EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Tessie (EMEA/V/C/005427/0000)

INN: tasipimidine

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

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Introduction

The applicant Orion Corporation submitted, on 27 November 2019, an application for a marketing authorisation to the European Medicines Agency (the Agency) for Tessie, 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 18 July 2019, as Tessie contains a new active substance (tasipimidine), 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.

On 17 June 2021, the CVMP adopted an opinion and CVMP assessment report.

On 16 August 2021, the European Commission adopted a Commission Decision granting the marketing authorisation for Tessie.

At the time of submission, the applicant applied for the following indication:

"Alleviation of situational anxiety and fear in dogs triggered by e.g. travel, noise, owner departure, veterinary visits".

The active substance of Tessie is tasipimidine, a selective alpha-2A adrenoceptor agonist. Alpha-2A adrenergic receptors are mainly found in the central nervous system (CNS). By binding this receptor, tasipimidine inhibits the release and, consequently, the action of noradrenaline on sympathetic neurons through a negative feedback mechanism. The reduction/block of noradrenaline-mediated neurotransmission in the CNS leads to dose-dependent sedation, analgesia and sympatholysis. However, antagonism of sympathetic signalling may, depending on the dose, also entail negative effects on the cardiovascular (e.g. bradycardia and hypertension/hypotension) and the respiratory system (e.g. hypoventilation) as well as induce other unwanted (side) effects (e.g. vomiting).

Tessie is presented as an oral solution containing 0.3 mg/ml tasipimidine. The product is presented in a pack containing 1 glass bottle.

The rapporteur appointed is Kim Boerkamp and the co-rapporteur is Sylvie Louet.

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

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 October 2019) 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

Batch release within the EU take place at the Orion Turku or Salo sites located in Finland, which both hold a manufacturing authorisation issued by the Finnish Medicines Agency.

For the proposed batch control sites GMP compliance was confirmed by the Finnish Medicines Agency.

A GMP declaration for the active substance manufacturing site was provided from the qualified person (QP) at the EU batch release sites. The declaration performed in June 2018 was based on an on-site audit of one of the manufacturing sites responsible for batch release (Orion, Turku, Finland).

The presented GMP certificate for Fermion Oy is based on an inspection performed over 3 years ago and the GMP certificate for Orion Corporation is based on an inspection performed almost 3 years ago.

Legal status

The applicant requested this product to be "subject to medical prescription which may be renewed".

Overall conclusions on administrative particulars

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

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

Part 2 - Quality

Composition

The finished product is presented as an aqueous oral solution containing 0.3 mg/ml of the alpha-2 adrenergic receptor agonist tasipimidine (as sulfate) as the active substance.

Other ingredients are trisodium citrate dihydrate and citric acid monohydrate, sodium benzoate, brilliant blue FD&C Blue No 1 and tartrazine FD&C Yellow No 5 and purified water.

The product is available in a clear glass bottle containing 15 ml.

Containers

The primary packaging consists of a 20 ml clear type III glass bottle closed with a polypropylene child-resistant closure and a high-density polyethylene liner integrated with a low-density polyethylene adapter. The materials comply with the relevant Ph. Eur. and/or EU requirements.

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

The secondary packaging is a cardboard box, each box containing 1 bottle of 15 ml and an oral syringe. The pack size is consistent with the dosage regimen and duration of use. The oral syringe of 3 ml is included as a measuring device.

Development pharmaceutics

Active substance

Tasipimidine sulfate salt is freely soluble in water at room temperature. The stability of tasipimidine sulfate in different conditions was studied.

Excipients

All excipients are well known pharmaceutical ingredients.

The quality of trisodium citrate dihydrate, citric acid monohydrate, sodium benzoate and purified water is in line with the relevant Ph. Eur. monograph.

For the excipients FD&C Blue No 1 and FD&C Yellow No 5, suitable in-house specifications are provided.

There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SPC.

Formulation

The aim was to develop an oral solution containing tasipimidine for dogs with systemic effect. The rationale was to provide a dosage form which can be easily administered to dogs.

Formulation development resulted in a green-coloured solution that facilitates accurate dosing, that includes a citrate buffer solution and a preservative for adequate preservative efficacy. Complementary data on preservative efficacy show that the chosen concentration of the preservative is appropriate. It was noted that the drug product has to be stored at 2–8 °C to achieve acceptable stability.

The formulations of the clinical batches are representative of the proposed commercial formulation. The composition differs only by the colouring agents used in the formulation.

The manufacture of the bulk solution employs conventional techniques and the manufacturing is a simple process, where the drug substance and the excipients are sequentially dissolved in water. Process scale-up from laboratory to production scale was successful and all in-process control tests and release analysis results were acceptable.

Type III glass bottles and closures with adapters were chosen as the primary packaging material because they are conventional, widely used and suitable for storage of the drug product. A child-resistant closure was chosen because of user safety.

The development of a smaller pack size is recommended through a variation procedure, to address leftover issues related to the treatment of smaller dogs, to treatment at reduced dose(s) and/or to single/intermittent administrations in cases of noise anxiety.

A multi-dose syringe is needed to be able to take doses of different volumes. Dosing accuracy of the proposed 3 ml plastic syringe has been demonstrated at different levels covering the range of graduations from 0.2 ml to 3.0 ml. Hence, the first 0.1 ml graduation should not be used.

Stability study results indicate no incompatibilities between the packaging and the drug product.

The proposed formulation is considered suitable with respect to its intended use, the compatibility between the components of the formulation, the compatibility with the container closure system and the compatibility with the manufacturing process.

Method of manufacture

The manufacturing process of the finished product consists of the following major steps: dissolution of the different excipients and the active substance sequentially in an appropriate amount of purified water and mixing of those solutions. The resulting solution is filtered into an intermediate vessel; the bulk solution is filled into glass bottles and closed with plastic closures and packed in the secondary packaging.

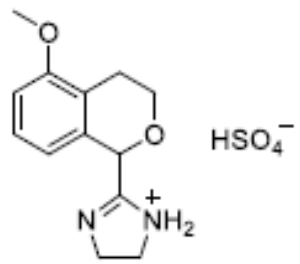
The process is considered to be a standard manufacturing process. No complex manufacturing processes have been used and no critical steps have been identified. The in-process controls are adequate for this type of manufacturing process. A holding time will be provided post approval.

Validation of the production process will be performed with three consecutive commercial scale batches post approval. A detailed process validation protocol was provided.

Control of starting materials

Active substance

The chemical name of tasipimidine sulfate is 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazol-1-ium hydrogensulfate and it has the following structure:



Tasipimidine sulfate is a crystalline white to off-white powder, which is freely soluble in water, soluble in methanol and very slightly soluble in acetone. Tasipimidine sulfate is not hygroscopic.

Tasipimidine sulfate exhibits stereoisomerism due to the presence of one chiral centre. Evidence confirming that the racemate is formed has been provided.

Polymorphism has not been observed for tasipimidine sulfate.

There are no physico-chemical characteristics liable to affect bioavailability since tasipimidine sulfate occurs as a single polymorphic form, whereas particle size distribution is not critical for solutions.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

The characterisation of the active substance and its impurities is in accordance with the "Guideline on the chemistry of active substances for veterinary medicinal products" (EMA/CVMP/QWP/707366/2017). Potential and actual impurities were discussed with regards to their origin and characterised.

The specifications and control methods for intermediate products, starting materials and reagents have been presented. No in-process controls applied during the synthesis were presented.

Tasipimidine sulfate is synthesised in three synthetic steps and one ion exchange step. Starting materials are acceptably defined.

Potential and actual impurities were characterised and discussed with regards to their origin.

There is no monograph for tasipimidine sulfate in the Ph. Eur. and an in-house monograph is defined. The active substance specification is generally acceptable and includes e.g. tests for appearance, identity , assay and impurities, water content, residual solvents and sulphated ash. The absence of control of microbial purity was justified by testing microbial quality in stability on several production batches. Limits for water content were tightened as requested. Limits retained for the assay were maintained based on batch data.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with VICH guideline (GL) 2. Information regarding the reference standards used for assay and impurities testing has been presented and is considered acceptable.

Data on the container closure system were also presented and are acceptable.

Batch analysis data for 3 pilot scale batches manufactured at a different production location and 4 production scale batches of the active substance, representative of the process described in the ASMF and manufactured at the proposed manufacturing site, have been provided. The results are within the specifications and consistent from batch to batch.

Stability data on the same 3 pilot scale batches and a production scale batch of active substance from the proposed manufacturer, which was stored in the intended commercial package, were provided. The studies were carried out in accordance with VICH GL3 for up to 36 months under long term storage/degradation conditions at 25 °C/60% RH and for up to 6 months under accelerated degradation conditions at 40 °C/75% RH.

Photostability testing in accordance with VICH GL5 was performed on one batch. Results on the stress conditions heat/humidity, alkaline hydrolysis, acidic hydrolysis as well as for oxidising conditions were also provided on one batch.

The following parameters were tested: appearance, assay, organic impurities and water. The analytical methods used were the same as for the active substance specification and were stability indicating.

All tested parameters were within the specification and no significant change was observed.

Preliminary stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. However, based on the stability results provided, no re-test period in the proposed container is proposed. The applicant agrees to test each active substance batch before use according to the specifications retained for tasipimidine sulfate.

Excipients

All excipients are well known pharmaceutical ingredients.

The quality of trisodium citrate dehydrate, citric acid monohydrate, sodium benzoate and purified water is compliant with Ph. Eur. standards. For the excipients FD&C Blue No 1 and FD&C Yellow No 5, suitable in-house specifications are used. Additional data on the conformity of both colorants with EU requirements was provided.

There are no novel excipients used in the finished product formulation.

The list of excipients is included in section 6.1 of the SPC.

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

The product does not contain any materials derived from human or animal origin. Valid TSE declarations from the manufacturers of the active substance and finished product are presented.

Control tests on the finished product

The specifications proposed for use at release and at the end of shelf life are in general appropriate to control the quality of the finished product. The acceptance criterion for total impurities has been tightened and the skip testing proposed for microbial contamination has been updated.

The finished product specification includes tests for clarity and colour of solution, pH, assay of tasipimidine and sodium benzoate, related impurities and microbiological purity. Where relevant, reference to Ph. Eur. methods has been made.

The analytical methods used have been adequately described and appropriately validated in accordance with VICH GL1 and VICH GL2. Validation data of the microbiological test are presented. Other analytical test methods are compendial or organoleptic test methods that require no validation. Supporting data to the forced degradation studies were provided.

Satisfactory information regarding the reference standards used for assay of tasipimidine, sodium benzoate and impurities as well as identification of the colouring agents has been presented.

Batch analysis results are provided for three production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability

Stability data on three production scale batches of finished product stored in upright and inverted positions for 36 months at 2–8 °C, and for 6 months at 25 °C/60% RH were provided according to VICH GL3.

The batches of finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for clarity and colour of solution, pH, assay of tasipimidine and sodium benzoate, related impurities and microbiological purity (only after 6 months under accelerated conditions and after 12, 24, 30 and 36 months under long-term conditions).

The analytical procedures used are stability-indicating. The observed physical and chemical changes were small, and not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SPC.

In addition, one batch was exposed to light as defined in VICH GL5 on "photostability testing of new veterinary drug substances and medicinal products" (CVMP/VICH/901/00). The study revealed that tasipimidine in the finished product is light sensitive.

An in-use shelf life test was also performed. The sampling protocol was justified.

Based on the available stability data, the proposed shelf life of 36 months when stored in a refrigerator (2–8 °C) and in the outer carton in order to protect from light, as stated in the SPC, is acceptable. The proposed in-use shelf life of 12 months in a refrigerator (2 °C to 8 °C) is acceptable.

The other proposed in-use shelf life of one month when stored below 25 °C is also acceptable considering batch data and because the applicant retains the following statement in section 6.3 of the SPC:

"Shelf life after first opening the immediate packaging: 12 months in a refrigerator (2 °C to 8 °C) **or** 1 month below 25 °C."

Overall conclusions on quality

The finished product is a clear, green aqueous oral solution containing 0.3 mg of tasipimidine (as base) per ml as the active substance, equivalent to 0.427 mg of tasipimidine sulfate.

Other ingredients are trisodium citrate dihydrate and citric acid monohydrate (buffering agents), sodium benzoate (preservative), FD&C Blue No 1 and FD&C Yellow No 5 (colouring agents) and purified water (solvent).

The primary packaging consists of a 20 ml clear type III glass bottle filled with 15 ml of solution closed with a polypropylene child-resistant closure and a high-density polyethylene liner integrated with a low-density polyethylene adapter. The materials comply with the relevant Ph. Eur. and/or EU legal requirements.

The choice of the container-closure system has been validated by stability data and is adequate for the intended use of the product when kept in the outer carton. A graduated oral syringe is included as a measuring device and accurate graduations cover the range of 0.2 ml to 3.0 ml, while the first 0.1 ml graduation should not be used.

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.

Formulation development resulted in a green-coloured solution that facilitates accurate dosing, including a citrate buffer solution and a preservative for adequate preservative efficacy.

The manufacture of the bulk solution employs conventional techniques and the manufacturing is a simple process, where the drug substance and the excipients are sequentially dissolved in water.

The manufacturing process has been described in detail and the in-process controls are adequate for this type of manufacturing process. The process is considered to be a standard manufacturing process.

Validation of the production process will be performed with three consecutive commercial scale batches post approval. A detailed process validation protocol is provided.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Detailed information on the manufacturing of the active substance has been provided. All questions regarding manufacturing, control of active substance and stability testing were resolved and complementary data were provided.

The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Batch analyses results of batches of the API demonstrate compliance with the proposed active substance specification.

On the basis of the available information, no re-test period can be claimed. The applicant will test each active substance batch before use in the manufacture of the finished product.

The excipients are well known pharmaceutical ingredients and their quality is compliant with their respective current Ph. Eur. monographs or appropriate in-house specifications.

Declarations provided by the manufacturers of the active substance and the finished product confirm reassurance of TSE safety.

The finished product specifications proposed for use at release and at the end of shelf life are generally acceptable. The finished product specifications include parameters relevant to the dosage form. Limits for total impurities and water content have been tightened.

Batch analysis results of production scale batches demonstrate compliance with the proposed finished product specification.

Based on the available stability data, the proposed shelf life of 36 months when stored in a refrigerator (2–8 °C) and in the outer carton in order to protect from light, as stated in the SPC, can be agreed upon. The proposed in-use shelf life of 12 months is acceptable with the justification of the sampling protocol. The other proposed in-use shelf life of one month when stored below 25 °C is also acceptable based on batch data.

In general, sufficient and clear information has been provided in the dossier to support the authorisation of this medicinal product, and current regulations and guidelines have been taken into account.

Issues raised during the procedure were solved and the product can be approved from a chemical-pharmaceutical point of view.

In addition, the applicant will perform process validation studies on 3 consecutive commercial scale batches post authorisation.

Part 3 – Safety

The active substance in Tessie, tasipimidine, is a new active substance not authorised for a veterinary medicinal product in the EU before. A full safety file in accordance with Article 12(3)(j) has been provided.

Safety documentation

Pharmacodynamics

Please refer to part IV for more details on the pharmacodynamic properties of tasipimidine.

Pharmacokinetics

Please refer to part IV for more details on pharmacokinetic properties of tasipimidine.

Toxicological studies

Single-dose toxicity

No single-dose toxicity studies was presented in the dossier. A 7-day maximum tolerated dose study in rats and dogs has been provided instead.

Rats:

In a non-GLP-compliant 7-day oral maximum tolerated dose (MTD) study, acute effects were observed in rats administered dose levels of 0, 5 and 20 mg/kg bodyweight (bw)/day. At the dose of 20 mg/kg bw/day, clinical signs such as lethargy with loss of reaction to stimuli were already noted between 0 and 4 hours after dosing but resolved at 24 hours post dosing. These effects were also observed at the dose of 5 mg/kg bw/day, though at a lower incidence and with lower severity.

In addition, severe bodyweight loss, reduced food consumption, lower body temperature and effects on respiratory parameters, including lower breathing frequency and lower respiratory volumes, were observed at the dose of 20 mg/kg bw/day. These effects correspond with the sedation-related effects of tasipimidine.

Furthermore, some haematology and clinical biochemistry parameters were affected and histopathological changes in lungs were observed at doses of 5 and 20 mg/kg bw/day.

Based on the effects at the lowest dose tested, which are considered adverse, a LOAEL of 5 mg/kg bw/day can be derived for this study.

Dogs:

In a non-GLP-compliant 7-day oral maximum tolerated dose (MTD) study, acute effects were observed in dogs administered dose levels of 0.03, 0.1, 0.3 later increased to 0.5 and 1 mg/kg bw/day.

The dose of 1 mg/kg bw/day resulted in the death of both test animals within 2 days. The cause of death/poor condition was most likely due to disturbances in blood circulation (particularly in the intestinal tract).

The dose of 0.3 mg/kg bw/day, which was later increased to 0.5 mg/kg bw/day, resulted in sedation-related effects such as lethargy, which were noted between 0 and 4 hours after dosing but resolved at 24 hours post dosing. A lower body temperature and lower heart rate, including lower blood pressure, were also observed, which correspond with the sedation-related effects of tasipimidine. Furthermore, some clinical biochemistry parameters were slightly affected. These effects were also observed at the dose of 0.1 mg/kg bw.

At the lowest dose of 0.03 mg/kg bw/day, only mild effects were observed, including a trend for lower blood pressure. However, only one male and one female dog per dose were tested, therefore no conclusion can be drawn regarding the derivation of a LOAEL/NOAEL.

It appears that dogs are more sensitive to tasipimidine than rats, most probably because of differences in systemic bioavailability (2% in rats and 60–82% in dogs after oral administration; see part 4).

Repeat dose toxicity

Repeated (28 days) dose toxicity studies were performed by administering tasipimidine via the oral route to rats and dogs. In addition, (pre-)clinical studies were performed, which are detailed in part 4.

Rats:

A 28-day repeated dose toxicity study in rats has been presented to investigate the systemic effects of tasipimidine at a dose levels of 0, 1.5, 5 and 15 mg/kg bw/day.

It is noted that this study was performed according to guideline ICH M3 (R2), which pertains to human medicinal products. However, the study design and parameters, i.e. clinical observations, bodyweight and food/water consumption, haematology, clinical biochemistry, gross necropsy and histopathology, are in line with OECD TG 407 ("Repeated dose 28-day oral toxicity study in rodents"), except for functional observations, i.e. sensory reactivity to stimuli in the fourth exposure week, which are missing. However, the effects of tasipimidine on the central nervous system (CNS) were sufficiently evaluated in several non-clinical studies, including behavioural studies.

The dose of 15 mg/kg bw/day resulted in sedation-related effects such as lethargy and uncoordinated movements, which were already noted between 0 and 4 hours after dosing but mostly resolved at 24 hours post dosing. Reduced food consumption and bodyweight loss were also observed, possibly related to sedation. Furthermore, focal corneal oedema and/or opacity, decreased weight of the spleen and uterus along with lower organ/bodyweight ratios were noted, and some clinical biochemistry and haematological parameters were slightly affected, although not accompanied by histopathological findings. Also, the prostate gland and seminal vesicles were reduced in size (though histological findings were normal) and urothelial hypertrophy was observed in almost all male and female rats. Treatment-related cellular alterations were present in the urinary bladder (in the form of PAS-negative urothelial eosinophilic inclusions and hypertrophy) as well as in the mandibular (salivary) glands (in the form of hypertrophy of the serous acinar cells in females) and in the lung (in the form of yellow-brownish pigments in perivascular/bronchial macrophages of male animals). Atrophy, due to decreased cytoplasmic content, was observed in the sublingual (salivary) glands in male (5/10 animals; 4 with slight, 1 with moderate atrophy) and female (2/10 animals with moderate atrophy) rats.

Clinical signs were also observed at the dose of 5 mg/kg bw/day, although at a lower incidence and with lower severity. At this dose, treatment-related cellular alterations were present in the male urinary bladder in the form of PAS-negative urothelial eosinophilic inclusions. Also, atrophy of the sublingual (salivary) glands was observed in male (3/10; 1 with minimal, 2 with slight atrophy) and female (3/10; 2 with minimal, 1 with slight atrophy) rats.

At the dose of 1.5 mg/kg bw/day, atrophy in the sublingual (salivary) glands was observed in male (6/10; 3 with minimal, 3 with slight atrophy) as well as female (3/10; 2 with minimal, 1 with moderate atrophy) rats at a higher severity and with a higher incidence than background findings, which was primarily characterized by a decreased cell size due to decreased cytoplasmic content. The study report states that alpha-2 adrenergic receptor agonists have been shown to inhibit salivation in different experimental protocols as well as in patients and that the histological finding of atrophy was therefore due to the (exaggerated) pharmacological activity of the test substance. On the other hand, it is noted that, in the 28-day dog study, salivation was increased. It remains undetermined whether the effects on the sublingual (salivary) glands are biologically (and toxicologically) relevant. The dose of 1.5 mg/kg bw/day, which is the lowest dose tested, is considered the LOAEL in this study.

Dogs:

A 28-day repeated dose toxicity study in dogs (in accordance with VICH GL43 ("Target animal safety") has been presented, investigating the systemic effects of tasipimidine at a dose levels of 0, 0.03, 0.15, 0.51 mg/kg bw/day.

The dose of 0.51 mg/kg bw/day resulted in sedation-related effects such as lethargy and uncoordinated movements. Vomiting and salivation were also observed, probably also resulting in adverse effects in the lungs due to aspiration of vomit.

At 0.15 and 0.03 mg/kg bw/day, clinical signs were comparable, although incidence, frequency and severity were dose-dependently decreased.

The great majority of the reported signs were noted directly after dosing until 4 hours after dosing.

It is noted that, in the study report, a decreased heart rate, increased PQ, ST, QT and/or RR intervals (ECG) as well as decreased blood pressure were observed in all dose groups, including the lowest dose, for which the applicant claims that they are due to the pharmacological effect of the substance and not of toxicological relevance.

Although the effects at the lower doses can be attributed to the pharmacological activity of the test substance, they should be considered as being toxicologically relevant. A LOAEL of 0.03 mg/kg bw/day should therefore be derived from this study, based on the observed clinical signs (lethargy, uncoordinated movements), effects on the heart (increased PQ, ST, QT and/or RR intervals, decreased heart rate) and decreased blood pressure, which are considered adverse.

Repeated dose toxicity has been studied in 28-day toxicity studies in rats and dogs. These studies are considered acceptable to determine toxicity after repeated exposure for a limited period.

Tolerance in the target species of animal

For more details on tolerance in the target species of animal, please refer to part 4. (Pre-)clinical studies demonstrated mild to moderate dose-dependent sedation and analgesia at doses between 10–100 µg/kg bw. A dose-dependent decrease of the heart rate and blood pressure were also observed.

The dose of 10 µg/kg bw was the lowest chosen dose level causing mild signs of sedation in some of the non-anxious laboratory dogs in calm surroundings. The intermediate dose level of 30 µg/kg bw produced a mild sedative effect generally associated with other adverse effects (see below) in all studied dogs. These adverse effects are in line with the ones observed in the toxicity studies.

A LOAEL of 10 µg/kg bw/day can be derived from the (pre-)clinical studies in the target species (i.e. dogs).

Reproductive toxicity

Study of the effect on reproduction

No reproductive study was presented. Directive 2001/82/EC states that, in case an active substance is to be used in food-producing-animals, a multi-generation study is required. The presently assessed product is intended for use in companion animals only and therefore information on reproductive toxicity is obtained from the other toxicity studies submitted. This is considered acceptable.

In the 28-day repeated dose study in rats, a reduced size of the prostate gland and the seminal vesicles in males were observed at the highest dose (15 mg/kg bw). At this dose however, the bodyweight and bodyweight gain were also significantly reduced, which was related to decreased food consumption, while the relative weights of the prostate and epididymides were normal. Moreover, no histopathological findings were observed. Therefore, it can be argued that the observed effects in rats are secondary to the reduction in bodyweight.

However, it is observed that in the 28-day repeated dose toxicity study in dogs, a significantly reduced size and weight of the prostate was observed at the mid and high dose (0.15 mg/kg bw and 0.51 mg/kg bw, respectively) as well, including a dose-dependent and significantly reduced relative

weight of that organ at all doses. No effect was observed on bodyweight or bodyweight gain. The weight of the epididymides was also significantly reduced at the highest dose, including a dose-dependent though non-significant reduction of the relative weight of that organ. Also, in the 28-day repeated dose study in rats, the absolute and relative weight of the uterus in female rats was dose-dependently and significantly reduced at the mid and high doses (5 mg/kg bw and 15 mg/kg bw, respectively).

In addition, it is also noteworthy that the SPC for a human medicinal product, which contains the alpha-2 adrenoceptor (AR) agonist guanfacine, indicates an adverse effect on male fertility based on animal studies. Overall, based on the available information, adverse effects on the reproductive organs cannot be fully excluded for tasipimidine.

Overall, 0.03 mg/kg bw (from the study in dogs) is considered as being the LOAEL for reproductive toxicity based on a dose-dependent reduction of the weight of the prostate.

Study of developmental toxicity

A dose range-finding study in rats has been presented in which the developmental effects of tasipimidine at a dose levels of 0, 1.5, 5 and 15 mg/kg bw/day were investigated.

This study demonstrated developmental effects (early resorptions resulting in post-implantation loss and smaller litter size) at a dose of 15 mg/kg bw/day. Also, lower foetal bodyweights were observed at this dose in addition to maternal toxicity, as demonstrated by sedative effects, lower food intake and lower bodyweight/bodyweight gain. No (externally visible macroscopic) malformations or variations were noted in any of the dose groups.

A pivotal developmental toxicity study in rats, investigating the developmental effects of tasipimidine at a dose levels of 0, 0.8, 2.5 and 7.5 mg/kg bw/day and performed in accordance with (the human) ICH GLS5 (R2) has been presented. Clinical signs (e.g. lethargy, uncoordinated movements) were observed at doses of 2.5 and 7.5 mg/kg bw/day. At the highest dose of 7.5 mg/kg bw/day, food consumption and bodyweight/bodyweight gain were also significantly decreased. Developmental toxicity was demonstrated by post-implantation loss (caused by early resorptions). Moreover, lower foetal body weights (4.6 compared to 5.2 g in control animals) and an increased number of foetuses with unossified metacarpal/metatarsal bones were observed (13.6% per litter compared to 0.8% in control animals), probably secondary to maternal toxicity.

No developmental toxicity was observed in the 0.8 and 2.5 mg/kg bw/day dose groups.

It is noted that this study is performed in accordance with ICH GLS5 (R2), which pertains to human medicinal products. The study design and observations are mostly in line with VICH GL32 and the therein referred OECD TG 414, i.e. it did include the critical period of organogenesis and skeleton development, although exposure to the compound occurred only during a limited period of the pregnancy. This is considered acceptable.

A NOAEL of 2.5 mg/kg bw/day for developmental toxicity can be derived from this study. Since the clinical signs observed at the dose of 2.5 mg/kg bw/day are considered adverse, the maternal NOAEL is therefore established at 0.8 mg/kg bw/day for this study. It should be taken into account that the developmental toxicity study is performed in rats, a species in which oral bioavailability is considered to be very poor when compared with dogs, and with the estimated bioavailability in humans.

Further, it is noted that in the EPAR for the alpha 2 adrenoceptor agonist dexmedetomidine (EMEA/V/C/003764 - IA/0009; https://www.ema.europa.eu/en/documents/product-information/sileo-epar-product-information_en.pdf) it is stated that pregnant women should avoid contact with the product,

as uterine contractions and decreased blood pressure of the unborn child may occur following systemic exposure.

Genotoxicity

Bacterial reverse mutation test:

A bacterial reverse mutation test using *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100 and TA102 was conducted in accordance with OECD TG 471.

Tasipimidine did not induce a significant increase of revertants up to a dose of 5.0 mg/plate with or without metabolic activation and appropriate results were obtained with the positive controls. The slight exceedance of the historical control range of some of the negative controls is considered not to impact the outcome of the study.

It is therefore concluded that tasipimidine showed no mutagenic potential in this study.

In vitro chromosomal aberration test:

An *in vitro* chromosomal aberration assay using human blood peripheral lymphocytes was conducted in accordance with OECD TG 473.

The top concentration of 343.0 µg/ml corresponded to 1 mM tasipimidine, which is not in accordance with VICH GL23. VICH GL23 refers to OECD TG 473, where it is stated that "if no precipitate or limiting cytotoxicity is observed, the highest test concentration should correspond to 10 mM, 2 mg/ml or 2 µl/ml, whichever is the lowest". The top concentration has therefore not been selected properly in this test.

Tasipimidine did not induce significant levels of chromosomal aberrations with or without metabolic activation when tested up to 343.0 µg/ml (i.e. 1 mM). It is noted that, upon a 4-hour exposure at the concentration of 112.0 µg/ml, a statistically significant increase in the number of aberrant cells was observed. However, given that the increase is within the historical control data and given the lack of a concentration-dependent response, this increase is considered as being not relevant. Appropriate results were obtained with the vehicle and positive controls, confirming the validity of the assay.

It is therefore concluded that tasipimidine showed no mutagenic potential in this study.

In vitro micronucleus test:

An *in vitro* micronucleus test using human lymphocytes was conducted in accordance with OECD TG 487.

Treatment of cells with tasipimidine in the absence and presence of S9 resulted in a percentage of micronucleated binucleate (MNBN) cells that was similar to and/or not significantly higher than that observed in concurrent vehicle controls. This was observed for all scenarios and concentrations tested, i.e. up to 2000 µg/ml for the 3-hour exposure scenario with or without S9 mix and up to 900 µg/ml for the 24-hour exposure scenario without S9 mix. A weak but statistically significant linear trend in dose-related percentage of MNBN was observed following the 24-hour treatment. However, as none of the test concentrations exhibits a statistically significant increase compared to the concurrent negative control, it is concluded that tasipimidine did not show genotoxic potential in this study.

In vivo chromosomal aberration test:

An *in vivo* chromosomal aberration test in bone marrow cells of rats was conducted in accordance with OECD TG 475.

Tasipimidine did not induce an increase in the number of bone marrow cells with chromosome aberrations of male treated rats at single oral dose levels of 3.75, 7.5 and 15 mg/kg bw. The maximum tested dose

of 15 mg/kg bw appears rather low. However, toxicokinetic data confirmed this dose to be in the range of systemic exposure to tasipimidine. Moreover, the doses of 7.5 and 15 mg/kg bw induced toxicity in the bone marrow cells. Therefore, significant exposure to bone marrow cells was demonstrated. It is concluded that tasipimidine did not show genotoxic potential in this study.

Based on the available genotoxicity tests (bacterial reverse mutation test, *in vitro* micronucleus test, *in vitro* chromosomal aberration test and *in vivo* chromosomal aberration test), it is concluded that tasipimidine is not expected to be genotoxic.

Carcinogenicity

No study on carcinogenicity of tasipimidine has been provided. No genotoxicity was observed in the *in vitro* mutagenicity studies, an *in vitro* micronucleus test in human lymphocytes and an *in vivo* chromosomal aberration test in rats. No neoplastic lesions were observed in the 28-day repeated dose toxicity studies, although this dosing period is rather short to conclude on the absence of neoplastic changes.

It is also noteworthy that the SPC for a product, which contains the alpha-2 adrenoceptor (AR) agonist guanfacine, indicates no verified carcinogenic effects when studied in a 78-week study in mice and 102-week study in rats.

There are no indications for tasipimidine having a carcinogenic potential.

Studies of other effects

Eye irritation:

An *in vivo* rabbit eye irritation/corrosion study was performed in accordance with OECD TG 405. The test item is slightly different from the product to be marketed with respect to colouring agents. However, the difference in colouring agents, present at concentrations of less than 0.003%, is minimal and not expected to affect the conclusion on eye-irritating properties.

A dose of 0.3 mg/ml tasipimidine induced very slight eye irritation, which was transient in nature. 1 hour after dosing, all three animals showed conjunctival redness (score 1), which fully resolved after 24 hours. A score of zero was noticed in all animals for corneal opacity, iritis and conjunctival chemosis.

It can be concluded that tasipimidine was minimally (transiently) irritating in an ocular irritation study.

Skin irritation:

An *in vitro* skin irritation test was conducted in accordance with OECD TG 439. The test item in the skin irritation study is slightly different from the product to be marketed with respect to colouring agents. However, the difference in colouring agents, present at concentrations of less than 0.003%, is minimal and not expected to affect the conclusion on skin irritation properties.

Cell viability upon treatment with 0.3 mg/ml tasipimidine was 95%.

Based on this study, tasipimidine is not considered to be irritating to the skin.

Skin sensitization:

An *in vivo* mouse LLNA test was conducted in accordance with OECD TG 429. The test item in the sensitisation study is slightly different from the product to be marketed with respect to colouring agents. However, the difference in colouring agents, present at concentrations of less than 0.003%, is minimal and not expected to affect the conclusion on skin sensitisation properties.

Stimulation index values were < 3 when tested with up to 100% of 0.3 mg/ml tasipimidine.

Based on this study, tasipimidine is not considered to be a skin sensitizer.

Notwithstanding this, it is noted that in a clinical study, hypersensitivity reaction occurred in one user, for which it was concluded that it might be attributed to the use of tasipimidine.

Percutaneous absorption:

An *in vitro* test for skin absorption was conducted in accordance with OECD TG 428. The test item is slightly different from the product to be marketed with respect to colouring agents. However, the difference in colouring agents, present at concentrations of less than 0.003%, is minimal and not expected to affect the conclusion on skin absorption.

At 24 hours following topical application to human skin *in vitro*, the absorbed dose (sum of receptor fluid and receptor wash) of 0.3 mg/ml tasipimidine was 0.59%. The exposed skin (sum of epidermis and dermis) contained 0.86% of the applied dose. This results in a dermal delivery of 1.45%. Moreover, the *stratum corneum*, minus layer 1–2 (i.e. the first 2 tape strips will represent material that will not become bioavailable due to desquamation), contained 0.75% of the applied dose. It is noted that the applicant does not consider the substance to be remaining in the skin when calculating the amount absorbed. This is not in line with OECD TG 428, which states that "the test substance remaining in the skin should be considered as absorbed unless it can be demonstrated that absorption can be determined from receptor fluid values alone". Nevertheless, dermal absorption of tasipimidine is limited, which would maximally amount to 2.2% when taking into account the amount remaining in skin.

Microbiological studies:

Tasipimidine is an alpha-2 adrenoceptor agonist and not considered to have microbiological properties.

Observations in humans:

Tasipimidine has not been studied in humans.

Excipients

Toxicity of this product will be determined by its active substance. The excipients are present in low concentrations and/or of low toxicity. It is noted that benzoates may cause hypersensitivity reactions. However, as the concentration of sodium benzoate contained in the current product is 0.05%, no hypersensitivity reactions due to the presence of this substance are expected.

User safety

The applicant has presented a user safety risk assessment, which has been conducted in accordance with CVMP guideline on "User safety for pharmaceutical veterinary medicinal products" (EMEA/CVMP/543/03-Rev.1).

The following has been considered:

Pet owners (including children) or care takers will be the main users. The users are non-professionals. The user may get exposed to the whole product, possibly mixed with saliva.

Oral exposure may occur when children get access to and accidentally ingest the product. Exposure may occur during the pre-application phase when the filled syringe is left unattended or when children gain access to the bottle. The packaging is child-resistant, therefore access to the product in the bottle will be negligible.

If the product is left unattended, the full content of the syringe may be ingested. However, it is noted that the child has to depress the plunger of the syringe. Therefore, it appears more reasonable to assume that 10% of the syringe content might be ingested, resulting in a dose of 7.2 µg/kg bw (i.e. 10% of 3 ml product containing 0.3 mg/ml tasipimidine divided by a bodyweight of 12.5 kg).

The user may also become dermally exposed during the filling of the syringe and/or the application of the product to the animal. This includes hand-to-mouth and hand-to-eye contact when personal hygiene measures are not maintained and may occur every time the product is administered (which may be up to three times a day) during a maximum period of 9 consecutive days. It is noted that the pack size (15 ml) currently allows for the total delivery of 4.5 mg of tasipimidine, which may be up to 75 doses of 0.2 ml, corresponding to the quantity recommended to treat an animal of 2 kg at the target dose of 0.1 ml/kg bw (i.e. 30 µg/kg). Smaller pack sizes are currently not available.

As a standard approach, it may be assumed that the user becomes dermally exposed to 10% of the content of the syringe. This would result in an (external) dose of 1.5 µg/kg bw for a 60 kg adult (i.e. 0.1 × 3 ml containing 0.3 mg/ml tasipimidine divided by a bodyweight of 60 kg).

Due to the expected hand-to-mouth contact, a part (i.e. 10%) of the dermal exposure may be ingested. This would correspond to a dose of 0.15 µg/kg bw.

Ocular exposure resulting in significant systemic exposure is considered negligible because of the packaging of the product, i.e. the syringe is connected to the bottle by an adapter and the syringe is placed in the mouth of the dog. In the worst case, if the dog struggles and/or sneezes, some product may reach the eyes and may cause local effects.

Based on the presented studies, tasipimidine is not expected to cause skin and/or hypersensitivity reactions. However, it is noted that, in a clinical study, hypersensitivity reaction occurred in one user, for which it was concluded that it was probably attributable to the use of tasipimidine. A suitable warning is included in the SPC.

Eye irritation may occur due to the presence of tasipimidine, though minimally and transiently. The excipients, taking into account their concentrations, do not raise concerns for local reactions.

Warnings for possible eye-irritating effects and hypersensitivity reactions are included in the SPC.

The lowest toxicological reference value from the toxicological studies is the LOAEL of 30 µg/kg bw/day, which is based on clinical signs (lethargy and uncoordinated movements), effects on the heart (increased PQ, ST, QT and/or RR intervals, decreased heart rate) and decreased blood pressure as observed in the 28-day repeated toxicity study in dogs. These effects are acute effects. Moreover, in (pre-)clinical studies in dogs, mild signs of sedation were already observed at a dose of 10 µg/kg bw/day.

Based on the lowest toxicological reference value (TRV), which is 10 µg/kg bw and the assumed accidental ingestion of 0.3 ml of product (7.2 µg/kg bw for a 12.5 kg child), the margin of exposure (MOE) is 1.4 (10/7.2). This is far below the default MOE of 100 used to account for intra and interspecies differences and does not consider the need for an additional safety factor for extrapolation from a LOAEL to a NOAEL. Warning and safety measures with respect to accidental ingestion have therefore been included in the SPC.

Based on the LOAEL of 10 µg/kg bw derived from (pre-)clinical studies in dogs (reversible mild sedative effects) and a dermal exposure level of 1.5 µg/kg bw (exposure to 0.3 ml of product), the resulting MOE would be 6.7 for dermal exposure when handling the product. This is below the default MOE of 100 for intra and interspecies differences and does not consider the need for an additional safety factor for extrapolation from a LOAEL to a NOAEL, consideration of which would result in an even lower MOE. However, it is noted that in this calculation a 100% dermal absorption is assumed for 0.3 ml of product, while a percutaneous absorption study demonstrated that the absorption of tasipimidine is minimal

(2.2%). This would result in an increase of the MOE by a factor of approximately 32 when accounting for the difference in dermal bioavailability versus oral bioavailability (i.e. the oral bioavailability in dogs is 60–80% with a mean of 70% divided by 2.2% dermal bioavailability). This would result in an MOE of 107 if an additional safety factor of 2 is chosen for extrapolation from a LOAEL (based on reversible sedative effects) to a NOAEL. Taking this as well as the proposed safety warnings into consideration, no risk for systemic effects is expected from the estimated dermal exposure levels to the product. In addition, the product is coloured and shall be easily noticed and washed in case of spillage.

Hand-to-mouth contact after dermal exposure was estimated to result in exposure levels of 0.15 µg/kg bw. The corresponding MOE would be 67 when compared to the LOAEL of 10 µg/kg bw/day. This is lower than the default MOE of 100 and does not consider the need for an additional safety factor for extrapolation from a LOAEL to a NOAEL. A warning is therefore included in the SPC.

The current risk characterization is based on the comparison of the estimated exposure levels with the toxicological reference value derived from (pre-)clinical (single dose and short-term) studies, taking into account that the 28-day repeated dose toxicity studies did not result in a lower TRV. As the product is to be administered for a maximum period of 9 consecutive days, this is acceptable.

When considering reproductive toxicity, the estimated exposure levels described above are compared to the LOAEL of 0.03 mg/kg bw derived from a study in dogs and based on a dose-dependently reduced weight of the prostate. For dermal exposure, the corresponding MOE would be 20 (30/1.5). For hand-to-mouth contact after dermal exposure, the corresponding MOE would be 200 (30/0.15). A MOE of 100 is generally considered acceptable, although, in this case, an additional safety factor would be required to account for the extrapolation from a LOAEL to a NOAEL. When considering this, the resulting MOE would therefore be lower for both dermal exposure and hand-to-mouth contact after dermal exposure. However, the risk regarding hand-to-mouth exposure is acceptable, considering the proposed warnings included in the SPC. For dermal exposure, the calculated MOE appears to be too low. However, a 100% dermal absorption is assumed for 0.3 ml of product, while a percutaneous absorption study demonstrated that the absorption of tasipimidine is minimal (2.2%), which results in an increase of the MOE by a factor of approximately 32. Overall, with the proposed warnings in section 4.5 ii) of the SPC, the risk for reprotoxic effects is considered to be adequately mitigated.

When considering developmental toxicity, the estimated exposure levels described above are compared to the NOAEL of 2.5 mg/kg bw derived from the developmental toxicity study performed in rats. However, the oral bioavailability in rats is poor (2%) when compared, for instance, to the oral bioavailability in dogs (60–80%; mean of 70%). Therefore, the NOAEL of 2.5 mg/kg bw/day derived from the rat developmental study might have been lower ($2.5 \times 2/70 = 0.07$ mg/kg bw) if oral bioavailability would have been higher, which should be taken into account when addressing user safety. For dermal exposure, the corresponding MOE would be 47 (70/1.5). However, a 100% dermal absorption is assumed for 0.3 ml of product, while a percutaneous absorption study demonstrated that the absorption of tasipimidine is minimal (2.2%). For hand-to-mouth contact after dermal exposure, the corresponding MOE would be 467 (70/0.15). Therefore, based on the developmental toxicity NOAEL of 2.5 mg/kg bw/day, no adverse developmental effects are anticipated for the user. It is noted that in the EPAR for the alpha-2 adrenoceptor agonist dexmedetomidine (EMEA/V/C/003764 - IA/0009; https://www.ema.europa.eu/en/documents/product-information/sileo-epar-product-information_en.pdf) it is stated that pregnant women should avoid contact with the product, as uterine contractions and decreased blood pressure of the unborn child may occur following systemic exposure. However, tasipimidine is considered a weaker alpha-2 adrenoceptor agonist than dexmedetomidine and the user safety warnings for dexmedetomidine containing-products are not applicable for tasipimidine.

The following user safety warnings and measures have been established:

"Exposure to tasipimidine may cause adverse effects such as sedation, respiratory depression, bradycardia and hypotension.

Avoid oral ingestion and skin contact, including hand-to-mouth contact.

In order to prevent children from getting access to the product, don't leave the filled dosing syringe unattended while preparing the dog for administration. The used syringe and the closed bottle should be returned to the original carton and stored out of the sight and reach of children.

In case of skin contact, wash the exposed skin immediately with water and remove contaminated clothes. In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician. Do not drive, as sedation and changes in blood pressure may occur.

This product may cause slight eye irritation. Avoid eye contact including hand-to-eye contact. In case of eye contact, rinse the eyes immediately with water.

This veterinary medicinal product may cause hypersensitivity (allergy). People with known hypersensitivity to tasipimidine or any of the excipients should avoid contact with the veterinary medicinal product.

Wash hands after use."

Environmental risk assessment

A phase I environmental risk assessment (ERA) was provided according to relevant CVMP/VICH guidelines (VICH GL 6).

Phase I:

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-producing animals.

Conclusions on the environmental risk assessment

An ERA was provided according to relevant CVMP/VICH guidelines (VICH GL 6). The veterinary medicinal product will only be used in non-food-producing animals and is therefore not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

Overview of toxicity findings:

Results of pivotal toxicity studies			
Study type	Tested species/test system	Result	Comments
Maximum tolerated dose (7 days)	Rats (dose levels of 0, 5 and 20 mg/kg bw/day) Dogs (dose levels of 0.03, 0.1, 0.3 increased to	LOAEL: 5 mg/kg bw/day No NOAEL/LOAEL derived	 Limited animal number per dose group

Results of pivotal toxicity studies			
	0.5 and 1 mg/kg bw/day)		
Repeat dose toxicity (28 days)	Rats (dose levels of 0, 1.5, 5 and 15 mg/kg bw/day) Dogs (dose levels of 0, 0.03, 0.15, 0.51 mg/kg bw/day)	LOAEL: 1.5 mg/kg bw/day LOAEL: 0.03 mg/kg bw/day	Functional observations were not included
Reproduction toxicity	No reproductive toxicity study was included		
Developmental toxicity (pivotal)	Rats (dose levels of 0, 0.8, 2.5 and 7.5 mg/kg bw/day)	NOAEL (maternal): 0.8 mg/kg bw/day NOAEL (foetal):2.5 mg/kg bw/day	The exposure period does not include the period up to the day before scheduled termination
Genotoxicity	Bacterial reverse mutation test *In vitro* chromosomal aberration assay using human blood peripheral lymphocytes *In vitro* micronucleus test in human lymphocytes *In vivo* chromosomal aberration test in bone marrow cells of rats	Not mutagenic Not mutagenic Not genotoxic Not genotoxic	 The top concentration has not been selected properly.
Carcinogenicity	No carcinogenicity study was included		
Other effects	*In vivo* rabbit eye irritation/corrosion study *In vitro* skin irritation test *In vivo* mouse LLNA test	Minimally irritating (transient) Non-irritating No hypersensitivity reactions	

Further to what is indicated in the table above, a LOAEL of 10 µg/kg bw/day can be derived from (pre-) clinical studies in the target species (i.e. dogs). This is the lowest TRV.

A user safety assessment in line with the relevant guidance document has been presented.

A risk for children has been identified regarding accidental ingestion of the product, i.e. when getting access to the filled syringe.

The packaging is child-resistant, therefore access to the product in the bottle will be negligible.

No risk is expected from the estimated dermal exposure levels to the product. However, hand-to-mouth contact may result in significant levels for which adverse effects cannot be excluded.

Eye irritation cannot be fully excluded, although it may be minimal and transient. Also, hypersensitivity reactions cannot be excluded.

Part 4 – Efficacy

Pharmacodynamics

Tasipimidine is a new active substance that is currently not approved for use in animals. It is an alpha-2 adrenergic receptor agonist (alpha-2 agonist). Tasipimidine is a racemate with a single stereogenic centre. Studies demonstrate that both enantiomers (ORM-23104 and ORM-23105) are pharmacologically active. The presented formulation is a solution, where the active substance is present in dissolved form.

Of the three alpha-2 receptor subtypes, alpha-2A is the dominant subtype in the central nervous system (CNS). It has a crucial role in mediating many of the main pharmacological and therapeutic effects of the alpha-2 agonists. Similarly to the parent compound tasipimidine, the metabolites, ORM-18662, ORM-22352, and ORM-22251, are also highly selective agonists of the human alpha-2A receptor, but much less potent and more partial agonists than tasipimidine. In human receptors, neither tasipimidine nor its metabolites have demonstrated measurable activity for the alpha-1A or alpha-1B adrenoceptors (AR), though some activity was demonstrated for the rat alpha-1A or alpha-1B adrenoceptors. A high selectivity for alpha 2A receptor has not been confirmed in dogs, though data from public literature support that there are clear similarities between canine and human alpha-2A AR. In addition, three cell-based assays and a receptor binding study presented by the applicant provide evidence that tasipimidine has a good selectivity towards the human alpha-2A subtype. Significant off-target binding of tasipimidine was demonstrated only to 5-HT1A, 5-HT1D and 5-HT7 receptors, imidazoline I1 and I2 receptors, and peripheral benzodiazepine receptor. However, pharmacological effects mediated by these receptors at therapeutic concentrations are unlikely.

A compilation of peer-reviewed published papers on the pharmacodynamic effects of alpha-2 agonists has been provided. It appears from these reports that the neurochemical basis of many of the effects known for alpha-2 agonists is caused by a reduced release and turnover of noradrenaline and some other neurotransmitters. In a fearful/anxious state, the physiological stress reaction is activated, which leads to an over activation of noradrenergic neurotransmission (increased release of noradrenaline in the locus coeruleus). Selective alpha-2 agonists decrease the amount of noradrenaline in locus coeruleus, and this is considered to cause a decrease of motor behaviour and signalling associated with distress. Blocking the noradrenergic system with an alpha-2 AR agonist is therefore likely to counteract this arousal. Dose-dependent sedation is also an apparent effect of the alpha-2-agonist activity in the CNS. According to

literature, the anxiolytic effect is considered to be mediated by the same CNS centre as for sedation, however smaller doses are needed.

Since over-activation of noradrenergic neurotransmission induces anxiety and fear in experimental animals exposed to stressful situations, it is likely that an alpha-2 agonist can be useful in treating fear and anxiety in a context dependent manner. Alpha-2 agonists have indeed been shown to be anxiolytic in rodent models at sub-sedative doses (Millan et al., 2000). There is also experimental evidence of the usefulness of alpha-2 agonists in canine fear-based problems (Korpivaara et al. 2017, Ogata et al. 2011). Recently, an oromucosal gel containing dexmedetomidine (a full agonist for all three alpha-2 AR subtypes) was licenced for the alleviation of acute anxiety and fear (noise anxiety) in dogs. An orally active dosage form and (as demonstrated in human receptors) a more selective receptor profile for alpha-2A differentiate tasipimidine from dexmedetomidine. Overall, the rationale of using an alpha-2 agonist for the indication of alleviation of anxiety and fear in dogs has been sufficiently justified.

Although the anxiolytic properties of the active substance tasipimidine were not specifically studied in pre-clinical models, the pharmacological effect that is typical for an alpha-2 agonist, such as a dose-dependent sedative- and haemodynamic effect, was demonstrated in several Beagle dog studies. The unwanted effects of any alpha-2 agonists are well known and were briefly summarised by the applicant. Most noticeable, alpha-2 agonists may induce sedation and analgesia, have cardiovascular effects (such as changes in arterial blood pressure and bradycardia) and can cause hypothermia. In theory, occurrence of other potential alpha-2 AR-mediated pharmacodynamic effects cannot be fully excluded, and the potential alpha-2 adrenoceptor agonist effects are therefore included in Section 5.1 of the SPC.

In conclusion, the applicant has supported that, at a low dose, alpha-2-agonists (such as tasipimidine) demonstrate an anxiolytic effect, whilst at this low dose, the sedative effect is less pronounced. The difference in effects is caused by the dose-dependent action in the locus coeruleus in the brain, where a small reduction in noradrenaline release could result in anxiolysis and a larger reduction in alertness.

Dose-dependent pharmacological effects typical for an alpha-2 agonist, such as sedation, were clearly demonstrated both *in vivo* and *in vitro*. Behavioural tests in rodent animal models were not performed in support of the presumed anxiolytic effect of tasipimidine. Supported by the outcome of the *in vivo* and *in vitro* studies, as well as by public literature in which the anxiolytic effect of alpha-2A agonist had been demonstrated in several animal models, the applicant assessed the anxiolytic effect of the product directly in client-owned dogs under field conditions.

Pharmacokinetics

Tasipimidine is rapidly absorbed after oral administration in fasted state. The mean plasma C_{max} is approximately 5 ng/ml and occurs at 0.5–1.5 hours after administration at the proposed dose of 30 µg/kg bw of tasipimidine. Re-dosing of 30 µg/kg bw at 3 hours apart gives a second C_{max} (approximately 30% higher than the first C_{max}) occurring at 3.5–6 hours after the first dose of 30 µg/kg bw. Only PK following a single re-dose was assessed, however PK data after oral dosing of tasipimidine was used to predict multiple dose pharmacokinetics of the current product. It was demonstrated that the systemic exposures (C_{max} and AUC) achieved after the first oral administration of tasipimidine (30 µg/kg bw by gavage) in the 4-week TAS study (study 499681) were comparable to those obtained in the final formulation PK study, with tasipimidine administered as a single oral dose of 30 µg/kg (PK study 509760). Considering the pharmacokinetic profile of the product (accumulation was not demonstrated, dose-proportional pharmacokinetics, and a short half-life in plasma) as well as a short maximum duration of treatment (nine consecutive days), omission of additional multiple dose studies was accepted.

The gastrointestinal absorption is moderate: in fasted state, at the proposed dose of 30 µg/kg bw, the mean systemic bioavailability is 60 ± 12%. There are no sex differences in absorption. In fed state (the whole daily food portion given at dosing), a slower absorption of tasipimidine was noted, though overall absorption was comparable to fasted state. In case dogs were treated one hour before or after being fed half of the daily portion of food, tasipimidine was however rapidly absorbed and showed absorption profiles comparable to that in the fasted state. The SPC provides clear guidance that the animal should not be fed for one hour before to one hour after treatment, as food may cause a delay in absorption.

Tasipimidine has a low degree of protein binding, with a free fraction of 83% in dogs. It is a highly distributed compound and rapidly eliminated from the body; total plasma clearance is 1.2 ± 0.3 l/h/kg. The half-life of elimination from circulation is approximately 1.7 hours both after i.v. and oral administration.

Tasipimidine is eliminated by hepatic metabolism and urinary excretion. Tasipimidine penetrates the brain tissue of dogs.

Biotransformation occurs mainly by demethylation (ORM-18662) or dehydrogenation (ORM-22352) and subsequent sulpho- or glucuronide conjugation. Metabolite ORM-22352 is hydroxylated prior to glucuronide conjugation. All conjugates are minor metabolites.

A total of 5 circulating metabolites (all of which much less potent than the parent compound) are found in dog plasma. Exposure to the main circulating metabolites ORM-18662 and ORM-22352 was less than to the parent substance, and exposure to ORM-22251 (demethylated dehydrogenation product) was at trace level.

Excretion mainly occurs as unchanged in the urine. The portion recovered as unchanged tasipimidine in the dog urine was 25% of the i.v. dose within the first 24 hours. All circulating metabolites are excreted into urine. However, their urinary excretion was much less than the parent compound. A total of 13 urinary metabolites were found.

The pharmacokinetics of tasipimidine was adequately characterised to support the dosage intended for the proposed product.

Dose justification

No dose titration studies for the anxiolytic *versus* sedative effects of tasipimidine in dogs were provided. The choice of doses used in the dose determination studies appears to be based on data derived from the public domain on the anxiolytic effects of alpha-2 agonists when used in doses lower than those used for sedation. The goal of the target dose establishment therefore was to utilise tasipimidine's anxiolytic, but not clinically sedating, effect; the pre-clinical studies aimed to find a dose with a good safety profile and at which also some effect was visible in healthy, calm, laboratory dogs. This is considered appropriate.

Doses ranging from 10 to 300 µg/kg bw were tested in pre-clinical studies on telemetry-operated, healthy Beagle dogs. The results of these pre-clinical studies indicated that a dose-dependent very mild to moderate sedation and analgesia could be observed at doses between 10–100 µg/kg bw. In these cardiovascular telemetry studies, dose-dependent pharmacological effects typical for an alpha-2 agonist, such as a dose-dependent decrease in heart rate and decrease in blood pressure, were also observed.

The dose of 10 µg/kg bw was the lowest chosen dose level causing very mild signs of sedation in some of the non-anxious laboratory dogs in calm surroundings. The intermediate dose level of 30 µg/kg bw produced a mild sedative effect generally in all studied dogs. These doses were assumed to have sufficient anxiolytic potential in client-owned dogs under sympathetic arousal and were chosen to be further evaluated in clinical studies; therefore, the 10 and 30 µg/kg bw doses were included for

evaluation in a clinical proof of concept field study. However, in this field study, dogs also required manipulation. It was thought that clinically relevant effects would in that case potentially not be observed for the 10 and 30 µg/kg bw doses. Therefore, a higher dose of 60 µg/kg bw was also tested. Based on the laboratory safety studies, this dose level was not expected to cause considerable changes in blood pressure or heart rate.

It is acceptable that no classical dose finding studies were performed. Instead, the desired anxiolytic effect was assessed in several clinical field studies, which is considered appropriate.

Target animal tolerance

The proposed dose for tasipimidine is 30 µg/kg of body weight for up to 3 times within 24 hours, as needed, for up to 9 consecutive days. Re-dosing would be allowed as soon as the dog shows first signs of becoming anxious or fearful again, but not sooner than 3 hours after the previous dose. In the context of this application, treated animals have to be systemically healthy for being considered candidates for owner administered treatment at home. Adverse events to be expected are sedation and other effects typically associated with the administration of an alpha-2 adrenoceptor agonist. The safety profile of the product appears not to raise concerns at the proposed dosing regimen. Safety during pregnancy or lactation and also in small animals (< 3 kg) has not been investigated. A warning that safety and efficacy have not been demonstrated in small animals (< 3 kg) is therefore considered appropriate and has been included in the SPC. Also, the dosing device cannot be used for safely delivering the product at the recommended dose of 30 µg/kg bw to animals requiring a lower dose than 0.2 ml. An appropriate warning has been implemented in the SPC that dogs requiring doses lower than 0.2 ml can therefore not be treated (SPC section 4.5.i), with specific information in SPC section 4.9 also. In section 4.7 of the SPC, a warning has been included not to use the product during pregnancy and lactation, considering the observations from laboratory studies in rats, that demonstrated evidence of developmental toxicity at maternotoxic doses.

Almost all studies presented in the dossier (field- as well as laboratory studies) did not use the final formulation, i.e. there were slight differences in the formulations concerning the excipients. However, the excipient(s) finally added in comparison to the studied formulation(s) do not raise any safety (or efficacy) concerns for the target species.

Target animal safety for tasipimidine was initially assessed in five preclinical safety pharmacology studies performed in healthy, telemetry-operated, conscious, non-pregnant Beagle dogs. Four of these were single-dose studies, and one was a re-dosing study with two consecutive administrations at 3-hour interval. One additional study evaluated the safety of tasipimidine when administered prior to anaesthesia.

The main focus of the five initial pre-clinical studies was to evaluate the effects of tasipimidine on cardiovascular function, body temperature, alertness and analgesic properties. Overall, tasipimidine was well tolerated in these studies. All the effects seen in these studies are considered normal pharmacological effects of an alpha-2 adrenoceptor agonist. At oral doses of 30–300 µg/kg bw, tasipimidine induced dose-dependent sporadic emesis, mild sedation and decreased heart rate, which could be accompanied by decreased body temperature. At lower doses (10–100 µg/kg bw), tasipimidine induced slight but dose-dependent decrease in mean arterial pressure, systolic arterial pressure and diastolic arterial pressure which may at higher doses (> 100 µg/kg bw) under certain conditions lead to compensatory increase in blood pressure, particularly increased diastolic arterial pressure. A study demonstrated that the effects of tasipimidine at 60 µg/kg bw could be antagonised by atipamezole at a dose of 300 µg/kg bw given intravenously 1 hour after dosing.

In another study the maximum tolerated dose was assessed in 8 animals. This study demonstrated that, when administered at a dose of 1 mg/kg bw, tasipimidine was lethal in the target species. The maximum tolerated dose of tasipimidine was considered to be 0.5 mg/kg bw/day.

In addition to the pre-clinical safety pharmacology studies and the maximum tolerated dose study, target animal safety has been evaluated in a GLP-compliant, 28-day target animal safety study. In this TAS study, tasipimidine was administered at 0, 30, 150, and 510 µg/kg bw (0X, 1X, 5X and 17X the proposed dose) by oral route (gavage), once daily. This study was originally performed to assess the general toxicity potential of tasipimidine and to provide a rational basis for toxicological risk assessment in man. The study was re-opened for target animal safety purposes. The study therefore does not fully comply with VICH GL 43 — "Guideline on target animal safety for veterinary pharmaceutical products". However, deviations from VICH GL43 were appropriately justified in the dossier, the quality of the study is acceptable, and the standard is sufficiently high. Therefore, this study is of clear additional value for the assessment of target animal safety. Taking the totality of data on target animal safety as provided by the applicant into consideration, target animal safety is sufficiently supported by the presented data and an additional VICH GL43-compliant TAS study was not considered appropriate nor necessary in case of incidental use of the product.

In the TAS study, clinical signs most commonly seen at all doses were dose-dependent sedation-related symptoms (lethargy, abnormal posture, ptosis, decreased body temperature, and uncoordinated movements). These signs correlate with the pharmacological profile of the molecule. Already at the proposed label dose (30 µg/kg bw), mild sedation-related signs were occasionally seen. However, it is acknowledged that the sedative effects of tasipimidine are likely to be more pronounced in these non-anxious dogs with more calm state of mind than in anxious dogs under the influence of stress factors. At the highest dose (17X the recommended dose), signs of sedation could be observed up to 24 hours after dosing. The potentially life-threatening observations in case of a (severe) overdose are adequately reflected in the SPC.

Other symptoms observed at all doses, but much more pronounced at the 5X and 17X doses, were all related to exaggerated pharmacological activity on cardiovascular targets (decreased heart rate, decreased blood pressure, pale or red mucous membranes) or to nausea (salivation, vomiting). No relevant treatment-related effects were noted on body weight, food consumption, ophthalmoscopy, haematology, urinalysis, and macroscopic pathology, except for reduced size and weight of prostate at 150 and 510 µg/kg (0.15 and 0.51 mg/kg) in dogs. Also, in a 28-day oral gavage study in rats, male reproductive organs at 15 mg/kg and uterus weight were dose-dependently decreased, from 5 and 15 mg/kg respectively. No associated histopathological findings were observed in both sexes. Slight changes in ECG (increase in PQ, ST, QT, RR), and blood pressure (slight decrease in systolic and mean blood pressure 2 hours after dosing) were observed without clinical consequences. No accumulation was demonstrated in this study, though study duration was only up to 28 days.

At the highest dose (17X of recommended dose), there was a slight increase in glutamate dehydrogenase in 2 females, occurring in the absence of histopathological liver effects. In addition, there were slight changes in triglycerides, creatinine, calcium, sodium, and potassium. Pathology results did not reveal relevant macroscopic test article-related abnormalities in all groups. Microscopic findings in lungs after treatment with 510 µg/kg/day (17X of recommended dose) demonstrated inflammatory cell infiltrate and a mixed alveolar inflammation. Also, two animals had an increased lung weight. These observations were likely caused by regurgitation following aspiration of vomit. However, since the risk of a repeated 17X overdose is considered negligible, the changes seen only at that high dose are not considered of clinical relevance. Risk of an aspiration pneumonia in case of an overdose is however appropriately reflected in the SPC.

In the six clinical field studies provided, dogs received tasipimidine as a single dose of 10, 30 or 60 µg/kg bw once a day or a dose of 30 µg/kg bw up to three times a day, as needed, for up to five weeks. In total, 187 dogs were treated with the proposed dose of 30 µg/kg bw. In these 187 animals, 162 AEs were reported for 30.5% of dogs (57/187). The most common adverse events were emesis, lethargy, ataxia, diarrhoea, somnolence and sedation (seen in 27.8%, 11.76%, 5.9%, 5.9%, 4.8% and 2.1% of dogs, respectively). In addition to the reporting of adverse events, safety was also assessed based on the separate assessment of the functional alertness of the dog with regard to the its sleeping/resting behaviour and its ability to walk. In general, treatment decreased functional alertness in some animals. Pooled data from the six clinical studies demonstrated that 29/151 dogs (19.2%) were scored with a decreased ability to walk and/or overall responsiveness. However, efficacy of the product was appropriately demonstrated in animals that did not show a decrease in alertness. The stated target of treatment ("a "fully functional" dog showing marked reduction or resolution of the signs of anxiety and fear despite the presence of the anxiety-inducing stimulus") is therefore considered met.

There were no serious adverse events reported in any of the field studies, which is consistent with the safe use of the substance. The observed AEs reflected mainly the alpha-2 pharmacology of the compound and included emesis, lethargy, ataxia, diarrhoea, somnolence and sedation. The severity of these AEs was mild to moderate, and transient in nature. To avoid that an animal that is "sedated" (with a possible decreased body temperature) as a result of the treatment is left alone, mitigating measures have been included in the SPC.

Also, in the field study relative to veterinary visit, delayed sedation and lethargy are noted for up to 2 hours after the dog returns home. This is also observed after use of the product in the field study relative to fear triggered by travel. The SPC therefore states that whenever the animal is meant to be left alone, it is required to administer a test dose prior to leaving the dog unattended.

The SPC also foresees for a dose reduction for subsequent doses in case sedation/reduced alertness is observed at an initial 30 µg/kg bw dose. Dose reduction was allowed (and assessed) in 3 multiple dose field studies. In 11.5% of the dogs (18/156), a reduced subsequent dose was required. In almost all cases, this reduction was necessary due to some form of "reduced alertness", or adverse event related to a reduced alertness (primarily lethargy, sedation, ataxia). Though the sample size was too small to allow for statistical comparison, in the subgroup dogs that received a lowered dose, the proportion of positive responses (excellent or good effect) was higher than those with negative responses (some, no or worse effect). Also, in these animals, alertness scores improved at this lower dose. Overall, in case an animal experiences a reduced functional alertness at the 30 µg/kg bw dose, a 20 µg/kg bw dose is considered safe, and likely effective in alleviating acute anxiety and fear in that animal.

In a study which assessed efficacy and safety following long-term (up to 5 weeks) use, a higher incidence of AEs was observed (71 AEs in 19 dogs were considered related to treatment). This is likely due to the prolonged duration of treatment (32 animals were treated up to five weeks and up to three times per day).

In conclusion, the maximum tolerated dose study demonstrated that, when administered at a dose of 1 mg/kg bw, tasipimidine is lethal in the target species. However, when dosed at 30 µg/kg bw and at the recommended number of daily administrations, the product appears to be sufficiently safe in most animals, and adverse effects are adequately described in the SPC. Based on the data presented in the 28-day TAS study and other pre-clinical safety studies, the tolerance of the product is considered to be sufficiently documented in case of incidental use and when used for a maximum of nine consecutive days. In dogs that show signs of decreased alertness or adverse events after the first dose, the SPC provides the option to reduce the dose to 20 µg/kg bw. The SPC as well as package leaflet section 9 state that the decision to administer a reduced dose should be left to veterinary professionals, which is considered appropriate.

Usability of the product

The treatment is intended to be used in the home environment by the dogs' owners. Usability of the product appears acceptable throughout most of the field studies (though it was noted that some dogs struggled when owners tried to administer the treatment). In the long-term study, however, usability was assessed as "somewhat difficult" by 19 owners (31.7%) and "very difficult" by 4 owners (6.7%). Most likely explanation for this observation is the high number of animals with a rescue background that were included in this study. Overall, usability of the product is considered acceptable for the proposed short-term use of the product.

Clinical field trials

The applicant chose to study the effectiveness and clinical safety of tasipimidine with respect to acute situational anxiety and fear in dogs triggered by events provoking sympathetic arousal (e.g. travel, noise, owner departure, veterinary visits). In the SPC, the applicant describes a number of signs considered typical of anxiety or fear, that have been shown to be recognizable by owners, such as panting, trembling, pacing, seeking people, and hiding. The SPC is clear that after treatment, these signs may be alleviated but may not be completely eliminated. This reflects the fact that a significant reduction of signs taken individually was not always demonstrated in the field trials.

The applicant provided three dose determination and three dose confirmation studies performed under field conditions in support of the proposed claim. In these six field studies, efficacy of the product for each of the four indications that were initially proposed (acute anxiety and fear association with noise (fireworks), travel, separation anxiety and veterinary visits) was assessed. Sufficient treatment effect was considered demonstrated to support the claim: "Short term alleviation of situational anxiety and fear in dogs triggered by noise or owner departure".

All six field studies were performed according to GCP principles and conducted in multiple European countries. All studies were randomised, double-blind, and placebo-controlled. In all studies, tasipimidine was administered orally to the dog at home by the owner. In all studies, pre-specified, primary endpoints were used as the main endpoints. In all studies, signs of acute anxiety and fear were collected based on the scale of Overall et al. (2006), modified for each study to include the most typical set of signs for the studied type of situational anxiety.

The effect of the treatment was assessed by owners in 5 out of 6 studies for the primary criterion using a similar, semi quantitative scale, adapted for the specific study population.

The studies typically contained a pre-screening/screening period during which the dogs' eligibility was confirmed, baseline identification of relevant behavioural signs and reactions to certain situations, a treatment period and an end-of-study contact or visit. The results were reported as difference in distribution of the dogs in five different categories ranging from excellent to worse (than earlier occasions) as primary variable, based on owner's assessment. Owners', and, in some studies, experts' assessment of signs and their extent was assessed using a similar scale, adapted to the individual anxiety-related situation. For this secondary variable, the extent of the signs (none, only a few times, some of the time, most of the time, continuously) as a sum score was assessed based on a modification of Overall et al. (2006).

Use of owners' assessment as a single primary endpoint can be accepted, as the presence of a positive correlation between the owner overall assessment and changes in the sum score of signs of fear and anxiety has been demonstrated in earlier studies. Also, data derived from public literature confirmed that owners/caregivers are familiar with and able to recognize acute anxiety (Mariti et al. 2012; Tiira et al. 2014). In addition, for current field studies, owners were trained to recognize signs of fear and anxiety

and to perform the study assessments (and, according to published literature, should therefore be considered as "pre-trained observers"). The outcome of the primary endpoints in these studies confirmed this position: a significant result was obtained in all studies that primarily evaluated owner's assessment of the effect. In addition, in the SALCAR study, the primary variable assessed by the external observer was in agreement with the owners' assessments.

Dose determination/finding studies

The applicant conducted three dose determination studies under field conditions. The three selected doses used in these studies (10, 30 and 60 µg/kg bw) were derived from observations in the laboratory studies, where all three dose levels resulted in a dose-dependent very mild to moderate sedation and analgesia with an acceptable safety profile in healthy, calm, laboratory dogs.

The first dose determination, proof of concept field study, was a parallel-group study that included 118 dogs (4 groups, n = 29–30/group). Patient demographics and baseline characteristics demonstrated that patients of different weights, sex and age were evenly distributed between the groups. To minimise the risk to veterinary personnel participating to the study, dogs suffering from fear-based aggression were excluded from the study. The aim of the proof of concept study was to evaluate the efficacy and clinical safety of a single dose of tasipimidine against placebo in dogs difficult to handle in veterinary clinics due to fear and/or anxiety (investigator's assessment). A single treatment was administered at home approximately 45 minutes before bringing the dog to the clinic. As a primary analysis, the distribution of responses between tasipimidine (pooled doses) and placebo was analysed with a generalised linear model. The secondary efficacy variables were behavioural stress level assessments from video recordings (assessed by three canine behaviour experts), the investigator's assessment of perceived treatment effect, and the owner's assessment of perceived treatment effect. In short, this study failed to demonstrate that the proposed product is superior to the placebo treatment when assessing the predetermined parameters. There was no statistically significant difference between treatment (pooled) and placebo in the ability to perform physical examination, which was the primary efficacy variable. According to the applicant, on hindsight, the primary variable "ability to perform the physical examination" was not ideal. Results did demonstrate that behavioural stress levels upon entering the examination room were significantly lower in animals that had received the 30 µg/kg dose compared to placebo. However, a beneficial effect was not present during the physical examination, and though it is acknowledged that for some of the more "intrusive" physical examinations a significant difference was observed, the clinical relevance of a limited beneficial effect for the overall veterinary visit is unclear. Considering the above, the CVMP was of the opinion that this indication was not sufficiently supported by data and should be removed. In response to CVMP's concerns, the applicant agreed to omit the indication for the alleviation of situational anxiety and fear triggered by veterinary visits. As in this study the 60 µg/kg bw dose resulted in more AEs, the applicant chose to pursue only with the two lower doses of 10 and 30 µg/kg for further evaluation in future studies that were aimed at assessing different potential indications. This is considered appropriate.

The second exploratory pilot and dose-finding clinical field study was also a parallel-group study that included 43 dogs (3 groups, n = 14–15/group). The study evaluated two doses, 10 and 30 µg/kg bw of tasipimidine. The primary (and secondary) efficacy variables were subjective variables. The primary variable was the owner assessment of the effect of study treatment on the dogs' signs of fear and anxiety at New Year's Eve. The first dose was given when the first (even distant) fireworks could be heard or the dog showed signs of anxiety or fear. Upon initiation of treatment, in all animals the reported sum score for signs of anxiety and fear was already very high. Efficacy of the product was therefore assessed in dogs that already displayed signs of anxiety. The dose could be repeated up to three times. In short, based on the primary efficacy variables, treatment effect was significant (p = 0.0003), favouring

tasipimidine over placebo. Secondary efficacy variables (sum of owners' assessment of signs and extent of anxiety and fear) analysed at 1- and 2-hour time points however did not reach statistical significance between the treatments. Dog owners did score the treatment effect of the 30 µg/kg bw dose more often positive compared to owners of dogs on placebo (p = 0.0021), whilst the difference between the lower dose of 10 µg/kg bw and placebo was not statistically significant. Therefore, the 30 µg/kg bw dose was selected as the dose to be used in the pivotal study. This is considered appropriate.

The third dose determination study was a small (n = 12), 3-period crossover clinical field study. Treatment was administered as 4 single doses on 4 consecutive days in each period. The primary variable was owner assessment of the effect of the treatment of acute anxiety related to owner departures (based on video recordings). The secondary efficacy variables were the owner's departure related acute anxiety severity scores, incidence of improvement of the individual acute anxiety behaviours related to owner departures and the owner's assessment of the signs of the attachment related behaviours. Assessment of efficacy was initiated once a test-dose confirmed that the dogs did not demonstrate a decreased functional alertness. During this test period, the animal was dosed according to label, and the dog was monitored for at least 2 hours to see if the level of alertness decreases. Should a decrease in alertness be noted as staggering gait or abnormal reduction in responsiveness the dog was not to be dosed on the following days during this period. Only in case the animal did not demonstrate a decrease in alertness, the study continued assessing the efficacy of the product, appropriately ensuring efficacy assessment in "fully functional" animals only. The results of this study confirmed that tasipimidine was more effective than placebo in alleviation of separation anxiety in dogs: a statistically significant treatment effect was seen for the primary efficacy variable (p = 0.0004). In contrast to the 30 µg/kg bw dose, the difference between the effect of the 10 µg/kg bw dose and placebo was however not statistically significant. Of the secondary efficacy variables, significant treatment effect in the owner-departure related acute anxiety severity scores was also seen (p = 0.0185). When assessed by dose, this was also only significant for 30 µg/kg bw (p < 0.0001). Also, a significant change from baseline in the owner's assessment of severity of signs of owner departure–related acute anxiety was observed, when all signs pre-defined in the protocol (except urination) were included in the model (p = 0.0003; and significant only for the 30 µg/kg bw dose). For the individual signs of fear and anxiety, significant treatment effect favouring 30 µg/kg bw over placebo was seen for destructive/ rearranging behaviour and vocalisation, both signs were among the most frequent complaint by the dog owners who have dogs suffering from separation anxiety. However, a significant treatment effect was lacking for other single signs.

Dose confirmation/clinical studies

Based on the results of the dose determination studies, which demonstrated that treatment difference was statistically significant in favour of the 30 µg/kg bw dose, the applicant pursued with the 30 µg/kg bw dose for further evaluation in the following three dose confirmation studies. This is considered appropriate.

The pivotal field study was a parallel-group, multicentre, clinical field study. The aim of this study was to investigate the safety and effectiveness of the candidate formulation under field conditions of use for the indication: "*alleviation of canine acute anxiety and fear associated with noise*". The model used in this study was fireworks noise.

This pivotal trial was well designed and adequately sized to demonstrate differences among the groups. One hundred and sixty dogs were included, of which 80 were treated with tasipimidine at 30 µg/kg bw, and 80 were treated with placebo. The main evaluation was performed on 2016 New Year's Eve and the effect of treatment was assessed once after New Year's Eve. The first dose was given when the first (even distant) fireworks could be heard or the dog showed signs of anxiety or fear. At that point, also in this study, the reported sum score for signs of anxiety and fear was already very high in all animals.

The primary efficacy variable was the owner assessment of the effect of the treatment on dog's signs of fear and anxiety (compared to previous noise events without treatment). These results were reported as difference in distribution of the dogs in five different categories ranging from excellent to worse (than previous years). The primary analysis was performed using generalised linear mixed model, cumulative logit as a link function. The secondary efficacy variables were the owner's scoring of individual signs and extent of anxiety and fear, administration frequency and time between doses. Demographic distribution between the two treatment groups was appropriate. Information on the distribution of the extent of the fear or information regarding the dogs' behaviour and possible treatment preceding New Year's Evenings were provided, and published literature was provided in support of the statement that owners are capable of recalling the level and signs of anxiety experienced by the animal. The intensity of the fireworks, was selected as an additional variable.

Inclusion criteria stated that the dog should have demonstrated at least three of the behaviours listed most of the time or continuously during previous noise exposure. As noise anxiety is known to increase over time, all animals included had to be over two years of age, ensuring that at least one New Year's Eve had been experienced. Additional exclusion criteria were introduced to ensure that the dog had not been effectively treated for the fear that was observed upon the occurrence of the event.

The effect of treatment was significantly better compared to placebo (p = 0.0118) in the full analysis set population (but not in the per-protocol population). A significant effect (p = 0.0315) was also demonstrated when, with a generalised linear mixed model, the primary variable was further derived into a binary variable (success ["excellent" and "good" effect] or a failure ["some", "no effect" or "worse"]) analysis. Furthermore, a significant reduction in behaviours indicating anxiety and fear was observed. The main secondary efficacy variable, the sum of behaviour scores of the 3 most severe signs (defined at screening by the owner) at 2 hours after dosing, was significantly lower (p = 0.0431) compared to animals treated with placebo, favouring the investigational product. However, a significant difference in the sum scores could not be demonstrated 2 hours after the second dose. The most likely cause for this observed lack of significance is insufficient statistical power, as only 4 animals receiving tasipimidine required a third dose (whereas 34 animals had received a second dose). It is expected that the group that required only a single treatment primarily included animals that were most responsive to treatment. In addition, in the placebo group, a number of dogs had to be discontinued (and as a result, the "less anxious" dogs remained). A last observation carried forward- imputation (LOCF) approach was therefore performed as *post-hoc* analysis. This approach did result in a significant outcome for the secondary efficacy endpoint following the second treatment 1 and 2 h after dosing.

In conclusion, the results of this study showed acceptable effectiveness of tasipimidine administered at a dose of 30 µg/kg bw for the alleviation of anxiety and fear associated with noise in dogs.

The second dose confirmation study, aimed at evaluating the long-term efficacy and clinical safety of the product for the alleviation of acute anxiety related to owner departure. This was a parallel-group, multicentre clinical field study. This trial was well designed, though size, 66 dogs of which 32 dogs received treatment with tasipimidine at 30 µg/kg bw, was somewhat limited for a confirmatory field study. However, significant differences between groups could be demonstrated in this study. Also, in this study, assessment of efficacy was initiated once a test dose confirmed that the dogs did not demonstrate a decreased functional alertness. Treatment was given to the dog at home as needed up to 3 times a day with a 3 hours' minimum interval for 5 weeks. Mean number of consecutive days of study treatment administration was 7 days (range 2–18 days). The primary efficacy variable was the owners' assessment of the effect of the treatment of acute anxiety related to owner departures. Secondary efficacy variable was a sum of score of the owner departure-related signs of acute anxiety. The first medicated departure of the day, starting from day 3, was assessed from the video recording for a minimum of 1 h. The mean duration of time during which the dogs were left alone was 4.1 h (min 0.9 h, max 9.5 h). The results of the primary variable were reported as difference in distribution of dogs in five different categories ranging

from excellent to worse (than previous experience). The dogs also wore an activity collar to collect data about their activity.

The recommendation of administering a test dose to assess the level of alertness following dosing is included in the product information, as appropriate.

A statistically significant treatment effect was observed favouring treatment over placebo (p = 0.0021). The owners rated the effect of the study treatment as positive more often for treatment with tasipimidine compared to placebo. As a supportive secondary analysis, a binary response analysis was performed to evaluate treatment effect (excellent or good effect vs. some effect, no effect or worse). The result supported the primary analysis (p = 0.0006). For the main secondary efficacy variable, the results demonstrated a reduction of the behavioural signs indicative for fear and anxiety as measured by the activity collar.

The results of this study showed acceptable effectiveness of tasipimidine administered at a dose of 30 µg/kg bw for the alleviation of anxiety related to owner departure in dogs.

The third dose confirmation study was a small (n = 19), cross-over study aimed to evaluate efficacy and safety of tasipimidine for alleviation of canine acute anxiety and fear associated with travel. Animals were included following completion of a confirmatory pre-screening questionnaire by the owner. The pre-screening questionnaire ensured that all animals demonstrated multiple signs considered related to fear and anxiety. In almost all animals, several signs were assessed as "difficult/during the whole travel time" (score 3; highest score). Following, the owners were trained and interviewed by the study personnel, further confirming the actual presence of fear on this additional car ride. In addition, presence of fear was confirmed by veterinarians on a taped short, standardized car ride, considered as a baseline. The "signs of fear" as assessed by the external observer (and by the owner), were selected based on public literature references.

In the actual study, two short (10 minutes) consecutive car-rides (one on placebo and one on tasipimidine) were compared in a randomised cross-over design. As this was a cross-over study, each dog served as its own control; the signs of anxiety assessed by the external expert were compared to the placebo period. A ten-minute drive to assess the overall behaviour of the animal is considered very short and potentially not fully representative for a longer trip. However, a prolonged car ride raised an ethical concern. From an ethical point of view, it was therefore considered appropriate to restrict the car ride. Also, validity and reliability of the primary outcome parameter, as well as the duration of car ride, were assessed in published studies conducted with another alpha-2 agonist (Amat et al. [proceedings, 2018]; Landsberg et al. [abstract, 2018]).

During both treatment periods, approximately 1 h before a car ride, the owner dosed the animal with a single oral dose of tasipimidine at 30 µg/kg bw or placebo. The primary efficacy outcome parameter was an external observer's assessment of signs of anxiety and fear. The external observer, blinded to the treatment, assessed the signs either by duration or by frequency, depending on the type of the behaviour. Signs based on duration and signs measured with frequency were analysed separately (as determined by a pre-defined ethogram). As a supportive analysis, a binary responder analysis was performed in which the dogs were dichotomised to responders, with total sum (duration or frequency) of signs reduced at least by 30% compared to placebo, and non-responders.

The secondary efficacy variables were the owner's assessment of the effect of the product during car travel, and an external observer's assessment of dog's body posture and dog's emotional state.

A statistically significant treatment effect was found both in duration (estimate -46.8 sec; SD 9.96; $p < 0.0001$) as well as frequency (ratio 0.59; SD 0.125; p = 0.0134). The binary responder analysis supported the primary analysis (p = 0.0031). In addition, also the main secondary efficacy variable, owner's assessment of the effect of the product, demonstrated a statistically significant (p = 0.0001)

favourable treatment effect. However, the CVMP was concerned that the indication "alleviation of situational anxiety and fear in dogs triggered by travel" was justified based only on this one study, SALCAR, that included only a very low number of animals (n = 19). In addition, the sequence effect that was observed affected the study results.

Even though a statistically significant difference in favour of the IVP was observed for the primary efficacy criterion, when clinical signs were analysed individually, panting was the only sign based on duration for which a statistically significant difference was obtained. When clinical signs were regarded based on frequency, a statistically significant effect was detected only when placebo was administered first, but not with the opposite sequence. Thus, the clinical relevance of the results obtained from this study was questioned. Taking into account this aspect, as well as the low number of animals included in this single study, the CVMP was of the opinion that this indication was not sufficiently supported and should be removed. In response to CVMP's concerns, the applicant agreed to omit the indication for the alleviation of situational anxiety and fear in dogs triggered by travel.

Overall conclusion on efficacy

Pharmacodynamics:

Tasipimidine is a new active substance. Assays based on the use of human receptors have been presented to support that tasipimidine is a potent, highly selective and specific alpha-2A agonist.

Pre-clinical data as well as public literature have been submitted to support an anxiolytic action of low doses of alpha-2 agonist substances. This effect has been suggested to be mediated by decreased release of excitatory neurotransmitters in the locus coeruleus. The anxiolytic effects of various other alpha-2 agonistic substances have been demonstrated in pre-clinical rodent models and in published clinical studies in dogs where dexmedetomidine and clonidine were used. The dossier does not contain any pre-clinical canine models of anxiety and fear in which proof of concept of the treatment with tasipimidine has been established. However, this is not considered pivotal for the evaluation of efficacy for the intended indication.

Pharmacokinetics:

The pharmacokinetic characteristics of tasipimidine are generally well documented and have been satisfactorily evaluated in the target species.

Tasipimidine is rapidly absorbed after oral administration in fasted state. The gastrointestinal absorption is moderate. The mean plasma C_{max} occurs at 0.5–1.5 hours after administration at the proposed label dose of 30 µg/kg bw of tasipimidine.

Tasipimidine is a highly distributed compound and is rapidly eliminated from the body. The half-life of elimination from circulation is approximately 1.7 hours. Tasipimidine is eliminated by hepatic metabolism and excretion. Excretion mainly occurs as unchanged in the urine.

Dose determination:

The goal of the target dose establishment was to utilise tasipimidine's anxiolytic, but not clinically sedating effect. No dose-titration studies for the anxiolytic *versus* sedative effects of tasipimidine in dogs were performed. The anxiolytic effect was however assessed in several clinical field studies, which is considered acceptable.

Pre-clinical studies indicated that a dose-dependent very mild to moderate sedation could be observed at doses between 10–100 µg/kg bw. Three dose determination and three dose confirmation studies performed under field conditions supported the desired anxiolytic effect at 30 µg/kg bw.

Tolerance:

Adverse events are primarily considered related to exaggerated alpha-2 pharmacological effects.

Target animal safety of tasipimidine was initially investigated in the pre-clinical studies that evaluated doses of 10 up to 300 µg/kg bw. The main adverse reactions seen in these experimental studies were dose-dependent sedation, emesis, decreased heart rate, and decreased body temperature.

In a TAS study, tasipimidine demonstrated acceptable tolerance in doses up to 5X the recommended dose, though adverse events (sedation-related effects such as lethargy) are very likely to occur, particularly in case the animal is calm and not fearful. Tasipimidine was less tolerated when dosed at 17X the proposed dose, and it was lethal when administered at 1 mg/kg bw dose, as demonstrated in a maximum tolerated dose study.

In the field studies, the most common adverse events in dogs treated with tasipimidine at the proposed label dose of 30 µg/kg bw were emesis, lethargy, ataxia, diarrhoea, somnolence and sedation. Signs were mild to moderate in severity and usually disappeared within 2-3 hours after administration. There were no serious adverse effects reported in any of the field studies. Functional alertness assessments demonstrated that, though treatment decreased functional alertness in some animals, the majority of the dogs were fully responsive and able to stand up and walk normally.

Overall, at the proposed dose of 30 µg/kg bw and in overdose up to 5X the recommended dose, safety profile was acceptable, especially since the product is indicated for short-term use in individuals of good systemic health only. Adverse events to be expected are sedation and other typical effects associated with the administration of an alpha-2 adrenoceptor agonist.

Efficacy:

At the proposed dose of 30 µg/kg bw, the results from four studies performed under field conditions showed that the product was considered efficacious by dog owners in alleviating anxiety and fear triggered by noise or owner departure in most dogs. The applicant was unable to demonstrate effectiveness when used for anxiety and fear in case of veterinary visits and travel indication was rejected due to the low sample size and questioning on the clinical relevance of the study results (sequence effect, reduction in the duration for only one clinical sign). The finally approved indication is "Short term alleviation of situational anxiety and fear in dogs triggered by noise or owner departure".

Part 5 – Benefit-risk assessment

Introduction

The product Tessie contains tasipimidine as active substance. The alpha-2A adrenoceptor agonist tasipimidine is considered a new active substance, as it is not authorised as a veterinary medicinal product in the Union. It inhibits noradrenergic transmission in central and peripheral sympathetic neurons and thereby leads, amongst general sympatholytic effects, to dose-dependent sedation and analgesia. At the time of submission of the application, Tessie was intended to alleviate situational anxiety and fear in dogs triggered by e.g. travel, noise, owner departure and veterinary visits. The proposed indication, however, was not considered fully justified, as the alleviation of anxiety and fear in dogs triggered by veterinary visits or travel was not considered supported by the data submitted.

The product is presented in a glass bottle as an oral solution for dogs containing 0.3 mg/ml tasipimidine.

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 the product is its efficacy in alleviating situational anxiety and fear in dogs triggered by noise or owner departure, which was investigated in four well-designed studies conducted in accordance with GCP standards under field conditions to an acceptable standard.

Additional benefits

The favourable oral bioavailability of tasipimidine allows its administration as an oral solution, which is easy to administer by the owner.

As demonstrated in human adrenoceptors, the product is a potent and selective alpha-2A adrenoceptor agonist. The product increases the range of available treatment possibilities for acute fear and anxiety in dogs.

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. The accuracy of the syringe is demonstrated only for doses of 0.2 ml and higher. Dogs requiring doses lower than 0.2 ml can therefore not be treated.

Safety:

Risks for the target animal:

The safety of Tessie has been investigated in healthy dogs when used up to five weeks, and according to the proposed dosing recommendations. Administration of the product in accordance with SPC recommendations allowed the observation of a number of common adverse reactions that usually are not long-lasting. Adverse events to be expected are sedation as well as other effects typically associated with the administration of an alpha-2 adrenoceptor agonist and are of non-serious nature. The most important expected adverse reactions are dose-dependent sedation and emesis. Accidental overdose up to 5X the proposed dose of 30 µg/kg bw may cause reversible physiological effects and clinical signs such as sedation, a decrease in heart rate and body temperature. A severe overdose can potentially be life-threatening. No data were submitted on reproductive toxicity in the target species and this is addressed in the product information.

The presented data sufficiently supports safety for the target animal for up to 9 consecutive days.

Risks for the user:

User safety risks have been identified, mainly associated with the exposure via dermal, oral and ocular contact. Exposure to tasipimidine may cause adverse effects such as sedation, respiratory depression, bradycardia and hypotension. This product may cause slight eye irritation. Also, this veterinary medicinal product may cause hypersensitivity (allergy).

Risk for the environment:

The product is not expected to pose a risk for the environment when used in accordance with 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 and the environment and to provide advice on how to prevent or reduce these risks.

User safety risks have been identified, mainly associated with exposure via dermal, oral and ocular routes. These risks are mitigated by the presentation of the product in a child-resistant packaging and user safety recommendations included in the SPC and other product information.

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the following indication:

"Alleviation of situational anxiety and fear in dogs triggered by e.g. travel, noise, owner departure, veterinary visits".

The product has been shown to be efficacious for the alleviation of anxiety and fear triggered by noise or owner departure, and the CVMP agrees to the following indication:

"Short term alleviation of situational anxiety and fear in dogs triggered by noise or owner departure".

Information on development, manufacture and control of the active substance and finished product has been presented and leads to the conclusion that the product should have a satisfactory performance in clinical use. It is well tolerated by the target animals and 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.

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

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 Tessie 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.