H. Jukes and co-rapporteur C. Muñoz.

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC.

UpCard are tablets containing torasemide (anhydrous) as active substance and are available in four different strengths (0.75 mg, 3 mg, 7.5 mg and 18 mg). The tablets are packed in blister packs, which are then packed into outer cartons containing either 30 or 100 tablets. The target species is dogs and the route of administration is oral use.

The applicant applied for the following indication: For treatment of oedema and effusion related to congestive heart failure in dogs.

The CVMP adopted an opinion and CVMP assessment report on 4 June 2015.

On 31 July 2015, the European Commission adopted a Commission Decision granting the marketing authorisation for UpCard.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (dated 29 January 2014) which fulfils the requirements of Directive 2001/82/EC. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

The active substance is manufactured by two different manufacturers. The finished product is manufactured and packaged in the European Union (EU). Batch release is carried out by Vetoquinol SA in Lure, France.

All sites have valid manufacturing authorisations or valid Good Manufacturing Practice (GMP) certificates as appropriate.

The qualified person (QP) has provided declarations concerning GMP compliance of the active substance manufactured by both manufacturing sites. The declarations are made on the basis of audits of these sites.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system and the GMP certification of the manufacturing sites were considered in line with legal requirements.

Part 2 - Quality

Composition

UpCard tablets contain torasemide (anhydrous) as the active substance and are available in four strengths, 0.75 mg, 3.0 mg, 7.5 mg, and 18 mg. All the excipients used are of pharmacopoeial grade except for bacon flavour which is used as a palatability agent.

The lower strength is divisible into halves and the other strengths are divisible into quarters.

Container

The tablets are presented in thermoformed blisters made of PVC-PCTFE laminate, heat sealed with aluminium foil inside a carton (30 or 100 tablets per carton). The primary packaging is adequately described and materials of construction comply with the Commission Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food.

Development pharmaceutics

A comprehensive description of the formulation and process development is given.

Torasemide (anhydrous) exists in at least three crystalline forms. The active substance suppliers have demonstrated that their manufacturing processes consistently lead to the same polymorphic form.

UpCard tablets contain torasemide, lactose monohydrate, povidone, crospovidone, sodium laurilsulfate, microcrystalline cellulose, bacon flavour, and sodium stearyl fumarate. With the exception of bacon flavour, the ingredients are all well-established excipients for tablets and are described in the European Pharmacopoeia (Ph. Eur.). Bacon flavour is not new to veterinary medicines in the EU, having been used in other veterinary medicinal products already authorised.

The applicant has declared that compliance with VICH GL18: Residual solvents in new veterinary medicinal products, active substances and excipients will be maintained throughout the life of the product.

Method of manufacture

The manufacturing process is summarised in narrative, with sufficient detail of times and temperatures and other parameters, and also described in a flow chart. The general type of the production equipment used is given and this level of detail is considered sufficient.

The tablets are produced from granules prepared by wet granulation containing the active substance and excipients. The process uses standard equipment. The manufacturing process is non-standard.

Process validation has been conducted on three full-scale batches. It can be concluded that the manufacturing process described generates tablets with adequate quality that fully comply with the specification set.

Control of starting materials

Active substance

Torasemide (anhydrous) has a monograph in the Ph. Eur. The applicant's specification includes additional tests for residual solvents appropriate to the source.

For one of the manufacturers of the active substance a valid certificate of suitability (CEP) from the European Directorate for the Quality of Medicines and Healthcare (EDQM) has been provided. The CEP indicates a re-test period of 3 years for torasemide (anhydrous), with no storage restrictions if stored in double polyethylene bags placed in a polyethylene drum. The CEP includes an additional test for a residual solvent.

For the other manufacturer an active substance master file (ASMF) is employed. The manufacture of torasemide (anhydrous) by this second manufacturer consists of four synthetic steps plus purification and drying steps. The choice of the starting materials is considered acceptable. The limits in the specification are the same or tighter than in the Ph. Eur. monograph, and there are additional tests for an in-house impurity and residual solvents. The specification has been appropriately justified. Analytical methods have been validated when applicable. Batch analysis data demonstrating compliance with the active substance specification have been provided for 3 commercial scale batches. The stability data show that the active substance is stable and a re-test period of 5 years is appropriate without any restriction on storage conditions.

The finished product manufacturer has established a specification for torasemide (anhydrous) as per the Ph. Eur. monograph with additional testing for particle size and additional impurities and residual solvents. The specification proposed is acceptable.

Certificates of analysis of 3 batches from each supplier have been provided by the finished product manufacturer. The results comply with the specification.

Excipients

The excipients in the finished product are lactose monohydrate, povidone, sodium laurilsulfate, crospovidone type A, microcrystalline cellulose, sodium stearyl fumarate and bacon flavour. The excipients, apart from the bacon flavour, are commonly used in veterinary medicines and comply with Ph. Eur. monographs. Bacon flavour is not new to veterinary medicine in the EU, having been used in

other veterinary medicinal products already authorised. Its composition and an in-house specification have been provided.

Certificates of analysis of each of the excipients from the manufacturer of the finished product have been provided and the results are satisfactory.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The lactose monohydrate used in the manufacture of the tablets is derived from milk and calf rennet. The supplier of the lactose monohydrate is specified and has provided a declaration in which it is stated that the milk is sourced from healthy animals in the same conditions as milk collected for human consumption and that the lactose is prepared without the use of ruminant materials, other than calf rennet. This is in compliance with the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev. 3).

A TSE declaration from the supplier of bacon flavour has also been provided and it is acceptable.

Therefore, the risk of transmitting animal spongiform encephalopathy agents via this veterinary medicinal product is negligible.

Control tests during production

The in-process controls are all considered appropriate for the manufacture of these tablets.

Control tests on the finished product

The finished product release specification includes tests for appearance (visual), dimensions, average mass, uniformity of mass (Ph. Eur.), uniformity of content of whole and part tablets (UHPLC), disintegration (Ph. Eur.), dissolution (Ph. Eur.), identification (UHPLC and UV), assay (UHPLC), related substances (UHPLC) and annual control of the microbiological quality (Ph. Eur.).

The proposed test parameters and limits are appropriate. The analytical methods have been adequately described and suitably validated, when appropriate.

Certificates of analysis have been provided for three batches of each strength. All demonstrate compliance with the proposed release specification. These batches have been produced at the proposed site of manufacture.

Stability

Stability data are provided for three batches of each tablet strength. All batches were manufactured at the proposed site of commercial manufacture and packed in the proposed commercial packaging. The stability studies are being conducted in the blister pack proposed for marketing. Samples will be stored at 25 °C/60% RH and 30 °C/65% RH for 36 months and 40 °C/75% RH for 6 months.

All twelve batches have completed 6 months storage at 40 °C/75% RH. Two batches of each strength have completed 24 months storage at 25 °C/60% RH and 30 °C/65% RH. The third batch of each strength has completed 18 months storage at 25 °C/60% RH and 30 °C/65% RH.

The proposed release and shelf-life limits are identical except for one degradation product. A wider limit at end of shelf-life for this impurity has been adequately justified.

The analytical methods used were identical to those used for routine control as discussed in part 2E above.

The data show that the tablets are chemically and physically stable in the proposed pack and no special storage precautions are required. The stability data are considered to support the proposed shelf-life of 36 months without any storage restriction.

An in-use stability study showed that half and quarter tablets are stable out of the pack for up to 8 days. A photostability study shows that whole and part tablets are not sensitive to light.

Overall conclusions on quality

The tablets contain torasemide (anhydrous) in four strengths, 0.75 mg, 3.0 mg, 7.5 mg, and 18 mg.

The lower strength is divisible into halves and the other strengths are divisible into quarters.

A comprehensive description of the formulation and process development is given. The excipients, apart from the bacon flavour, are commonly used in veterinary medicines and comply with Ph. Eur. monographs. Bacon flavour is not a new excipient in veterinary medicinal products in the EU.

The active substance is sourced from two suppliers. In one case this is in accordance with a CEP from EDQM and for the second an ASMF is employed. Particle size is controlled by the finished product manufacturer.

Satisfactory process validation has been conducted on full-scale batches of the finished product.

The tablets are presented in blister packs in cartons. The blister packs are adequately described and materials of construction comply with EU Regulations on plastic materials intended to come into contact with food.

The lactose monohydrate used in the manufacture of the tablets is derived from milk and calf rennet. The supplier of the lactose monohydrate is specified and this excipient is in compliance with the requirements of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev. 3). Therefore, the risk of transmitting animal spongiform encephalopathy agents via this veterinary medicinal product is negligible.

The finished product specifications include appropriate tests and limits for a tablet. The analytical methods have been satisfactorily validated. Certificates of analysis have been provided for three batches of each strength. All demonstrate compliance with the proposed release specification.

Stability data show that the active substance is stable and a re-test period of 5 years is appropriate for material from one of the manufacturers of the active substance. A 3 year re-test period is stated on the CEP from the other active substance manufacturer.

Stability studies on the tablets show that they are chemically and physically stable in the proposed pack and no special storage precautions are needed. An in-use study showed that half and quarter tablets are stable out of the pack for up to 8 days, supporting a 7-day in-use shelf life. A photostability study shows that whole and part tablets are not sensitive to light. The applicant has requested a shelf-life of 3 years and this is supported.

In addition, the applicant is recommended to provide the following data post-authorisation:

- An in-use stability study will be performed for a second batch of each strength close to end of shelf life.

Part 3 – Safety

Safety documentation

Pharmacodynamics

See part 4.

Pharmacokinetics

One study from published literature, conducted in dogs and rats, and six proprietary studies, two of which were in-vitro and four conducted in dogs, were provided.

See part 4 for a summary of the studies conducted in dogs, and the in-vitro studies.

The published study was conducted using ^{3}H-labelled torasemide. Torasemide was practically fully absorbed by the gastrointestinal tract and its bioavailability by the oral route ranged from 80 to 100%. Plasma half-life was about 1.5 h in the rat after administration of 10 mg/kg by oral or intravenous (IV) routes. In the dog, it was 7.9 and 14.2 h after 5 mg/kg by IV and oral routes, respectively. These figures are in accordance with the duration of the diuretic effects.

Torasemide was 98–99% bound to plasma proteins. It was mainly excreted through the urine. In rats and dogs, approximately 70% of the ^{3}H-labelled torasemide was found after 24 h in the urine. In the rat, torasemide was mainly excreted as hydroxylated metabolites, less than 1% being unchanged torasemide. In the dog, more than 50% of torasemide was excreted as unchanged drug. The rest was due to a dealkylated metabolite and to a hydroxylated compound which is identical to one of the hydroxylated metabolites found in the rat.

In summary, the pharmacokinetic property most relevant to user safety is the oral bioavailability of torasemide which is very high in both species studied, and so could be expected to also be high in humans. Torasemide is metabolised slightly differently in rats and dogs, leading to more or less of the parent drug being eliminated unchanged. The metabolites appear to be qualitatively the same in the two species studied, but quantitatively different, although there was an additional dealkylated metabolite found in dogs. Because of the high oral bioavailability, the adverse effects seen in oral toxicity studies conducted in laboratory species could manifest when humans accidentally ingest the drug.

Toxicological studies

Single dose toxicity

Single-dose studies were conducted in rats and dogs. In the rat study, doses up to 5000 mg/kg bodyweight (bw) administered orally were used, and there were no deaths recorded at any dose. In

the dog study, doses up to 2000 mg/kg bw administered orally were used and there were no deaths at any dose. Effects noted included polyuria, electrolyte imbalances, bodyweight decrease and histopathological changes to the liver and kidneys at the higher doses.

Repeat dose toxicity

The reports of one study in rats lasting 52 weeks and two studies in dogs lasting 13 weeks and 52 weeks were provided, in line with requirements.

In both rats and dogs, the adverse effects of torasemide were linked to the pharmacodynamic mode of action of the drug and its intended use as a diuretic. Water consumption increased with dose, as did food consumption in rats only. Food intake decreased in dogs. Urine production increased, whereas concentrations of electrolytes in urine decreased. Kidneys showed signs of toxicity, including increased blood urea nitrogen (BUN), increased kidney weights, fibrosis, calcium deposition and changes to the renal tubules. These signs were dose-related, and did not return to normal after drug withdrawal (in dogs dosed at 8.0 mg/kg/day). Studies of ocular and auditory toxicity failed to reveal any signs in either species.

In rats, in the highest dose group (25 mg/kg bw/day), there were increases of adrenal gland weights and blood leukocyte counts, which may point to the potential for endocrine disruption and/or immune system modulation. The rat LOAEL can be considered as 5.0 mg/kg bw/day due to changes in kidneys, and the NOAEL is 1.0 mg/kg bw/day.

In the 13-week study in dogs, there was a lowering of the leukocyte count at the highest dose (8.0 mg/kg bw/day), as well as changes in many other blood biomarkers, which for the most part returned to normal levels after ceasing administration. At this dose, only BUN and creatinine levels, which are markers of kidney function, remained high during the 5 week recovery period. There was also an increase in the weights of adrenal glands at necropsy, which did not recover when drug administration was stopped.

In the 52-week study in dogs, there were considerably fewer adverse effects noted, reflecting the lower doses used. The maximum dose in this study was 0.4 mg/kg bw/day, at which level food consumption decreased and water consumption increased. Kidney function appeared normal, although BUN and creatinine levels remained significantly higher than in the controls and there were changes in the kidneys noted at necropsy, including those mentioned above. There were histopathological changes in the kidney at 0.08 mg/kg bw/day and at 0.01 mg/kg bw/day, although those in the lowest dose group appear to be quite minor. The LOAEL for dogs can therefore be considered to be 0.08 mg/kg bw/day and the NOAEL is 0.01 mg/kg bw/day. This is therefore the overall NOAEL for repeated dose toxicity.

Tolerance in the target species of animal

See part 4.

Reproductive toxicity

Two studies into the reproductive effects of torasemide were submitted, one conducted in rats and one in rabbits.

After daily administration of 1.2, 6.0 or 30 mg/kg bw/day in pregnant female rats between day 7 and day 17 of pregnancy, there were signs of maternal toxicity in the 30 mg/kg group, including one

death. Other signs, such as decreased food consumption, reduced grooming and piloerection were also noted in this group.

No significant effects compared to the control group were detected in foetuses regarding the number of dead or reabsorbed, the number of viable foetuses, the sex ratio, the body weight and placental weight. No external abnormalities were observed in any torasemide treated group. There were, however, internal anomalies noted in skeletal features, such as wavy ribs, which appear to be dose-related, although only significantly different from controls in the highest dose group. The observation of wavy ribs is a well-known effect of loop diuretics in foetuses when administered in dams before completion of organogenesis. However, this effect was reversible and wavy ribs were not observed in newborn pups. In terms of skeletal abnormalities, there was splitting of the sternebrae observed in one case in the 30 mg/kg group. In terms of skeletal variation, there were 1 – 5 cases of accessory sternebra observed in each group, and additionally, there were 2 cases of a 14^{th} rib observed in the 6 mg/kg group. No significant difference was observed between the control group and in each of the torasemide administration groups in terms of the incidence of foetuses with these abnormalities and the incidence by type. It was concluded that torasemide had no teratogenic effects in rats.

After daily administration of 0.04, 0.2 or 1.0 mg/kg bw/day in pregnant female rabbits between day 6 and day 18 of pregnancy, there were signs of maternal toxicity in the 1.0 mg/kg bw/day group, including several deaths. A significant decrease in bodyweight and in food consumption was observed between control animals and animals in the 1.0 mg/kg bw/day group.

No difference was detected between the control and the torasemide treated groups with regard to the rate of dead or reabsorbed foetuses, the number of viable foetuses, the viable foetus bodyweight and sex ratio and the placenta weight. Despite not being significantly different compared to controls, the rate of foetal death or reabsorbed foetuses was higher in animals receiving 1.0 mg/kg bw/day, suggesting a mild lethal effect on rabbit foetuses. The NOAEL in rabbits was considered to be 0.2 mg/kg bw/day in dams and foetuses.

With the data provided it can be concluded that torasemide is not toxic for reproduction.

Mutagenicity/genotoxicity

Three proprietary studies were provided including a bacterial reverse mutation test (Ames test), an in vitro mammalian gene mutation test and an in vivo test for chromosomal effects using rodent haematopoietic cells. Data from the literature were also provided. All the data presented showed that there were no signs of mutagenic potential for torasemide.

Carcinogenicity

Since there were no signs of neoplastic changes or increases in tumour formation in the repeat-dose studies, no signs of mutagenic potential and no obvious molecular moieties that induce carcinogenicity, no data were required for this section. It can be concluded that torasemide is highly unlikely to be carcinogenic.

Studies of other effects

Studies on the dermal sensitisation and irritancy, as well as ocular irritancy of the product as formulated were provided. There were no signs that the product would cause dermal sensitisation or

be irritating to the skin or eyes.

As for other loop diuretics, torasemide may have ototoxic side-effects which may limit its usefulness. Ototoxic effects were investigated in cats after experimental exposure. After application of 3 separate doses of 25 mg/kg intravenously, once a week for 3 weeks, acute ototoxicity was observed, but complete recovery occurred within a week. No evidence of ototoxicity had been reported in humans after 4 weeks' administration of torasemide up to 400 mg/day.

It is considered that the doses required to induce ototoxicity in cats are far higher than those proposed for therapeutic doses in dogs. In addition, the drug was given via intravenous bolus in the study. The human data also demonstrate that ototoxicity would not be a likely hazard when considering the accidental self-administration of the product.

Two published papers on the current state of knowledge on the pharmacology and therapeutic efficacy (including adverse reaction reports) in humans were provided. The most commonly reported adverse effects after torasemide administration in humans included dizziness, headache, gastrointestinal disturbances, orthostatic hypotension and fatigue. After exposure to torasemide at therapeutic doses ranging between 2.5 mg and 40 mg/day, the most common side-effects concerned the modification of blood biochemical parameters, especially the electrolytes. They are mild with a tendency to be transitory and are rarely accompanied by severe clinical signs requiring the withdrawal of treatment.

User safety

The applicant presented a user safety assessment conducted in accordance with CVMP guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1). All the potential routes of accidental contact with the product (except inhalation) had been considered and it was concluded that the most likely are those of dermal and/or oral exposure. It is not considered likely that adverse events will occur as a result of dermal contact with these tablets. Good Laboratory Practice (GLP) sensitisation and irritation studies have confirmed that the product does not cause these effects in the test animals used. This is also the case for eye irritation.

With regard to accidental oral exposure, the applicant has considered that ingestion of three of the largest (18 mg torasemide each) tablets by a small child (10 kg) should be used as a worst-case scenario. Taking into account that the product is supplied in blister packs, and these packs are considered to be a major hindrance to the ability of children to access this type of product, this assertion can be agreed.

When comparing this level to the oral NOAEL, the margin of exposure is below the trigger value of 100. This means that some adverse effects could be observed after an accidental ingestion. However, these effects would likely be relatively minor, based on the pharmacological activity of the product; that is, polyuria and electrolyte imbalance, gastrointestinal effects and/or dizziness/headaches, and would be unlikely to endanger the life of the user. Furthermore, the NOAEL is based on the results of a repeated dose study, whereas, accidental exposure is considered to be a single exposure. The results of the single dose toxicity studies show evidence that the LD_{50}s are very high; therefore, no significant risk is expected.

As result of the user safety assessment the following warnings for the user are considered to be appropriate:

- People with known hypersensitivity to torasemide or other sulfonamides 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.

The CVMP concluded that the product does not pose an unacceptable risk to the user when used in accordance with the SPC.

Environmental risk assessment

A phase I environmental risk assessment (ERA) was provided according to the VICH GL6 on Environmental impact assessment (EIAS) for veterinary medicinal products (CVMP/VICH/592/98-FINAL) and the CVMP guideline on the Environmental impact assessment for veterinary medicinal products in support of the VICH GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1).

No phase II assessment is required because the product will only be used in non-food producing animals. Based on the data provided the ERA can stop at phase I. UpCard is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

The pharmacology of torasemide is well-established and is similar to other loop diuretics, such as furosemide. The toxicology of the substance has been addressed mainly through the provision of data from published literature, along with some proprietary studies.

Torasemide is not genotoxic, teratogenic, or toxic for reproduction.

The major adverse effects of the active substance are mainly exaggerations of the desired pharmacological effects, such as polyuria, electrolyte imbalances and increased thirst. Data from rats, dogs and humans indicate that severe adverse events only occur at very high doses and/or long durations of treatment, and these include renal and adrenal changes, which may not be reversible. These are highly unlikely outcomes after accidental ingestion of the largest tablets in the range (18 mg), since dose levels would not reach toxic levels, even in small children.

A comprehensive user safety assessment has been provided, which covers all the aspects required in the user safety guideline (EMA/CVMP/543/03-Rev.1).

Studies using the actual product have been provided that investigate the potential for dermal sensitisation and irritation, as well as eye irritation. It was concluded from the data that the product will not induce these effects. Adequate user safety warnings have been proposed. Torasemide is widely used in human medicine and is considered relatively safe in use. Adverse effects in humans follow the same pattern as those seen in laboratory animals.

The CVMP concluded that the product does not pose an unacceptable risk to the user when used in accordance with the SPC.

An environmental risk assessment has been provided which demonstrates that no unacceptable risk for the environment is expected when the product is used in accordance with the proposed SPC.

In conclusion, the data provided are sufficient to conclude that the product is not expected to pose a risk for the user or the environment, when used as recommended. It is also well tolerated by the target animals (see part 4).

Part 4 – Efficacy

Pharmacodynamics

The pharmacodynamics of torasemide are supported by literature references as well as dose determination studies performed by the applicant (see below). Torasemide is a loop diuretic of the pyridyl sulfonylurea class. Its primary site of action is the thick ascending limb of the loop of Henle in the kidney where it inhibits the $Na^+/2Cl^-/K^+$ symporter. The result is a limitation on tubular reabsorption of sodium and chloride, which subsequently leads to a decrease in interstitial hypertonicity, reduced reabsorption of water and diuresis with saluresis. This effect is of direct relevance to the proposed indication. Reducing extracellular volume in turn reduces cardiac filling pressure and ventricular end-diastolic volume, thereby improving cardiac function and lowering the incidence of systemic and/or pulmonary oedema.

Secondary pharmacological actions of torasemide include antihypertensive and anti-aldosteronergic effects demonstrated in laboratory animals, and anti-fibrosis within the myocardium in humans.

The applicant highlighted a pharmacodynamic interaction between loop diuretics and non-steroidal anti-inflammatory drugs (NSAIDs). In humans, NSAIDs are known to decrease the natriuretic and diuretic responses to loop diuretics. Such an interaction has not been investigated in dogs to the applicant's knowledge.

Development of resistance

Not applicable.

Pharmacokinetics

The pharmacokinetics of torasemide in dogs are supported by one literature reference and studies, including two single dose studies (cross-over design; GLP-compliant), one multiple dose study (14 days; GLP-compliant) and three studies (one in-vivo and two in-vitro; non-GLP) investigating the metabolism of torasemide. A toxicokinetic study (13 weeks) was also performed as part of the target animal safety study. Given an intended dose range of 0.1–0.6 mg/kg bw, the single dose studies determined the pharmacokinetics of torasemide administered at doses of 0.1, 0.2, 0.8 and 1.6 mg/kg bw, and the multiple dose study investigated the pharmacokinetics of 0.2 mg/kg bw torasemide.

Torasemide is well absorbed by the oral route (bioavailability approximately 90%), with a mean T_{max} of less than 1h, and absorption is influenced by feeding (AUC_{last} increased by 36% and delayed T_{max}). Pharmacokinetic parameters, C_{max} and AUC, increased in a dose proportional manner over the range 0.2–1.6 mg/kg bw and there is no evidence of significant accumulation in plasma. According to the literature, torasemide is highly bound to plasma proteins (approximately 98%). Systemic clearance was low (0.0173 l/h/kg) and volume of distribution (V_{ss}) was small (0.142 l/kg), with an elimination half-life of 6.90 h (data for 0.1 mg/kg PO dose). The primary elimination route is renal, with renal

clearance amounting to approximately 70% of total body clearance and approximately 70% of the administered dose eliminated as unchanged parent drug. Two metabolites of torasemide, namely 5878 and 5946, were detected in urine and in in-vitro assays using canine hepatic microsomes. Phase I enzymes involved in the metabolism of torasemide were cytochromes P450 3A4, 2E1 and, to a lesser extent, 2C9.

Torasemide may have pharmacokinetic-based interactions with drugs metabolised by the same cytochrome P450 enzymes or drugs that are also highly bound to plasma proteins.

Dose determination/justification

Dose determination under laboratory conditions

Two dose determination studies were performed in healthy dogs using the percentage increase in the weight of urine excreted over 24 hours as the primary end-point. The first was a pilot study with two to four animals per group, while the second used ten animals in a five-period, five-sequence, cross-over design.

In the pilot study (0.05–10 mg/kg bw single doses), both 0.05 and 0.1 mg/kg bw doses gave rise to increases in urine output of approximately 50%. At the higher end of the dose range, the mean percentage increase in urine output at 5 mg/kg bw was higher than the effect observed at either 1 or 10 mg/kg bw. In the following study (0.15–4.5 mg/kg bw/day for 5 days), a mean percentage increase in urine output of 33–50% was observed at 0.15 mg/kg bw. At 0.75 mg/kg bw, results were not significantly different from those at 1.5 and 4.5 mg/kg bw, indicating that a ceiling effect had been attained (mean percentage increase in urine output of 264–418%).

To justify the proposed dosing interval (i.e. once daily administration), a turnover response model was constructed based on the data from the pharmacokinetics dose linearity study to predict the diuretic effects of torasemide when administered using different dosage regimens. The model was used to simulate diuresis if torasemide is administered as a single (0.1 mg/kg bw, once daily) or divided (0.05 mg/kg bw, twice daily) dose. The volume of excreted urine was shown to be almost identical for these regimens, although it would have been more informative to determine whether this finding holds true for higher dose levels as proposed in the SPC.

To address safety, a target animal safety study was provided in which healthy animals were dosed with either torasemide (0.6 mg/kg bw once daily or 0.3 mg/kg bw twice daily) or furosemide (6 mg/kg bw twice daily) for 14 consecutive days (study reports 182VT4F3 and 182VT4F4). Similar efficacy in terms of the volume of excreted urine was observed in both torasemide treatment groups. However, among torasemide treated dogs serum urea levels were higher in the group dosed twice daily compared with once daily. Indeed, 3 out of 8 animals dosed twice daily with torasemide received fluid therapy suggesting that this regimen may precipitate greater dehydration. In contrast, these findings were not correlated with histopathological findings which revealed a trend toward greater renal histopathologic change among dogs treated with torasemide once daily relative to twice daily. Results from necropsies performed 14 days after the end of torasemide treatment (both regimens) suggested partial recovery of renal changes can be expected by this point. However, given the small number of animals and short duration of treatment it is difficult to make any firm conclusions regarding either the relative safety of torasemide administered once or twice daily, or the relative safety of equivalent doses of torasemide and furosemide. From these data, the safety profiles of the two torasemide dosage regimens and the furosemide treatment regimen appear to be similar.

A dose range of 0.2–0.8 mg/kg bw/day was initially proposed for field studies based on literature data and pharmacodynamic data, although it was not clear why 0.2 mg/kg bw was chosen as the lowest limit of the dose range despite evidence of a diuretic effect for a dose of 0.05 mg/kg bw in the pilot study referenced above. The applicant subsequently conducted a laboratory-based study to compare the diuretic effects of torasemide (0.1 and 0.6 mg/kg bw) and furosemide (0.5–40 mg/kg bw) following single oral administrations to dogs (cross-over design). Data from the study were used to model the relationship between furosemide dose and pharmacodynamic response, i.e. diuresis. It was shown that doses of 0.1 and 0.6 mg torasemide/kg bw translated to doses of furosemide that were approximately 20 times higher. Owing to the small number of animals and large inter-individual variability in the pilot dose determination study, it is difficult to draw firm conclusions from this data. Instead, data from the turnover response model were used and the level of diuresis predicted for 0.05 mg torasemide/kg bw was found to correspond to a furosemide dose of 1.45 mg/kg bw/day. As this falls below the recommended starting dose for the reference product, this could suggest that a dose of torasemide of 0.05 mg/kg bw might not be sufficiently effective in clinically diseased animals.

Dose determination under field conditions

In absence of a validated model of experimental congestive heart failure, a dose of 0.2–0.8 mg torasemide/kg bw/day was investigated in dogs with congestive heart failure under field conditions (182VC1F1, see below under "field trials"). The results of this pilot field study suggested that the efficacy of torasemide was non-inferior to that obtained with the product containing furosemide at a dose of 1–5 mg/kg bw/twice daily, but an increased frequency of renal adverse events was seen among torasemide treated dogs. The results suggested the need for availability of a lower dose of torasemide in some dogs as well as greater dose flexibility.

Based on these findings a revised dose range of 0.2–0.6 mg/kg bw/day (dose adjustments of 0.1 mg/kg bw/day and availability of a lowest dose of 0.1 mg/kg bw/day from day 7) was proposed and assessed by the applicant in the pivotal field study (182VC1F2, see below under "field trials"). Effectiveness of torasemide during this field study was non-inferior to treatment with furosemide. However, while the overall risk of serious adverse events was comparable to that experienced by furosemide treated dogs, safety results for the subset of serious renal adverse events were not significantly improved in torasemide treated dogs when compared with the pilot study (182VC1F1). This was considered by the applicant to be confirmation that adverse effects relating to hypovolaemia and dehydration can exacerbate renal dysfunction relating to underlying cardiac disease.

Target animal tolerance

A thirteen-week target animal safety study was conducted in 32 healthy beagle dogs at 0x, 1x, 3x and 6x the lowest proposed dose of 0.1 mg/kg bw administered orally once daily (i.e. 0–0.6 mg/kg bw). The only clinically apparent reaction attributed to product administration was erythema of the inner pinnae and the frequency of the finding increased in a dose-dependent manner. In addition, water consumption significantly increased at 0.6 mg/kg bw compared to the placebo control.

Small but statistically significant changes in clinical chemistry and haematology were observed as follows: increased haematocrit, increased plasma urea, creatinine and albumin concentrations, decreased plasma potassium, chloride, phosphate and magnesium concentrations and increased serum aldosterone levels. With regard to urinalysis, there were significant increases in urine volume, which were accompanied by reductions in specific gravity and urine concentrations of creatinine, sodium, potassium, chloride and phosphate, and increases in the fractional excretion of calcium and phosphate. Changes mostly appeared to be dose-dependent. These changes are considered to be related to the

pharmacological action of torasemide or to result from haemoconcentration secondary to diuresis. However, inconsistent with its pharmacology, reductions in the fractional excretion of chloride and potassium were observed, although the changes in the latter were only transient.

There was no mortality during the study. On necropsy, kidney weights were significantly higher in the 0.6 mg/kg bw group compared to placebo. Histopathological changes were minimal to mild and included the presence of basophilic tubular epithelial cells in the renal cortex and outer medulla, which correspond to regeneration of damaged tubular cells. In addition, there was dilation of the proximal and distal tubules, a mononuclear cell infiltrate and tubular mineralisation, though the latter was observed in one animal only.

The product was well tolerated in healthy animals administered torasemide at 0.6 mg/kg bw/day (the upper end of proposed dose range) for 13 weeks. Although this study was not conducted with 3x and 5x the upper proposed dose (as recommended in VICH GL43), the toxicological profile of torasemide is well characterised in part 3 and the margin of safety is likely to differ between healthy dogs and those with heart disease. Consequently, requirement of a new study would not be consistent with 3Rs principles.

Tolerance to a single dose (0.6 mg/kg bw once daily) versus divided dose (0.3 mg/kg bw twice daily) of torasemide and to furosemide (6 mg/kg bw twice daily) for 14 consecutive days is reported under "Dose determination/justification", see above (study reports 182VT4F3 and 182VT4F4). It was concluded that the safety profiles of these dosage regimens appear to be comparable. In addition, despite the low number of animals and short duration, this study offered the best opportunity to observe the reversibility of renal injury. One group of animals was necropsied immediately after therapy while the other was necropsied 14 days after cessation of therapy. The necropsy findings supported at least partial reversibility of renal lesions within this short period of time. Furthermore, recovery of lesions was similar in animals treated with either torasemide or furosemide at equivalent dosages. It is considered that an extended period for recovery would be expected to improve on these findings.

Tolerance in the target population is further reported under "Field trials". In summary, during the 84 day pivotal field study (182VC1F2), torasemide administered to dogs with congestive heart failure at a dose of between 0.1 and 0.6 mg/kg bw/once daily is associated with a similar overall incidence of serious adverse events to furosemide. The most frequently observed adverse events were polyuria and/or polydipsia, death, renal insufficiency, diarrhoea and emesis. An increased incidence of polyuria, polydipsia and renal insufficiency adverse events were observed among torasemide treated compared with furosemide treated dogs. Adequate risk mitigation on the risk of serious renal insufficiency adverse events is included within the SPC and product literature (see below).

In conclusion, the toxicological profile of torasemide has been sufficiently well characterised in the target species. With the exception of erythema of the inner pinnae, clinicopathological findings in treated animals reflect the pharmacodynamic activity of loop diuretics. It is plausible that the pathophysiological basis for the renal adverse events observed during the field studies was renal injury secondary to the pharmacological action of torasemide and hypoperfusion. However, reversibility of renal pathology, at least in part, has been supported by data from a target animal safety study, with similar findings in animals treated with either torasemide or furosemide. The CVMP considered that the analysis of the data provided support the conclusion that lesions "are not irreversible".

Field trials

Two field studies were provided to compare the safety and efficacy of torasemide with a reference

product containing furosemide for the treatment of signs secondary to congestive heart failure. The pilot study (182VC1F1) was the first study conducted by the applicant in the target population and evaluated a dose range of torasemide extrapolated from experimental studies in healthy animals and the published literature. Following this study, adjustments were made to the product (additional tablet dose sizes (dose in milligrams) and greater tablet divisibility) to increase the number of dosing levels. The study protocol was repeated with amendments to the posology (reduction in maximum and minimum dose and reduced size of dose adjustment when change required) in a confirmatory (pivotal) field study (182VC1F2).

Pilot field study (182VC1F1)

This randomised, single-blinded, positively controlled field study (2013) was conducted in centres across France, Spain and Germany over 84 days. This study (ITT population, n=176) compared torasemide administered orally at a starting dose of 0.2–0.6 mg/kg bw/once daily (dose adjustments of 0.2 mg/kg/once daily within the range 0.2–0.8 mg/kg/once daily), to reference product containing furosemide administered orally at a starting dose of 1–5 mg/kg bw/twice daily (dose adjustments of 1 mg/kg bw/twice daily within this range).

All eligible dogs were diagnosed with congestive heart failure and considered suitable for outpatient diuretic therapy for signs of pulmonary oedema, pleural effusion and/or ascites at inclusion. They were enrolled into one of two strata based on anticipated response to treatment.

Stratum 1: anticipated to improve following diuretic treatment based on history and clinical signs. Animals were either previously diagnosed with heart failure, being treated with furosemide but requiring dose re-evaluation or seen for first time with signs of congestion and requiring immediate outpatient diuretic treatment.

Stratum 2: anticipated to remain stable following diuretic treatment. Animals were either already receiving *per os* diuretics and stable, or just hospitalised and considered for outpatient diuretic treatment.

The inclusion criteria were broadly appropriate (dog ≥ 3 kg, New York Heart Association (NYHA) stage II, III or IV congestive heart failure and 1 or more episodes of pulmonary oedema, pleural effusion or ascites secondary to heart failure requiring long-term outpatient diuretic treatment).

The primary efficacy endpoint was response to treatment at day 84. This was based on (i) an improvement (stratum 1) or stabilisation (stratum 2) in the composite clinical score, and (ii) no change in the degree of pulmonary oedema, pleural effusion and/or ascites torasemide on day 84. The composite score was based on assessments of dyspnoea, cough frequency, exercise tolerance and ascites (possible score range -1 to +9). This composite clinical scoring system was based on similar validated scoring systems. An improvement of one point on the clinical composite scoring system used is considered a clinically relevant and desirable improvement in patient condition; criteria for response in stratum 1 are therefore supported. A range of secondary efficacy endpoints were evaluated. The preliminary safety analysis was based on the classification of adverse events compliant with VeDDRA and descriptive analysis of most frequently observed events as well as analysis of the progression over time in the values of haematological and biological parameters.

This study demonstrated the non-inferiority (delta -20%; α=2.5%; lower limit of CI for the OR >0.43) of torasemide to furosemide for the primary efficacy endpoint (OR 1.383; CI 0.703–2.721). Secondary analysis, including a repeated measures model analysis comparing response to treatment over time, confirmed non-inferiority. A greater overall frequency of renal and urinary adverse events was observed in torasemide (n=25) compared with furosemide (n=5) treated dogs. In particular renal

insufficiency adverse events[1] were more frequent in torasemide treated dogs (n=18 *vs.* n=2) and, while both dogs in the furosemide-group had pre-existing renal damage on day 0, 14 out of these 18 torasemide treated dogs had no azotaemia at baseline. Enrolment was terminated early due to the concerns from the study monitor that the posology required adjustment (availability of lower doses and greater opportunity for dose adjustment had been repeatedly sought by investigators in order to optimise clinical management of patients).

Pivotal field study (182VC1F2)

Design and methods for this confirmatory study (2014) were identical to the pilot study (182VC1F1) except for the posology and minor amendments to post-inclusion withdrawal criteria. Conducted in centres across France, Spain and Germany, this study (ITT population, n=251) compared torasemide administered orally at 0.2–0.6 mg/kg bw/day (dose adjustments of 0.1 mg/kg bw/day and availability of a lowest dose of 0.1 mg/kg bw/day from day 7), to reference product containing furosemide administered orally at 1–5 mg/kg bw/twice daily (dose adjustments of 1 mg/kg bw/twice daily). During the study, regular clinical and cardiorespiratory examinations were performed on day 0 (start of the study), 7, 28, 56 and 84 (end of the follow-up period), including peripheral blood biochemistry and haematology. Blood creatinine results were used retrospectively to stage animals according to the International Renal Interest Society (IRIS) system and across time. Additional visits were performed within 7 days following all dose changes. Non-inferiority (delta -20%; α=2.5%; lower limit of CI for the OR >0.43) of torasemide to furosemide for the primary efficacy endpoint was demonstrated in the ITT population (OR 1.113; 95% CI 0.621–1.993); within ITT stratum 1 and ITT stratum 2; and also in the PP population (OR 1.234; 95% CI 0.66–2.308). Findings for secondary efficacy endpoints were supportive of non-inferiority.

Despite more comparable efficacy between torasemide and furosemide during this field study (182VC1F2) compared with results of the pilot study (182VC1F2), a greater overall frequency of adverse events was recorded in torasemide (n=184 events) compared with furosemide (n=104 events) treated dogs. The following adverse events, potentially related to treatment, were observed with greater frequency among torasemide compared with furosemide treated dogs: polyuria, polydypsia, urinary incontinence, diarrhoea, emesis, anorexia and electrolyte disturbance (hypokalaemia, hypochloraemia and hypomagnesaemia). Adverse events related to diarrhoea, cardiovascular and respiratory systems occurred with similar frequency. The frequencies of adverse events in torasemide *vs.* furosemide treated dogs for selected adverse events were as follows: polyuria/polydypsia syndrome (n=20 *vs.* 4), renal insufficiency (n=17 *vs.* 8), mortality (12 *vs.* 18), urinary incontinence (n=11 *vs.* 2) and vomiting (n=10 *vs.* 4). The total number of 'over pharmacology' adverse events observed in torasemide *vs.* furosemide treated dogs was 63 *vs*. 12 events, respectively.

However, importantly, it should be noted that the overall risk of a serious adverse event resulting in death or withdrawal from the study (all causes) was similar between torasemide and furosemide treated dogs, 0.222 and 0.192 respectively, and that there were fewer mortalities in the torasemide treated dogs compared to those treated with furosemide.

A relative increase in the risk of serious adverse events due to renal insufficiency is observed among torasemide treated dogs compared with furosemide treated dogs during this study (relative risk = 3.96) based on the applicant's analysis. Blood urea and creatinine levels (median) were greater across all time points in torasemide *vs.* furosemide treated dogs and were still rising in this group on day 84. Using the IRIS staging parameters (increase in creatinine concentration in plasma or

[1] In line with the VeDDRA terminology, "renal insufficiency adverse events" may include acute renal failure, azotaemia, chronic renal failure, elevated BUN, creatinine or renal parameters, renal failure, renal insufficiency, uraemia.

serum), a greater proportion of the torasemide treatment group was observed to experience the more severe signs of kidney damage compared with furosemide treated dogs, i.e. 11% of torasemide treated dogs were classified as stage 3 by day 84 compared with 5% of furosemide treated dogs. 12 of 17 torasemide treated dogs developing renal insufficiency during follow-up were non-azotaemic at baseline compared with 1 of 8 dogs treated with furosemide mirroring the experience in the pilot study. An association between renal insufficiency adverse events and dose/duration of treatment was not identified by the applicant. However, the lower proportion of dogs experiencing a renal insufficiency adverse event during the pivotal (182VC1F2) field study compared with the pilot (182VC1F1) suggests that optimisation of the posology following the pilot study may have reduced the risk of these adverse events in the individual patient.

The applicant was asked to comment on the possible reversibility of renal changes observed following torasemide treatment. In addition to a review of the findings from the experimental study 182VT4F3 (reported under "Dose determination/justification" and "Target animal tolerance"), the applicant performed a reanalysis of the IRIS stage changes observed during the pilot and pivotal studies. During both field studies a proportion of the torasemide treated animals experiencing increased IRIS stage was observed to complete the study with a creatinine level equal to that at baseline. Also, more than 50% of torasemide treated dogs that experienced a dose decrease during the two field studies also showed an improvement in their renal panel. These analyses indicated that blood creatinine levels can recover following a dose reduction and support the findings of the experimental study 182VT4F3 which showed a similar pattern of reversibility of renal lesions between healthy dogs treated with torasemide and furosemide.

Conclusion on the field studies

The pivotal field study (182VC1F2) demonstrated non-inferiority of torasemide (final formulation) administered at doses of 0.2–0.6 mg/kg bw/day (dose adjustments of 0.1 mg/kg bw/day and availability of a lowest dose of 0.1 mg/kg bw/day from day 7) to furosemide for the outpatient treatment of signs relating to congestive heart failure in the presence of pulmonary oedema, pleural effusion and/or ascites in dogs.

Based on the findings of two field studies with follow-up over 84 days, the overall risk of serious adverse events was similar for furosemide and torasemide treated dogs. Within the population of dogs experiencing a serious adverse event a relatively higher risk of serious renal adverse events can be expected for torasemide treated animals (whereas for furosemide, there was a relatively higher risk of serious non-renal adverse events). Taking into consideration both serious and non-serious adverse events a greater combined frequency of adverse events can be anticipated in torasemide treated compared with furosemide treated dogs largely due to the higher frequency of non-serious over pharmacology events (e.g. non-serious polyuria and/or polydipsia).

Efficacy of torasemide, prescribed at a dose of between 0.1–0.6 mg/kg bw/day, is adequately supported. Dosing instructions (section 4.9 of the SPC) reflect the fact that treatment must be tailored to the individual animal's needs.

Overall conclusion on efficacy

The pharmacodynamic and pharmacokinetic characteristics of torasemide are generally well documented and have been satisfactorily evaluated in dogs. Absolute oral bioavailability was approximately 90% with a mean T_{max} of less than 1h. Systemic clearance was low (0.0173 l/h/kg) and volume of distribution (V_{ss}) was small (0.142 l/kg), with an elimination half-life of 6.90 h (data for 0.1 mg/kg PO dose). The primary elimination route is renal.

Dose determination studies were conducted using healthy animals and furosemide was not included in initial studies as a comparator. The applicant subsequently conducted a study, again in healthy animals, to compare the diuretic effects of torasemide and furosemide, showing that the dose of furosemide needed to be approximately 20 times higher than that for torasemide for the same diuretic response. However, the limitations of these pre-clinical studies for optimisation of the dosage regimen are recognised, particularly the uncertainty of extrapolating data from healthy to diseased animals. As such, it was necessary to investigate the dose in diseased animals under field conditions.

The target animal safety study demonstrated that torasemide is well tolerated in healthy animals at a dose of 0.6 mg/kg bw/day (the upper end of the proposed dose range) for 13 weeks (noting that this treatment may be administered life-long). Minor changes were seen that were consistent with the pharmacological action of the substance. The safety profile (margin of safety) of torasemide is potentially different in the target population of clinical patients. The short term follow-up of patients during the field studies leaves some uncertainty over the long-term risk of adverse events for a treatment potentially administered life-long. However, a 52-week repeated dose toxicity study in dogs is presented in part 3, this issue is not considered to be pivotal and sufficient data have been submitted to enable a reasonable evaluation of the risks to the target population with torasemide treatment. The greater risk of renal insufficiency adverse events among torasemide treated dogs compared to furosemide treated dogs is a concern, events occurring independent of baseline renal status (based on blood urea and creatinine at initiation of therapy). Renal insufficiency adverse events may necessitate discontinuation of therapy with torasemide, and could lead to renal failure, possibly euthanasia. Based on the lower incidence of renal insufficiency adverse events during the pivotal field study (182VC1F2) compared with the pilot field study (182VC1F1) during which higher torasemide doses and larger dose increments were available, a relationship between posology and renal adverse events may exist. However, given the similar pattern of reversibility of renal lesions between healthy dogs treated with torasemide and furosemide during an experimental study (182VT4F3), and the observations made during the field studies, similar reversibility of renal lesions can be expected with furosemide and torasemide therapy. During the pivotal field study (182VC1F2), the risk of serious a adverse event resulting in death or withdrawal from the study (all causes) was similar between torasemide and furosemide treated dogs. Furthermore, there were also fewer mortalities in the torasemide treated dogs compared with dogs treated with furosemide during this study.

Based on the findings of the pivotal field study (182VC1F2) it can be concluded that the efficacy of torasemide administered at between 0.1 and 0.6 mg/kg bw/day (starting dose 0.2–0.6 mg/kg bw/day) was non-inferior to furosemide for the outpatient treatment of signs relating to congestive heart failure in the presence of pulmonary oedema, pleural effusion and/or ascites in dogs over 84 days.

Based on the findings of the two field studies, the overall risk of serious adverse events resulting in death or the need to discontinue treatment is expected to be similar between torasemide and furosemide treated dogs.

Part 5 – Benefit-risk assessment

Introduction

UpCard is tablets for dogs containing torasemide (anhydrous) as active substance and are available in 4 different strengths. The 0.75 mg tablets are divisible in halves and the 3.0 mg, 7.5 mg and 18 mg strengths are divisible in quarters.

Torasemide is a loop diuretic of the pyridyl sulfonylurea class. Its primary site of action is the thick ascending limb of the loop of Henle where it inhibits the Na+/2Cl-/K+ symporter. The result is a limitation on tubular reabsorption of sodium and chloride, which subsequently leads to a decrease in interstitial hypertonicity, reduced reabsorption of water and diuresis with saluresis.

The product is proposed for the "treatment of clinical signs, including oedema and effusion, related to congestive heart failure." in dogs. Torasemide is a new active substance in veterinary medicine.

The dossier was submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC (full dossier).

Benefit assessment

Direct therapeutic benefit

The benefit of UpCard is its efficacy in the treatment of clinical signs, including oedema and effusion, related to congestive heart failure. This benefit has been indirectly shown in two laboratory studies which confirmed the diuretic action of torasemide in healthy dogs. Direct demonstration of the therapeutic benefits of torasemide in the target population was performed in two field studies with the final formulation but only one used the proposed posology. The second which used a very slightly different posology can only be considered supportive. Both studies showed the response to torasemide treatment at 84 days to be non-inferior to the response to furosemide.

Based on the findings of the pivotal field study it can be concluded that the efficacy of torasemide administered at between 0.1 and 0.6 mg/kg bw/day was non-inferior to furosemide for the outpatient treatment of signs relating to congestive heart failure in the presence of pulmonary oedema, pleural effusion and/or ascites in dogs over 84 days. 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.

Additional benefits

The active substance is a member of the loop diuretic family and is authorised for use in humans. UpCard increases the range of available loop diuretics for dogs.

The once daily dosing regimen may aid compliance.

Risk assessment

Main potential risks have been identified as follows:

Quality:

The formulation and manufacture of the finished product is well described and the specifications set will ensure that product of consistent quality will be produced. However the applicant is recommended to perform an in-use stability study for a second batch of each strength of tablets close to the end of their shelf-life.

For the target animal:

In the target animal safety study, the toxic effects of torasemide were dose-dependent and appeared to be primarily related to the pharmacological (diuretic) action of the active substance.

Observations from the field studies showed a very common risk of renal insufficiency adverse events in treated dogs regardless of baseline renal status (based on blood urea and creatinine at initiation of therapy). These adverse events may necessitate discontinuation of therapy with torasemide, and could potentially lead to renal failure and euthanasia. Mitigation measures and warnings have been added to the product information to ensure that renal risks are minimised.

The following adverse events potentially attributable to torasemide treatment were also observed during pivotal field study: polyuria, polydipsia, urinary incontinence, reduced or absent faeces, diarrhoea, emesis, anorexia and electrolyte disturbance (hypokalaemia, hypochloraemia and hypomagnesaemia).

Lack of efficacy could be encountered if torasemide is concomitantly administered with other highly plasma protein bound drugs or NSAIDs. In addition, the effect of antihypertensive drugs given concomitantly may be potentiated and torasemide can reduce the renal excretion of salicylates, leading to an increased risk of toxicity.

For the user:

A comprehensive user safety assessment has been provided. The potential risks to those who accidentally ingest up to three 18 mg tablets (largest tablet size) at once were identified as being linked to the pharmacodynamic effects of the product (polyuria, electrolyte imbalances and increased thirst). Severe adverse events only occur at very high doses and/or long durations of treatment, and these are highly unlikely outcomes after accidental self-ingestion of the largest tablets in the range (18 mg), even in small children.

The CVMP concluded that the user safety for this product is acceptable when used as recommended and taking into account the safety advice in the SPC.

For the environment:

UpCard is not expected to pose a risk for the environment when used as recommended.

Risk management or mitigation measures

The following measures are included in the SPC to minimise the above mentioned risks in the target species:

- Warnings are arranged such that renal warnings are listed above other product warnings, as appropriate. A warning is included to contraindicate the use of this product in patients with renal failure. Warnings also advise on the need to regularly monitor renal parameters and hydration before and during treatment. Warnings have been added that concomitant treatment with drugs known to be potentially nephrotoxic should be avoided. A contraindication against concomitant treatment with a loop diuretic is included, as well as a warning against treating patients previously prescribed high doses of an alternative loop diuretic. Furthermore, a warning is included that dogs stable on an alternative loop diuretic for the treatment of signs of congestive heart failure should not be changed to torasemide without taking into account the risk of de-stabilising the clinical condition and of adverse reactions.
- Warnings are included alerting prescribers to the likely occurrence of polyuria and/or polydipsia and the possible development of dehydration with prolonged treatment.

- Similar warnings indicate that prolonged treatment may result in electrolyte deficiency and that serum electrolytes need to be regularly monitored before and during treatment.
- Warnings also state that gastrointestinal signs (i.e. vomiting, reduced or absent faeces, transient soft stools) may occur during treatment. The directions for use advice on the need for regular re-evaluation of the dose and seeking of the lowest effective dose as early in treatment as possible to avoid or reduce the frequency of adverse events while also avoiding lack of efficacy.
- Statements to make veterinarians aware of potential interactions between torasemide and other highly plasma protein bound drugs, NSAIDs, antihypertensive drugs and salicylates are included in section 4.8 of the SPC. In addition, there are warnings regarding concurrent use of torasemide with drugs affecting electrolyte balance (corticosteroids, amphotericin B, digoxin) and nephrotoxic or ototoxic drugs (aminoglycosides, cephalosporins). It is also stated that torasemide may increase the risk of sulfonamide allergy.

Appropriate information has been included in the SPC to inform on the potential risks of this product relevant to the target animal, user and environment and to provide advice on how to prevent or reduce these risks.

Evaluation of the benefit-risk balance

The formulation and manufacture of UpCard is well described and the proposed specifications would ensure that a product of consistent quality will be produced.

The main risk in the target population is in regard to renal insufficiency adverse events, which require careful monitoring of treatment, and may necessitate discontinuation of therapy. However, reversibility of renal lesions can be expected, and adequate warnings are included in the product information addressing this risk.

The product presents an acceptable risk for users and the environment when used as recommended.

The efficacy of torasemide at a dose of between 0.1 and 0.6 mg/kg bw/day, once daily, in the treatment of clinical signs, including oedema and effusion, related to congestive heart failure has been demonstrated.

The product has been shown to have a positive benefit-risk balance overall.

Conclusion on the benefit-risk balance

The overall benefit-risk evaluation for the product is deemed positive with a sufficiently clear and complete SPC and product literature.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for UpCard is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above mentioned medicinal product.