8 November 2018
EMA/802659/2018
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for Isemid (EMEA/V/C/004345/0000)

International non-proprietary name: torasemide

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Introduction

The applicant Ceva Santé Animale submitted on 20 June 2017 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Isemid, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004 (optional scope).

The eligibility to the centralised procedure was agreed upon by the CVMP on 10 December 2015 as Isemid contains a new active substance (torasemide) which was not authorised as a veterinary medicinal product in the Union on the date of entry into force of Regulation (EC) No 726/2004.

The active substance of Isemid is torasemide, 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 natriuresis. The target species is dogs.

The applicant applied for the following indication: For treatment of clinical signs related to congestive heart failure in dogs, including pulmonary oedema.

Isemid chewable tablets contain 1 mg, 2 mg or 4 mg of torasemide and are presented in packs containing 30 or 90 chewable tablets.

The rapporteur appointed is Cristina Muñoz Madero and the co-rapporteur is Helen Jukes.

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

On 8 November 2018, the CVMP adopted an opinion and CVMP assessment report.

On 9 January 2019, the European Commission adopted a Commission Decision granting the marketing authorisation for Isemid.

Scientific advice

The applicant received scientific advice from the CVMP on 13 September 2012. The scientific advice pertained to dose justification, dose confirmation studies, and the design of target animal safety and clinical field studies. The advice was followed by the applicant.

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 December 2015) 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

Manufacture of the dosage form, packaging and batch control take place within the EU.

Batch release takes place in two sites within the EU at Louverne (France) and Loudéac (France).

GMP certifications, which confirm the date of the last inspection and show that all sites are authorised for the manufacture and batch release of such veterinary dosage forms, have been provided. A GMP declaration for the active substance manufacturing site was provided from the Qualified Person at the EU batch release site. The declaration was based on an on-site audit by a third party.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system was considered in line with legal requirements.

The GMP status of both the active substance and finished product manufacturing sites has been satisfactorily established and are in line with legal requirements.

Part 2 - Quality

Composition

The finished product is presented as oblong brown scored chewable tablets containing torasemide as active substance. Three strengths of tablets are proposed: a 103 mg tablet (small tablet or S-tablet) with 1 mg of torasemide, a 206 mg tablet (medium tablet or M-tablet) with 2 mg of torasemide and a 412 mg tablet (large tablet or L-tablet) with 4 mg of torasemide.

Other ingredients are: lactose monohydrate and cellulose microcrystalline, povidone K30, crospovidone type B, magnesium stearate, compressible sugar and pork liver powder flavour.

The product is available in blisters as described in section 6.5 of the SPC.

Containers

The primary packaging is a blister pack of polyamide/aluminium/PVC thermo-sealed by aluminium foil. The material complies with the relevant EU requirements. Specifications, analytical methods and certificates of analysis are provided.

The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Each blister contains 10 tablets. The blisters are packed in outer cardboard boxes containing 30 or 90 tablets. The pack sizes are consistent with the dosage regimen and duration of use.

Development pharmaceutics

The aim of the development pharmaceutics was to develop a chewable tablet containing torasemide for the treatment of pulmonary oedema in dogs with congestive heart failure with a formulation that will

have a good acceptance by the dogs and in three homothetic tablet sizes to cover a large animal weight range. Development pharmaceutics of the formulation have been explained adequately in relation to the choice of the formulation, the manufacturing process and packaging.

The selection of the excipients was based on a preliminary compatibility study performed between some common excipients used in the manufacture of tablets and the active substance, the manufacturing requirements the results obtained in a field safety study in terms of palatability and the results of a preliminary stability study. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, except for the sweetener which complies with the USP standard and the flavouring agent for which an in-house monograph is presented. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SPC.

Preliminary stability studies conducted with three laboratory scale batches at two different storage conditions (3.5 months at 25 ºC/60% RH and 6 months at 40 ºC/75% RH) showed no significant changes.

The formulation used during clinical studies is the same as that intended for marketing.

Method of manufacture

The manufacturing process is considered to be a standard manufacturing process. The manufacturing process has been clearly described and it is reproducible from batch-to-batch regardless of the manufacturing site.

The in-process controls are adequate for this type of manufacturing process and pharmaceutical form, and they are generally appropriate.

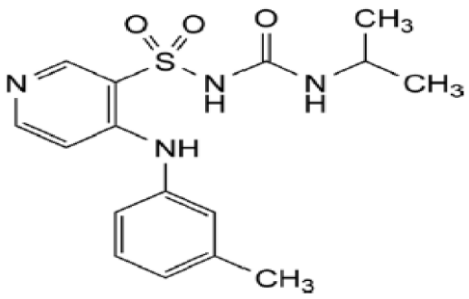
The validation of the manufacturing process has been carried out with three production bulk batches manufactured at one manufacturing site and two production bulk batches manufactured at the other manufacturing site. These batches have been manufactured with different batches of the active substance. Confirmation has been provided that a third production batch manufactured at the second site will be validated before being placed on the market.

As a whole, the validation of the manufacturing process has taken into account the critical aspects of the process and data reflect that the process is capable of producing batches of the medicinal product of consistent quality.

Control of starting materials

Active substance

The chemical name of torasemide is 1-(1-Methylethyl)-3-[[4-[(3-methylphenyl)amino]pyridin-3-yl]sulfonyl]urea and has the following structure:



The active substance is a white or almost white powder, practically insoluble in water.

Torasemide has a non-chiral molecular structure.

Polymorphism has been observed for torasemide.

There is a monograph for torasemide in the Ph. Eur., and the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for torasemide, a copy of which has been provided within the application. The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability. The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph.

Additional specifications have been set in the CEP for residual solvents. The annex includes the method used for their control.

The active substance specification includes tests for appearance, solubility, identity (IR), assay (potentiometry), impurities (HPLC), residual solvents (GC), loss on drying (Ph. Eur. 2.2.32) and sulfated ash (Ph. Eur. 2.4.14). A specific grade of torasemide in relation with its granulometry has been selected, and consequently, control of the particle-size distribution of the active substance has been added to the specification.

Batch analysis data from three batches of the active substance have been provided. The results are within the specifications and consistent from batch to batch.

There are certificates of analysis of three batches of torasemide to confirm compliance with the CEP.

Excipients

All the excipients are commonly used in the manufacturing of tablets. All of them are described in the Ph. Eur., except the sweetener, which is described in the USP and the flavouring agent, for which a monograph is presented. Representative certificates of analysis are provided to confirm compliance with the pharmacopoeia monographs. For the flavouring agent (pork liver powder flavour) the information provided is considered sufficient. It has been used in the EU in a veterinary medicinal product before, and a viral risk assessment has been provided to demonstrate that the manufacturing process is capable of keeping the risk of viral contamination under control.

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

A valid TSE declaration from the manufacturer of the finished product has been provided.

Pork liver powder flavour and lactose monohydrate are from animal origin.

Pork liver powder is obtained from pigs which are not considered a TSE-relevant species in the context of the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products.

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Control tests on the finished product

The finished product specification includes relevant quality attributes for this kind of dosage form and comprises: appearance, dimensions of the tablets, average mass, identification of torasemide, uniformity of dosage units , subdivision of tablets, water content, dissolution, assay and microbial contamination

Ph. Eur. analytical methods are followed whenever there is a method described. The validation data are in accordance with the VICH GL2 on Validation of analytical procedures: Methodology. The method is suitable for the intended use and stability indicating.

No excipients need to be controlled. The microbial contamination test is appropriately validated. The results from nine tablet sub-batches (three of each strength) made from production scale bulk batches confirm compliance with the proposed specifications.

A certificate of analysis of the reference material used is presented. The use of the USP standard instead of the Ph. Eur. standard utilised in its characterisation has been justified.

Stability

Stability studies are performed under VICH conditions and comprise a primary stability study, a photostability study and an in-use stability study.

Stability data are provided from three batches of tablets of each strength produced with final blend bulk production batches used in the validation of the process. They were stored under long-term conditions for 48 months at 25 ºC/60% RH and for up to 6 months under accelerated conditions at 40 ºC/75% RH according to VICH GL3. The batches analysed are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for the same parameters as those for release with the addition of a test for degradation products (HPLC). The proposed specifications during shelf-life are considered appropriate.

Analytical methods are those described in section 2E (control tests on finished product), except for the dissolution test, which is described and validated as part of the stability studies. The analytical procedures used are stability indicating.

No significant changes have been observed either at long-term or at accelerated storage conditions. The study has finished, and the proposed shelf-life period of 4 years without any special storage conditions is acceptable.

In addition, one batch of the small size tablet (103 mg tablet) was exposed to light as defined in the VICH GL5 on photostability testing of new veterinary drug substances and medicinal products. No significant change was observed. Based on the data provided it is concluded that the product is not

sensitive to light and the container is appropriate for the intended use.

An in-use stability study is performed with half tablets. The study demonstrated that here are no stability issues for tablet fractions and since the veterinary medicinal product is administered on a daily basis, no in-use shelf-life will be established. The statement "the remaining tablet portion should be given at the next administration" has been added to the SPC and labelling. This conclusion is based on the position paper CMDv/POS/004 on in-use shelf-life of tablet fractions (published on the CMDv website).

Based on the available stability data, the proposed shelf-life of 4 years without any storage conditions as stated in the SPC are acceptable.

Overall conclusions on quality

Information on the development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Based on the review of the data on quality, the manufacture and control of Isemid are considered acceptable.

Part 3 – Safety

The product includes a range of tablet sizes containing the active substance torasemide. They are for the treatment of heart failure in dogs. A full safety file in accordance with Article 12(3)(j) has been provided.

Safety documentation

Non-GLP published studies have been provided in support of the toxicity of the active substance. In addition, a battery of genotoxicity tests conducted with torasemide, and user safety studies (skin irritation, eye irritation and skin sensitisation) using the final formulation have been submitted. These were conducted in GLP facilities. The user risk assessment (URA) and environmental risk assessment (ERA) have been conducted in accordance with appropriate guidelines.

Pharmacodynamics

See part 4.

Pharmacokinetics

See part 4.

Toxicological studies

Many of the studies provided in this section were originally conducted in Japan, and so the original reports are in Japanese. The assessment has been conducted based on translations of the originals that were published in the Journal 'Japanese Pharmacology & Therapeutics, Volume 22'. These studies were not conducted according to GLP.

Single dose toxicity

Acute toxicity studies of torasemide were carried out in male and female CD rats by single oral and intravenous dosage. This study is compliant with the rescinded OECD guideline 401 for acute toxicity. The doses were calculated based on the body weight of each rat and the product was administered in fasted rats as follows: 800 mg/kg bw orally, 2000 mg/kg bw orally, 5000 mg/kg bw orally, 80 mg/kg bw intravenously (IV), 200 mg/kg bw IV and 500 mg/kg bw IV.

After oral and intravenous exposure in rats, no mortality was observed in either dosed groups and the LD50 value was set to not less than 5000 mg/kg and 500 mg/kg body weight, respectively, in animals of both sexes.

After oral administration in rats, body weight decrease and polyuria was noted in all animals of both sexes from each torasemide-dosed group from day 0 of administration until day 7 after administration. There were no histopathological findings relevant to torasemide dosing.

After intravenous administration in rats, body weight decrease in groups dosed with 200 and 500 mg/kg bw torasemide was noted. Polyuria was noted in all treated groups from 2 hours to day 6 after administration, as well as reduced locomotor activity and respiratory depression at the highest dose (500 mg/kg bw). There were no significant histopathological changes.

Acute toxicity studies of torasemide were carried out in male Beagle dogs exposed to 1000 or 2000 mg/kg bw by single oral dosage. This study does not comply with OECD guidelines for acute toxicity, nevertheless it can be considered acceptable and would comply with the current criteria. After oral exposures in dogs, no mortality was observed in either dosed groups and the LD50 value was set to not less than 2000 mg/kg bw in animals of both sexes. In both doses and all treated groups, clinical signs included polyuria (from 10 to 30 minutes), reduced motor activity and recumbency (from 6 to 8 hours), and reduced electrolytes, as well as a decrease in bodyweight and food consumption. In regards to pathology, in the 2000 mg/kg bw torasemide group, cellular infiltration and basophilic tubules were observed in the kidneys, but consisted of localised and minor changes.

Repeat dose toxicity

Torasemide was orally administered to male and female rats once daily for 12 months at dose levels of 0.2, 1, 5 and 25 mg/kg bw/day. The study was carried out according to OECD guideline 452.

Although five animals died during the administration period, the deaths cannot be attributed to a toxic effect derived from torasemide in the absence of any dose-dependent treatment-related changes. At the highest dose (25 mg/kg bw/day), both male and female rats increased their food consumption, however male subjects significantly decreased their body weight, while female rats showed this same decrease at doses of 5 mg/kg bw/day and above. In the highest dosed group, high values for white blood cell count were recorded in animals of both sexes, and the blood chemistry analysis showed low K+ values.

At doses of 5 mg/kg bw/day and above, urinalysis showed increased osmotic pressure and creatinine in animals of both sexes, blood chemistry reported low values for total proteins and Cl-, and high values for blood urea nitrogen. Necropsy showed fine granular surface patterns in kidneys in both sexes and increased adrenal weight and kidney weight. Histopathological findings included basophilic change of urinary tubular epithelium, dilatation of urinary tubules, cellular infiltration and fibrosis.

At 1 mg/kg bw, high water intakes were observed in animals of both sexes.

In conclusion, a NOEL of 1 mg/kg bw per day of torasemide was determined.

Torasemide was orally administered once daily for 13-, 26- and 52-weeks in male and female Beagle dogs.

In the 13-week study torasemide was administered at dose levels of 0.8, 2.5 and 8.0 mg/kg bw/day. The study was carried out according to OECD guideline 409. Some of the animals of the group being given 8.0 mg/kg bw/day were subjected to a recovery period for five weeks. Although some clinical signs were observed during the treatment period, there was no noticeable change after the recovery period. Necropsy showed that in all treated groups, fine granular surface patterns in kidneys were found in animals of both sexes. Similar changes were still seen in animals of the 8.0 mg/kg bw/day group at the end of the recovery period. An increase in adrenal weights was detected in males from all treated groups, and increased kidney weights in males from the 0.8 and 2.5 mg/kg bw/day groups. Fairly high kidney weights were still found in animals in the 8.0 mg/kg bw/day group at the end of the recovery period. The histopathological study showed tissue changes in kidneys in all treated groups. These changes were also found in animals of the 8.0 mg/kg bw torasemide treated group at the end of the recovery period. Based on these findings, a NOEL of 0.8 mg/kg bw/day of torasemide was determined in dogs.

In the 52-week study, torasemide was administered at dose levels of 0.01, 0.08 and 0.4 mg/kg bw/day. The study was carried out according to OECD guideline 452. At the highest dose, significantly high volumes of urine in males and females were observed, the haematological examination showed lower corpuscular volume, and the blood chemical analysis revealed high urea nitrogen and creatinine values. Necropsy showed fine granular surface patterns in kidneys in the 0.4 mg/kg bw/day group. Histopathological analysis showed that kidneys exhibited degeneration/dilatation of urinary tubules, cellular infiltration, calcium deposition, fibrosis and thickening of the basement membrane in Bowman's capsule. A NOEL for torasemide was established at 0.01 mg/kg bw/day.

Tolerance in the target species of animal

See part 4.

Reproductive toxicity

Study of the effect on reproduction

The teratogenic potential of torasemide was evaluated in the pregnant rat after the daily oral administration of 1.2, 6 and 30 mg/kg bw/day from day 7 to day 17 of gestation, and for two generations. In the 30 mg/kg bw/day group, the maternal effects included a decrease in body weight or suppression of body weight gain, an increase in adrenal gland weight, and two animals presented changes in their general condition. At the dose level of 6 mg/kg bw/day the animals decreased their level of food consumption. No effects were detected in foetuses (F1) and offspring (F2). Consequently, the NOEL for torasemide was evaluated to be 1.2 mg/kg bw for general toxicity of dams and the first generation, and 30 mg/kg bw/day for reproductive performance of dams and the second generation.

The teratogenic potential of torasemide was evaluated in the rabbit after the daily oral administration of 0.04, 0.2 and 1 mg/kg bw/day from day 6 to day 18 of gestation. At 1 mg/kg bw/day maternal effects were observed including, a decrease in body weight and food consumption, a decrease in water consumption, a reduced spontaneous mobility, a decrease in epidermal temperature, a slowing of breathing and prone position beyond day 12 of gestation; however, torasemide administration showed no

effects on the number of corpora lutea, number of implantations, rate of implantation, or uterus weight at necropsy. In foetuses exposed to 1 mg/kg bw/day, there was a high rate of death or resorption (foetuses and embryos), suggestive of a lethal action. No effects attributable to the administration of torasemide were seen either for the number of live foetuses, sex ratio, placental weight, foetal body weight, or as regards the incidence of external abnormalities, ossification abnormalities or variations, visceral abnormalities and degree of ossification. Consequently, the NOEL of torasemide was evaluated to be 0.2 mg/kg bw/day for reproductive performance in dams, and for foetal development.

The safety of the product has not been studied in the target species during pregnancy and lactation or in breeding animals and based on the above-mentioned results in rabbits, the following wording has been included in the relevant sections of the product information (4.7 of the SPC and 12 of the package leaflet):

"Laboratory studies in rats and rabbits have shown foetotoxicity at maternotoxic doses. As the safety of the product has not been established in the target species, the use of the product is not recommended during pregnancy, lactation and breeding animals".

Genotoxicity

The genotoxic potential of torasemide was evaluated in a standard test battery in accordance with VICH GL23.

The mutagenic potential of torasemide was tested on Salmonella typhimurium (strains TA1535, TA 1537, TA 98, TA 100, TA 102), with and without metabolic activation (rat S9 liver fraction (S9 mix)), and with positive and negative controls. The bacterial strains were initially exposed during 48 or 72 hours to 312.5, 625, 1250, 2500 and 5000 µg/plate with and without S9 mix. A separate experiment was also performed with the TA 102 strain using the same dose levels with S9 mix. No increase was observed in the number of revertant colonies in the five strains with or without S9 mix, however a moderate toxicity was noted at 5000 µg/plate in the TA 102 strain with S9 mix.

In a mouse lymphoma assay, L5178Y TK+/- cells at the tk locus were exposed to different concentrations of torasemide with and without metabolic activation). In the 3-hour treatment the highest dose-level selected was 300 µg/ml, while for the 24-hour treatment the highest dose-level selected was 500 µg/ml. There was no increase in mutation frequency in either treatment.

An in vivo micronucleus test was performed in male and female rats exposed to 2 administrations of 500, 1000 and 2000 mg/kg bw/day torasemide with a 24-hour interval. Bone marrow was sampled from femurs and prepared for microscopic analysis. No induction of micronuclei in bone marrow erythrocytes in the high dose of torasemide (2000 mg/kg bw/day) was shown, compared to the vehicle control data.

Based on the above studies, it is concluded that torasemide was devoid of mutagenic activity in the three tests performed.

In addition to these studies, Brambilla et al. (2006) reports that the following tests were found negative for torasemide:

- Reverse mutation test in Escherichia coli (strain WP2 uvrA).
- Unscheduled DNA synthesis (UDS) test in mouse primary hepatocytes.
- UDS test in rat primary hepatocytes.
- In vitro sister chromatid exchanges in human lymphocytes.
- In vitro chromosomal aberration in human lymphocytes.

- In vivo chromosomal aberration in mouse bone marrow.
- In vivo chromosomal aberration test in hamster bone marrow.

Carcinogenicity

No data were provided as torasemide fulfils the following criteria:

- No structure-activity relationship indicating a close chemical analogy with known carcinogens.
- No pre-neoplastic lesions have been identified in toxicity studies.
- No mutagenic potential was detected in the standard battery of tests.

Additionally, these results are in accordance with the data published by Brambilla et al. (2006) where the following tests were found negative for torasemide: Long term carcinogenicity in mice, and long term carcinogenicity in male rats. In a separate, non-standard carcinogenicity study in female rats weakly positive findings were reported (renal adenomas and carcinomas). However, no further information relating to the findings is available.

Based on the totality of available data (no structural alerts, the results from mutagenicity studies were negative and no significant neoplastic findings were reported in the repeat dose studies) torasemide is not considered to have carcinogenic potential.

Studies of other effects

Ototoxicity

Ototoxicity has been reported with loop diuretics; therefore, a review of the information from the public domain was undertaken. Literature has reported results from a study where torasemide was administered to cats by the intravenous route in order to test the ototoxic effect. The toxic dose that completely suppressed the compound action potentials (CAP) of the auditory nerve in 50% of animals (TD50) was determined. To test acute effects, single doses of 15.8, 20, 25.3 and 32 mg/kg bw torasemide were injected. To test chronic effects, a pre-dose of either 32 mg/kg bw was injected one week before starting the study or 3 single doses of 25 mg/kg bw were administered at a rate of one injection per week. Before administration, kidney vessels were ligated to avoid a drop in blood pressure due to increased diuresis by large doses of torasemide and subsequent non-specific ototoxicity. The TD50 by the IV route was determined to be 20.80 mg/kg, with a 95% confidence interval 17.84 - 24.25 mg/kg. Depending on the dose, the suppression of CAP began 1 to 15 minutes after the beginning of the injection. After 3 hours, there was a tendency to recover, except in one cat receiving the highest dose, 32 mg/kg bw, and in one cat receiving 25.3 mg/kg bw. After application of 3 separate doses of 25 mg/kg bw IV, once a week for 3 weeks, in cats with intact kidney vessels, no ototoxic effects were observed. Acute ototoxicity is observed, but complete recovery occurred within one week. It is considered that the doses required to induce ototoxicity in cats are far higher than those proposed for therapeutic doses in dogs.

In humans, where the cochlear function was monitored in a clinical trial, no hearing loss was noted in patients with advanced renal failure who received a chronic high dose (200 mg/day).

Irritation studies

The potential of torasemide to induce skin irritation was evaluated in male New Zealand white rabbits: firstly, a dose of 0.5 g of torasemide tablet ground in fine powder was applied on the skin of one rabbit for 3 minutes, 1 hour and 4 hours and cutaneous reactions were observed at 24, 48 and 72 hours after patch

removal. The study was carried out according to GLP and OECD guideline 404. Since the mean value was below 2.3 for erythema or oedema, torasemide was applied to 2 additional animals for 4 hours: animals were observed for clinical signs and cutaneous irritations were evaluated after 1 hour, 24, 48 and 72 hours, and also daily for reversibility.

No clinical signs and no mortality were observed, with no impact on the body weight of animals. After a 4-hour application, a very slight erythema was noted in one male on day 1. All the mean scores for erythema and oedema were zero, showing no inflammation. Therefore, torasemide is considered a very slightly irritant when applied topically to rabbits.

The potential of torasemide to induce ocular irritation was evaluated in male New-Zealand white rabbits. The study was carried out according to GLP and OECD guideline 405. A single dose of 0.1 g of torasemide tablet ground in fine powder was placed into the left conjunctival sac and observations were made at 24, 48 and 72 hours following the administration. Since the mean value for grading was below 2 for conjunctival oedema or for conjunctival redness and/or below 1 for iris lesion or for corneal opacity, torasemide was administered to 2 additional animals and ocular reactions were observed at 1 hour, 24, 48 and 72 hours after the administration. No clinical signs and no mortality were observed, with no impact on the body weight of animals. On day 1, a slight chemosis and moderate redness of the conjunctiva were observed in all animals. In one animal, slight conjunctiva reactions persisted up to day 2, but were reversed on day 3. A mean score of 0.3 for the redness of the conjunctiva at 24 hours was calculated, all other scores (chemosis, iris lesions, corneal opacity and redness of the conjunctiva at 48 hours and 72 hours) were zero.

Therefore, torasemide is considered as slightly irritant when applied by the ocular route to rabbits.

Sensitisation study

The potential of torasemide to induce delayed contact hypersensitivity was evaluated in female mice using the local lymph node assay. The study was carried out according to GLP and OECD guideline 429. Five treated groups of 4 animals received the test item at the concentration of 2.5, 5, 10, 25 and 50 %, dissolved in dimethylformamide; one negative control group of 4 animals received the vehicle (dimethylformamide); and one positive control group of 4 animals received α-hexylcinnamaldehyde, a moderate sensitiser, at the concentration of 25% in a mixture acetone/olive oil.

During the induction phase, the test item, vehicle or reference item was applied over the ears (25 µl per ear) for 3 consecutive days (days 1, 2 and 3) and the thickness of left ear, local reactions and clinical signs, if any, were recorded. On day 6, the proliferation of lymphocytes in the lymph node draining the application site was measured by incorporation of tritiated methyl thymidine. The obtained values were used to calculate stimulation indices. During the study, no mortality, no systemic toxicity or no local irritation were observed. Erythema of ear skin was observed in 25% of animals receiving 50% of torasemide on day 6. Dryness of ear skin was noted on day 6 in 50% of animals given the test item at 25% on day 3 and in 75% animals receiving torasemide at 50% on days 2 and 3. No notable lymphoproliferation was noted with torasemide at any test concentrations.

Therefore, the formulation containing torasemide did not induce delayed contact hypersensitivity in the murine local lymph node assay (LLNA).

Excipients

The safety of the excipients included in the product has been previously assessed and they are not considered to represent a concern.

User safety

The user risk assessment was presented in accordance with the CVMP Guideline on User safety for pharmaceutical veterinary products (EMA/CVMP/543/03-Rev.1), identifying dermal and accidental oral ingestion as the main routes of exposure. Dermal exposure to the final formulation is likely to be brief, however slight irritation was seen in the rat/rabbit study, therefore the provision to wash hands after use has been proposed which is acceptable. Subsequent hand-to-mouth oral exposure is likely to be negligible and can be mitigated with the recommended personal hygiene measures.

Exposure of a child to more than one tablet could occur with the proposed dosing regimen while the quantitative risk assessment was not based on this scenario. However, it is agreed that the aluminium blister and pork flavouring will be deterrents; therefore the applicant's calculations based on one tablet can be accepted. A MOE below 100 has been calculated, indicating a risk to a child from accidental ingestion. Given that the expected side effects would be mild and transient, the risk is acceptable with the advice to seek medical attention. The phrases mentioned below have been included in the SPC to indicate the concerned risk should this unlikely event occur. These detail the likely side effects and the provision to ensure that tablets are not left unattended during the preparation for dosing. Appropriate storage of part tablets are addressed in sections 4.5 and 6.4 of the SPC, as a part tablet of the smallest size would also give a low MOE, indicating a risk for children.

The applicant has also not considered the risk to pregnant women, although this is acceptable given that no teratogenic signs were seen at maternotoxic doses in reproductive toxicity tests.

The final formulation was not classified as a skin sensitiser in the LLNA; however the possibility of a reaction in sensitised individuals cannot be excluded and has been documented in human adverse reactions and the SPC of the human product. Therefore the proposed hypersensitivity warning is acceptable.

Based on the above risk assessment the product does not pose an unacceptable safety risk to the user when used in accordance with the SPC.

The following warnings for the SPC and package leaflet have been added:

"This veterinary medicinal product may cause increased urination, thirst and/or gastrointestinal disturbances and/or hypotension and/or dehydration if ingested. Any part-used tablets should be returned to the blister pack and then to the original carton to help prevent access by children. In case of accidental ingestion, particularly by a child, seek medical advice immediately and show the package leaflet or the label to the physician.

This veterinary medicinal product may cause hypersensitivity (allergic) reactions in persons that are sensitised to torasemide. People with known hypersensitivity to torasemide, to sulfonamides or to any of the excipients should avoid contact with the veterinary medicinal product. If symptoms of allergy occur, seek medical advice and show the product packaging to the physician."

Environmental risk assessment

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guideline 6.

The environmental risk assessment can stop in Phase I, and no Phase II assessment is required because the veterinary medicinal product will only be used in non-food animals.

Overall conclusions on the safety documentation

In acute toxicity studies, the oral limit dose for lethality is greater than 5000 mg/kg bw and the intravenous limit dose is greater than 500 mg/kg bw in rats.

In a 12-month repeat dose toxicity study, the NOEL was 1 mg/kg bw/day by oral dosage in rats. Increase of osmotic pressure and creatinine, low blood values for total proteins and chloride and high values for blood urea nitrogen were observed at higher dose levels. These effects are linked to the pharmacological activity of torasemide. Necropsy showed fine granular surface patterns in kidneys and increase in adrenals weight and kidney weight.

In repeat dose oral toxicity studies, the NOAEL in a dog 90-day study was 0.8 mg/kg bw/day and in a 12-month dog study was 0.01 mg/kg bw/day.

The main target organ in the repeat dose toxicity studies was the kidney. Effects on the kidney were observed at 8 mg/kg bw/day.

Torasemide has no potential for embryo/foetotoxicity or teratogenicity.

Reproduction toxicity was only studied in laboratory animals and not in the target species. Data in rats and rabbits indicate that torasemide is not a developmental or reproductive toxicant.

Carcinogenicity studies have not been performed and are not required.

The product was shown to be slightly irritant to skin, slightly irritant to eyes and a non-sensitiser of skin.

In summary, the data presented are considered adequate to characterise the toxicity profile of the active substance.

Results of pivotal toxicity studies			
Study type	**Tested species/test system**	**Result**	**Comments**
Single toxicity	Rats (401 OECD) Dogs	LD50>5000 mg/kg bw LD50>2000 mg/kg bw	
Repeat dose toxicity	Rats (452 OECD) Dogs (409 OECD) Dogs (452 OECD)	NOEL 1 mg/kg bw/day NOEL 0.8 mg/kg bw/day NOEL 0.01 mg/kg bw/day	12 months 90 days 12 months
Reproduction toxicity	No data		
Developmental toxicity	Rat (414 OECD) Rabbit (414 OECD)	NOEL 1.2 mg/kg bw/day NOEL 0.2 mg/kg bw/day	
Genotoxicity	VICH guideline GL23	Torasemide was devoid of mutagenic activity in the three tests performed	
Carcinogenicity	No data		

Results of pivotal toxicity studies			
Other effects	Cats ototoxicity Rabbit (404 OECD) Rabbit (405 OECD) Mice (442a OECD)	ED_{50} 20.8 mg/kg bw/day Formulation is very slightly irritant. Formulation is very slightly irritant. Formulation does not induce delayed contact hypersensitivity in the murine Local Lymph Node Assay.	

A user risk assessment was provided, highlighting the probable routes of exposure. A risk resulting from accidental ingestion by children was identified; however this is acceptable as appropriate risk mitigation measures are proposed.

An appropriate environmental risk assessment was provided. The product is not expected to pose a risk for the environment when used according to the SPC.

Part 4 – Efficacy

Pharmacodynamics

Torasemide is a loop diuretic that belongs to the pyridine-3-sulfonylurea class, also called high-ceiling diuretics with a potent diuretic activity in dogs. The applicant has provided a number of literature references to characterise the mechanism of action and pharmacological effects of the active substance as well as different pharmacokinetic-pharmacodynamic studies (see below) with the aim of dose determination/confirmation. The literature references consist of articles published in scientific peer-reviewed journals and selected chapters from scientific books, and are considered reliable.

Torasemide acts in the thick ascending limb of the loop of Henle, where it binds to the Na+-K+-2Cl- cotransporter and inhibits the active reabsorption of sodium and chloride, increasing the excretion of these ions and thus increasing the volume of water excreted with urine. The resulting main pharmacodynamic effect is diuresis and this has been demonstrated in the target species in several laboratory studies. In addition, according to the provided literature, torasemide induces a similar diuretic effect as furosemide, with doses 10-20 times lower.

Secondary pharmacological effects of torasemide include an anti-aldosterone effect as well as anti-hypertensive and anti-fibrotic effects. These effects may also be beneficial in dogs with Congestive Heart Failure (CHF) together with the main therapeutic action of the drug (diuresis).

Information on the main pharmacodynamic drug interactions for torasemide is based on references from human medicines. Although no specific data are available for the target species, interactions may occur with other loop diuretics, ACE-inhibitors (and other vasodilators), NSAIDs, antibiotics (e.g. aminoglycosides, cephalosporins), oral hypoglycaemic agents and medicinal products affecting electrolyte balance. These interactions have been addressed in the product information.

Pharmacokinetics

The pharmacokinetics (PK) of torasemide was supported by different pharmacokinetic-pharmacodynamic studies conducted by the applicant and several literature

references. There were two main studies, one aimed to determine bioavailability and food effect, and another one assessing dose linearity and accumulation (both were GLP-compliant).

In the bioavailability study, 12 dogs were included in a cross-over design. The most relevant PK parameters after intravenous and oral administration (single dose of 0.2 mg/kg bw) were determined and absolute bioavailability was calculated based both on plasma and urine data. In addition, AUC0-∞ and Cmax were compared between fasted and fed animals.

In the second study, 12 dogs were included in a cross-over design comparing different oral doses of torasemide (dose range of 0.1-0.4 mg/kg bw/day) with furosemide (dose range of 1-8 mg/kg bw/day). Both, single dose and repeated daily administration for 10 days were evaluated and PK parameters were calculated. Dose linearity and accumulation were assessed.

Based on these studies, torasemide is highly and readily absorbed, with an absolute bioavailabilty of more than 98%. The Tmax is less than 1h. The Cmax is approximately the same in fasted or fed conditions (2015 vs 2221 µg/L). However, the AUC is significantly greater (+37%) in fed animals compared to fasted dogs. Nevertheless, despite the increased AUC in fed animals (Cmax was comparable between fed and fasted dogs), food administration is not expected to impact on the efficacy and safety of torasemide after oral administration.

With increasing doses (0.1-0.4 mg/kg bw/day), it appeared that the rate and extent of absorption of torasemide increased more than dose proportionally. No accumulation of torasemide in plasma was observed after 10 days administration whatever the dose administered. Total body clearance was low (22.1 mL/kg/h). The volume of distribution was small (0.166 L/kg), which is likely to correspond to that for plasma proteins given the high plasma protein binding (98-99%). The plasma elimination half-life was approximately 6h after oral or IV administration of 0.2 mg/kg.

The highest concentrations were found in the liver, gastrointestinal tract and kidney (data from rats). Torasemide is metabolised by the hepatic cytochrome P450 system although up to 66% of an intravenous dose appeared in the urine as unchanged drug by 72 h post- administration. The apparent clearance after oral administration was between 15 and 23 ml/h/kg. The renal clearance corresponded to approximately 62% of the total clearance.

In general, the conclusions drawn from the provided data are appropriately addressed in the pharmacokinetic section of the SPC. Information on the elimination half-life, clearance and volume of distribution values, as well as the significantly greater AUC in fed animals (+37%) compared to that in fasted animals, is included in section 5.2 of the SPC. Also, warnings regarding potential interactions of torasemide with substances metabolised by the cytochrome P450 system and with other drugs that are highly plasma protein bound have been included.

Dose justification

The proposed dose of the product is 0.13-0.25 mg/kg bw/day. This dose can be increased, if necessary, for a maximum of 5 days without exceeding a maximum dose of 0.4 mg/kg bw/day.

The proposed dose was established based on two dose-determination studies (one using furosemide and another one using torasemide, see below) conducted after performing a bibliographical review comparing the PD effects of torasemide and furosemide at different doses of both substances.

Scientific advice was given concerning dose justification and this advice was followed.

Dose determination / finding studies

Two non-GLP-compliant PK/PD studies were performed by the applicant in healthy male dogs for dose determination:

One study consisted of a cross-over designed study administering furosemide to 5 dogs at total doses of 2 and 8 mg/kg bw/day (that is, 1 and 4 mg/kg bw/12 h) for 14 days. The purpose of this study was to obtain PK and PD data of furosemide in order to compare them to those obtained from torasemide, and to establish a relationship between doses and effect of both substances. This first step of the dose-finding approach was accepted by the CVMP in the scientific advice provided. The doses were justified based on the scientific literature and furosemide products authorised in different countries. Blood and urine samples were taken at several time points. The main PD effect assessed was diuresis. The diuretic effect was confirmed, being higher after the 14-day treatment period than after one day. Urinary volume increased 2 to 4 times depending on the dose administered. The dose-effect relationship was calculated based on diuretic effect on day 14.

The second study was also a cross-over designed trial and included the same animals used in the previous study. Torasemide was administered at a dose range of 0-0.8 mg/kg bw once a day. The doses were justified based on the scientific literature. Plasma and urine samples were collected. Diuresis was measured as cumulative 24-h urinary production on day 1 and day 14. The diuretic effect of torasemide was clearly observed, being higher after 14 days of treatment than after one day (at doses 0.4 and 0.8 mg/kg bw).

The maximal effect occurred at one hour after the administration and persisted for approximately 12 h. Within the dose range studied, the urinary volume increased 1.4 to 4 times after single administration and 1.5 to 6 times after repeated doses. The dose-effect relationship was calculated based on the diuretic effect on day 14. This study was not conducted with the final formulation of the proposed product. However, the applicant provided the detailed composition of both products. Although the formulations are not identical, they are qualitatively and quantitatively very similar, and the differences between them are not expected to affect the study results.

The applicant established a relationship between doses of furosemide and torasemide and the diuretic effect obtained after 14 days. Similar diuresis was obtained by both substances with doses of 0 - 0.5 mg/kg bw torasemide and 0 – 10 mg/kg bw furosemide.

Concerning justification for the dose interval (24 hours), although the applicant did not provide a study investigating different frequencies of dosing scientific references were provided showing that the diuretic effect of torasemide has a longer duration than that of furosemide, which is administered twice daily. Also, the applicant has adequately justified the efficacy of the proposed posology (24-hour dose interval) through a clinical field trial in which non-inferiority with furosemide administered every 12 h was demonstrated.

Dose confirmation studies

A dose-confirmation study was conducted by the applicant.

This was a GLP-compliant PK/PD study involving 12 healthy dogs in a cross-over design. Dogs were administered torasemide over a dose range of 0.1-0.4 mg/kg bw/once a day. This dose range was based on the previous studies and also used in the tolerance and efficacy studies. Furosemide was administered as a positive control over a dose range of 1-8 mg/kg bw/day given in two daily doses. Single and repeated administrations (10 days) were assessed. Blood and urine samples were collected. The PD effect (24 h

diuresis) was determined after the single and repeated doses of both substances. Evolution of diuresis during the 10-day period of treatment was also measured. The diuretic and natriuretic effects of torasemide were comparable to those of furosemide over the tested dose ranges after single and repeated administration. Renal function, as assessed by blood levels of urea and creatinine, was not modified after repeated administration of increasing doses of both drugs.

The applicant subsequently conducted a population PK/PD analysis with data obtained from the previous study and those obtained from the dose-determination study carried out with torasemide. Combining both data sets, a dose-response curve was generated. The results of the previous studies were confirmed. However, while daily diuresis remained fairly constant for doses up to 0.2 mg/kg bw over the duration of treatment (10 days), the mean diuretic response and absolute variability increased with time at higher doses. Thus, the applicant recommended limiting treatment with the higher doses to a maximum of 5 days in order to avoid any potential adverse effects, taking into account the increase in the diuretic response (and possible increase in other pharmacological effects). This posology was further justified by the results from the pivotal field study, in which no higher risk of adverse reactions was seen in those animals that received the highest dose level for 5 consecutive days (including a few animals that received this dose for 6 consecutive days).

The proposed minimal dose is 0.13 mg/kg bw/day. The applicant justified this dose based on scientific literature and PK/PD studies in which a relationship between dose-effect of torasemide and furosemide was established. A minimal dose within the range of 0.1-0.2 mg/kg bw was selected. This approach was accepted by the CVMP in the scientific advice given to the applicant. Taking into account the dog bodyweight ranges and the tablet strengths, a dose range of 0.13-0.25 mg/kg bw was selected as the maintenance dose.

Target animal tolerance

One pivotal, GLP-compliant TAS study was conducted by the applicant. Tolerance was also assessed in the dose-determination and dose-confirmation studies mentioned above, and the clinical field studies. Scientific advice was given concerning the design of the tolerance study, which was followed by the applicant.

No significant adverse effects were observed in the dose-determination and dose-confirmation studies.

The pivotal target animal tolerance study was conducted in compliance with VICH GL43 and the overall design was accepted by the CVMP in the scientific advice provided. Thirty two healthy dogs were enrolled in 4 treatment groups: 0 (no treatment), 1x (induction dose of 0.5 mg/kg bw/day for 5 days and then maintenance dose of 0.25 mg/kg bw/day up to a total 26-week period), 3x and 5x the maximal recommended therapeutic dose (RTD). The RTD is 0.13 mg/kg bw (range of 0.13-0.25 mg/kg bw) and can be doubled, if necessary (range of 0.26-0.4 mg/kg bw) for up to 5 days. The applicant performed the study considering a worst case scenario, administering the highest dose (0.5 mg/kg bw, which is slightly in excess of the highest recommended increased dose of 0.4 mg/kg)) at first (to stabilise a dog with severe clinical condition), and then administering the highest value of the lower dose range (0.25 mg/kg bw) to maintain the dog stabilized. It is acknowledged that the maximum dose stated in the SPC is 0.4 mg/kg bw, while the maximum dose administered in the 1x group in the TAS study was 0.5 mg/kg bw.

Six animals per group were euthanised and necropsied after 26 weeks, while the remaining two animals per group were observed for an additional recovery period of 28 days and then necropsied. Safety parameters included physical examination of the animals (including bodyweight), behaviour (including food and water consumption), cardiovascular examination (ECG and blood pressure), clinical pathology (haematology, blood chemistry, urinalysis) and macro/microscopic examination of the organs and

tissues.

There was no mortality during the study. The majority of effects observed were consistent with the pharmacological action of torasemide: dry mucosa of the oral cavity, signs of haemoconcentration (increased RBC, haemoglobin and haematocrit), reversible increase of plasma urea and creatinine and reversible alteration of other blood parameters (glucose, electrolytes, aldosterone), decreased urine specific gravity and increased urine pH. After the administration of up to 5x the maximal RTD (2.5 mg/kg bw for 5 days followed by 1.25 mg/kg bw for 177 days), in addition to the alterations observed in the 1x group, a decrease of appetite with associated weight loss, and ECG changes were observed and histopathological changes were noted: interstitial inflammation, dilatation of tubules and cysts in the kidneys together with a slight hypertrophy/hyperplasia in the adrenal glands. The renal lesions were still present after the 28-day recovery period, possibly due to renal haemodynamic changes subsequent to administration of torasemide. This pathology was also observed in animals in the 3x group, albeit to a lesser extent. All the findings observed in the tolerance study have been included in the SPC.

The tolerance of the product was also assessed in the clinical field studies. In the pivotal clinical study , a number of adverse events (AEs) occurred, with a significantly higher incidence in the torasemide group compared to the control (furosemide) group. Most of these AEs affected the renal and urinary system and, within this category, most of them were classified as 'renal insufficiency'. Renal insufficiency AEs occurred in 42.5% of torasemide treated dogs compared with 16.5% of furosemide treated dogs. The majority of 'renal insufficiency' AEs represented the occurrence of elevations in renal parameters and generally did not require any treatment. The same trend was observed for the serious AEs (SAE), affecting a higher percentage of animals in the test group than in the control group, and leading to premature study discontinuation of 21 dogs in the torasemide group vs 12 dogs in the furosemide group. Mortality was 4.3% in the test group and 3.8% in the control group.

The different categories used to describe AEs were the ones defined by the VeDDRA dictionary. Since the different categories do not have the same clinical relevance, the renal AEs were grouped into two bigger groups: "renal failure" (presumed higher clinical relevance) and "elevated renal parameters" (presumed lower clinical relevance). After a re-analysis of the data, it can be seen that most of the renal AEs were considered as "elevated renal parameters" (86%), while 14% of them were considered as "renal failure". These proportions are similar to those observed in the control group, although the absolute numbers of events was significantly lower in the control group. Overall, the majority of the "elevated renal parameters" AEs in the torasemide group were considered as non-serious events, asymptomatic, and not requiring treatment. On the other hand, the majority of "renal failure" AEs were classed as serious and were symptomatic.

A second clinical field study was conducted in order to follow up selected cases from the pivotal field study. The aim was to evaluate the long-term safety of the product for an additional period of 6 months after the 3-month period of the previous study. Although the study conclusions are limited by its small sample size and the eligibility criteria, the results were in line with those obtained in the pivotal field study: the incidence of AEs was higher in the test group compared to the control one. Again, the most frequent kind of AE was renal and urinary disorders. In both groups, all the AEs within this category were classified as renal insufficiency and treatment-related, but none of them were considered as SAE (mostly increased BUN and/or creatinine).

In conclusion, based on the incidence of treatment-related adverse events in the studies, it was considered that renal insufficiency (14 %) and increases in renal blood parameters (86%) were observed very commonly (more than 1 in 10 animals treated). Haemoconcentration and alterations in electrolyte levels were also observed very commonly, while gastrointestinal signs (vomiting, diarrhoea), dehydration, polyuria, polydipsia, urinary incontinence, anorexia, weight loss and lethargy were

reported commonly (more than 1 but less than 10 animals in 100 animals treated). These data have been reflected in section 4.6 of the SPC.

Clinical field trials

Three clinical field studies were conducted by the applicant to address the efficacy and safety of the product in dogs with clinical signs of CHF.

An uncontrolled pilot field study was carried out over two months with a small number (n=26) of animals diagnosed with CHF and with moderate to severe pulmonary oedema. Animals were divided into two categories, one involving dogs naïve to diuretic treatment (n=12) and another one involving dogs that had been treated with furosemide and considered as clinically stabilised (n=14). The recommended dose for administration on day 0 was a target dose of 0.20 mg/kg bw/day (theoretical range from 0.17 - 0.32 mg/kg bw/day determined based on bodyweight using a dosing chart). The actual initial doses administered were in the range 0.18 - 0.29 mg/kg bw/day. This dose could be doubled, depending on the clinical response, to a target dose of 0.4 mg/kg bw/day (theoretical range 0.33 - 0.65 mg/kg bw/day). The increased doses (level 2) actually administered were in the range 0.42 - 0.51 mg/kg bw/day. The animals treated with double dose were re-evaluated 3 days (+/- 1 day) after the dose change based on the clinical response. The criterion defined for treatment success was considered adequate.

Good efficacy was obtained in terms of treatment success (67%) and improvement of oedema during the study. Renal adverse events (increased blood renal parameters) were observed in several dogs, considered as slight to moderate.

The pivotal clinical field study was conducted with the objective of evaluating the clinical effectiveness and safety of torasemide under field conditions as a first time treatment of pulmonary oedema in dogs with CHF due to degenerative mitral valve disease. Torasemide was compared with a positive control (furosemide) and non-inferiority with the control product was tested, using a non-inferiority margin of 15%. This study design was in line with scientific advice provided by the CVMP. The field trial was a multicentric, randomized, double blinded, positive controlled, parallel-design, GCP-compliant study. The animals enrolled in the trial (n=321) presented clinical signs due to a diagnosed CHF, including pulmonary oedema confirmed radiographically. According to the modified ACVIM Consensus Classification System for Canine Chronic Valvular Heart Disease (ISACHC classification, staging classes of I – III), these dogs belonged to class II and class IIIA of CHF. All dogs were all naive to diuretics; some dogs were naïve to other cardiac treatments while others were on treatments already but at a stable dose for several weeks. The dogs were randomly allocated into the two treatment groups (torasemide or furosemide). Within each group, two dose levels were established: a low dose (level 1, dogs with interstitial pulmonary oedema and class II CHF): torasemide at 0.13-0.25 mg/kg bw/day or furosemide at 1.3-2.5 mg/kg bw/day; and an increased dose (level 2, dogs with alveolar pulmonary oedema and class IIIA CHF): torasemide at 0.26-0.5 mg/kg bw/day for 4 days (+/- 1 day) and then level 1, or furosemide at 3.5-7.5 mg/kg bw/day for 4 days (+/- 1 day) and then level 1.

The inflexible dosing regimen is not in line with the ACVIM consensus statement recommendation to titrate the diuretic dose to effect across a much wider dose range; but the applicant justified this as it was in line with the dosing regimen of the positive control (furosemide) as authorised in Germany and France (an initial dose with the possibility of doubling this dose in severe cases). However, the applicant revised the dosing regimen proposed in the SPC taking into account the ACVIM consensus statement recommendation and the study results, in order to allow a more flexible titration of the dose to effect. An initial maintenance dose range is therefore proposed, which can be stepwise increased, if necessary, up to double the initial dose but not exceeding a dose of 0.4 mg/kg bw (resulting in an overall dose range of

0.13-0.4 mg/kg bw). In line with the study conditions, the increased doses from 0.26 mg/kg bw should only be administered for a maximum period of 5 days. The increased dose level 2 was administered at a maximum of two occasions.

A schedule of visits was established in which the following parameters were assessed: clinical examination, thoracic radiographies, echocardiography, ECG, haematology and blood chemistry, cardiac biomarker and urinalysis. Adverse events (AEs) were registered throughout the 84 day study period.

The primary efficacy criterion was treatment success at day 14 visit (V14), defined as oedema score reduction + cough score reduction + no worsening of both dyspnoea and exercise intolerance scores in comparison with day 0. A number of secondary efficacy criteria were also considered, including 'treatment response at day 14' and 'at day 84' based on revised success criteria (oedema score reduction OR oedema score maintenance to 1 + cough score reduction + no worsening of both dyspnoea and exercise intolerance scores in comparison with day 0). The safety evaluation was based on the incidence of AEs, serious AEs and evolution of blood parameters throughout the 84 day study.

The efficacy achieved in both study groups was similar (74.4% in the test group vs 73.5% in the control group for the intention to treat population), as could be expected based on preclinical data. Thus, the dosing rate/regimens used during this study for the test and control products were considered satisfactory. The applicant followed the statistical guideline EMA/CVMP/EWP/81976/2010 for the demonstration of non-inferiority. A non-inferiority margin of -15%, as defined by the applicant for this trial, was based on an expected efficacy of about 65% for both the reference and the test products (value derived from the pilot study), translating to a risk ratio of 0.77. A margin of 15% is commonly acceptable for this kind of study, as stated in the scientific advice given to the applicant. The risk ratio for success at day 14 for the test compared with the control treatments was 1.04 for the per-protocol (PP) population (95% CI: 0.92 - 1.19) and 1.01 for the intention-to-treat (ITT) population (95% CI: 0.89 - 1.15). Thus, non-inferiority of the test product compared with the positive control regarding the primary efficacy endpoint is considered to be demonstrated. No statistically significant differences were observed between the study groups regarding the secondary efficacy endpoints.

A high number of AEs were recorded during the study (447 affecting up to 60.5% of the dogs, meaning a very common incidence of AEs). These AEs were more frequent in the test group compared to the control group regardless the kind of AE considered. The most frequent AEs were renal and urinary disorders, followed by systemic and digestive disorders (anorexia, appetite disorders, deaths, dehydration, hyperthermia, lethargy, polydipsia, suspected infectious agent transmission and weight loss). (See above in the tolerance section).

A supportive GCP-compliant, double blinded, positive-controlled, multicentre field study was conducted to assess the safety of the test product for a period of 6 months additionally to the 3 months assessed in the previous study. The animals used in this trial were selected from the population included in the efficacy and safety study with the same treatment groups (torasemide or furosemide). These dogs had to present a stable clinical (including renal and cardiac) condition. The same products (test and positive control, furosemide) were administered in this trial. The dose administered corresponded to the (lower) maintenance dose (level 1). The follow-up parameters measured were also the same as those considered in the previous study. Assessment of the test treatment safety was mainly based on the incidence of adverse events (AEs) and serious AEs (SAEs). Some additional (efficacy and palatability) criteria were also established.

The results of this trial were in line with those obtained in the previous study. The incidence of AEs was higher in the test group compared to the control one. Again, the most frequent kind of AE was renal and urinary disorders (see above in the tolerance section).

Overall conclusion on efficacy

Pharmacodynamics:

The mechanism of action and pharmacological effects of torasemide have been adequately documented. Torasemide is a loop diuretic and it acts in the thick ascending limb of the loop of Henle, where it binds to the Na+-K+-2Cl- cotransporter and inhibits the active reabsorption of sodium and chloride, increasing the excretion of these ions and thus increasing the volume of water excreted with urine. The resulting main PD effect is diuresis and it has been proven in the target species in several laboratory studies. In addition, according to the provided literature, including new PK/PD studies provided by the applicant, torasemide induces similar diuretic effect as furosemide with doses 10 to 20 times lower. Secondary pharmacological effects of torasemide include an anti-aldosterone effect as well as anti-hypertensive and anti-fibrotic effect. These effects are also beneficial in dogs with CHF together with the main therapeutic action of the drug (diuresis). The main pharmacodynamic interactions of torasemide were stated based on a reference from human medicine.

Pharmacokinetics:

The pharmacokinetic characteristics of torasemide are generally well documented and have been satisfactorily evaluated in dogs based on scientific literature and on different studies conducted by the applicant. Absolute oral bioavailability was approximately 98% with a mean Tmax of less than 1 h. Systemic clearance was between 15 and 23 ml/h/kg and volume of distribution is small, with an elimination half-life of about 6 h. The primary elimination route is urine. Food administration is not expected to impact on the efficacy and safety of torasemide after oral administration.

Dose determination:

The proposed dose of the product is 0.13-0.25 mg/kg bw/day. This dose can be increased, if necessary, for a maximum of 5 days without exceeding a 0.4 mg/kg bw/day. The proposed dose was established based on two dose-determination studies and one dose-confirmation study (with subsequent PK-PD analysis) comparing the PD effects of torasemide and furosemide at different doses of both substances.

Tolerance:

A high incidence of adverse effects was observed in the field study, mainly renal and urinary alterations. The applicant provided detailed information regarding adverse events within the renal category to fully characterise the tolerance of the product. The relevant information has been included in the SPC.

In the TAS study, torasemide was relatively well tolerated in doses up to 5x the recommended dose. At the maximum recommended treatment dose (1xRTD), signs of haemoconcentration and reversible alterations of blood parameters (mainly renal enzymes) were observed. With the higher dose (5xRTD), a decrease of appetite was also observed and histopathological changes were noted in kidneys and adrenal glands. These renal lesions were still present after the 28-day recovery period.

Efficacy:

Three clinical field trials were conducted: an uncontrolled pilot study, a pivotal field study, and an extension of the pivotal field study to allow long term follow-up.

Based on the results of the pivotal field study (treatment success defined as oedema score reduction + cough score reduction + no worsening of both dyspnoea and exercise intolerance scores in comparison with day 0), it is concluded that the product is effective (non-inferior to furosemide) for the treatment of clinical signs related to congestive heart failure in dogs, including pulmonary oedema,. Two different dose levels were administered depending on the initial clinical condition of the animals, and the clinical

response to the treatment. The efficacy of the product at the proposed dose regimen is considered adequately demonstrated.

Part 5 – Benefit-risk assessment

Introduction

Isemid is presented as chewable tablets for dogs containing torasemide as active substance and are available in 3 different strengths (1 mg, 2 mg and 4 mg) to allow the treatment of dogs of different sizes.

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 natriuresis.

The product is intended for use in treatment of clinical signs related to congestive heart failure in dogs, including pulmonary oedema. The proposed dose is 0.13-0.25 mg per kg bodyweight per day. This dose can be increased, if necessary, for a period of up to 5 days without exceeding a maximum dose of 0.4 mg/kg bw/day.

The dossier has been submitted in line with the requirements for submissions under Article 31 of Regulation (EC) No 726/2004 of 31 March 2004.

The application has been submitted in accordance with Article 12(3) of Directive 2001/82/EC (full application).

Benefit assessment

Direct therapeutic benefit

The proposed benefit of Isemid is its efficacy in the treatment of clinical signs, including pulmonary oedema, due to CHF in dogs. This benefit has been indirectly shown in different laboratory studies, which confirmed the diuretic action of torasemide in healthy dogs. Direct demonstration of the therapeutic benefit in the target population was performed in one pivotal field study with the final formulation administered in accordance with recommended dosing regimen (i.e. the dosing chart presented in the summary of product characteristics). Dogs were either dosed at a low or high dose level on day 0, dependent on the severity of their presenting signs. Non-inferiority of the test product compared to an authorised control product containing furosemide was shown for the primary endpoint 'treatment success' (composite variable including oedema + cough + dyspnoea + exercise intolerance). The efficacy of the product at the proposed dose has therefore been demonstrated for the proposed indication.

Additional benefits

Isemid increases the range of available diuretic treatment options for the treatment of clinical signs related to congestive heart failure, including pulmonary oedema, in dogs.

Isemid is intended to be administered once a day, thus increasing treatment compliance. The proposed

dose interval is considered to be justified based on data from scientific literature and clinical study data.

Risk assessment

Quality:

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Safety:

Risks for the target animal:

The main risks associated with treatment are the very common occurrence of renal effects: In the pivotal clinical field study, renal insufficiency, an increase in renal blood parameters, haemoconcentration and alterations in electrolyte levels (chloride, sodium, potassium, phosphorus, magnesium, calcium) were very commonly observed (more than 1 in 10 treated animals). The following clinical signs were observed commonly (more than 1 but less than 10 animals in 100 animals treated): episodic gastrointestinal signs such as vomiting and diarrhoea, dehydration, polyuria, polydipsia, urinary incontinence, anorexia, weight loss and lethargy.

The majority of effects observed in the target animal safety study (e.g. dry mucosa of the oral cavity, signs of haemoconcentration, reversible alterations of biochemical parameters, decreased urine specific gravity) are likely to be related to the pharmacological action of torasemide. However, in animals dosed at 3x and 5x the recommended dose level, pathology possibly due to renal haemodynamic changes was observed.

Risk for the user:

The CVMP concluded that user safety for this product is acceptable when used according to the SPC recommendations and when the tablets are stored correctly to avoid accidental ingestion by a child.

Risk for the environment:

The product is not expected to pose a risk for the environment when used according to the SPC recommendations based on use in non-food producing animals only. Standard advice on waste disposal is included in the SPC.

Risk management or mitigation measures

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

User safety:

The risk to the user is considered acceptable. Additional information is included in the SPC on correct storage of the product to avoid accidental ingestion by a child. The product is not expected to pose a risk for user safety when used in accordance with the SPC.

Environmental safety:

The product is for the individual treatment of companion animals. The product is not expected to pose a risk for the environment when used in accordance with the SPC.

Evaluation of the benefit-risk balance

Based on the data presented, the overall benefit-risk is considered positive.

The applicant applied for the following indication: "For treatment of clinical signs related to congestive heart failure in dogs, including pulmonary oedema", and the CVMP agreed with this proposed indication.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Risks for the target animal (very common renal effects) are addressed in the SPC and package leaflet. The product presents an acceptable risk for users and the environment, when used as recommended. Appropriate precautionary measures have been included in the SPC and other product information.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) considers that the application for Isemid 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.