SCIENTIFIC DISCUSSION

1. SUMMARY OF THE DOSSIER

Cerenia is a veterinary medicinal product with anti-emetic effects for dogs. It is available as solution for injection or as tablets (in four different strengths).
The active substance of Cerenia is maropitant, a neurokinin-1 (NK_1) receptor antagonist, which acts in the central nervous system by inhibiting Substance P, the key neurotransmitter involved in vomiting. By inhibiting substance P, maropitant acts as an anti-emetic.

The approved indications for Cerenia tablets are:

- Prevention of vomiting including that induced by chemotherapy.
- Treatment of vomiting, in conjunction with Cerenia solution for injection and in combination with other supportive measures.
- Prevention of vomiting induced by motion sickness.

The approved indications for Cerenia solution for injection are:

- Prevention of vomiting except that induced by motion sickness.
- Treatment of vomiting in combination with other supportive measures.

The different indications for the tablets require different dosages.
The most common side effect seen after administration of the tablets at the higher dosage required to prevent motion sickness, is pre-travel vomiting.

Since vomiting can be associated with serious, severely debilitating conditions, good veterinary practice indicates that Cerenia should only be used in conjunction with other veterinary and supportive measures while addressing the underlying cause(s) of emesis.

2. QUALITY ASSESSMENT

Cerenia is licensed for use in dogs for the prevention or treatment of vomiting and is presented as a multi-dose solution for subcutaneous injection (10 mg/ml maropitant) and tablets of four different strengths (16, 24, 60 and 160 mg maropitant). Maropitant is a novel active substance in veterinary medicine. Details under each heading are given for the solution for injection followed by the tablets in each section.

Composition

Cerenia solution for injection contains 10 mg/ml maropitant (as maropitant citrate), sulphobutylether-beta(β)-cyclodextrin sodium (SBECD) and metacresol, made to 20 ml final volume with Water For Injections.

Maropitant citrate as the monohydrate has been formulated as 16 mg, 24 mg, 60 mg and 160 mg tablets, which have a break line to support dosages of 2 mg/kg and 8 mg/kg. Conventional pharmaceutical excipients for tablets are used and full details are included in the SPC. A tablet colorant is also included giving the tablets their pale orange colour.

Container

Cerenia solution for injection is presented as a multi-dose injection in a 20 ml amber Type I moulded glass vial, with a 20 mm rubber stopper and a 20 mm aluminium overseal with a polypropylene disk. The vials, stoppers and seals are all controlled by suitable in-house specifications. It was shown that the packaging integrity is maintained following multiple punctures of the stopper and throughout the shelf life of the product.

The tablets are packaged into cold formed aluminium foil blisters. The foil base is a combination of nylon, aluminium foil and PVC film. The backing is a combination of paper, polyester film, aluminium foil and a vinyl heat seal coating. Four blistered tablets are placed in each outer carton. All packaging components are suitable for pharmaceutical use and the packaging meets the requirements for Ph.Eur. 3.2.2 (Plastic containers and closures for pharmaceutical use).

Clinical Trial Formulae

Several injectable presentations and tablet presentations of maropitant, but mainly the final formulation, have been used in clinical trials and/or pharmacokinetic/target animal safety studies. Full details of the batches are provided in the dossier and any differences to the final formulation are considered as minor. Two blend strengths of 8% and 16% were used to manufacture tablets for some clinical trials using the same excipients as per the final formulation, however, only the 16% blend was used to produce tablets for final trials. Other changes, such as the tablet shape and presence of a break-line, embossing, were shown not to have an effect on the performance characteristics of the tablets. The final tablet formulation was used both for the final clinical trials and for the registration stability studies.

Development Pharmaceutics

The citrate salt of maropitant exists in different crystalline forms, including a hydrated form (the monohydrate, Form A), a methanol solvate, acetone solvates and acetone/water solvates. The monohydrate (Form A) was chosen as the commercial salt and was shown to be chemically and physically stable under all registration stability conditions.

Due to the low aqueous solubility of maropitant citrate, SBECD was selected as a solubilising agent . The antimicrobial preservative metacresol was selected because of its effectiveness against bacteria, yeasts and moulds; its acceptable injection site tolerance and the absence of mercury.

The vial and stopper were shown to be compatible with the drug product and no sorption of drug product components was observed. The container-closure integrity following needle puncture has been demonstrated. The choice of amber vials following photostability studies was justified.

Some losses of maropitant and metacresol, due to sorption to the filter membranes or silicon tubing used during drug product manufacture, were seen during development. Suitable filter membranes/tubing and appropriate flush volumes were identified, which when used during the solution manufacturing process, successfully overcame these losses.

Differences in particle size of the active for the tablet formulations were investigated and the specification set was justified. The formulation contains conventional excipients for tablets produced by dry granulation. The 16% common blend gives acceptable size tablets (1000 mg being the largest). Tablets are differentiated by their size and have embossed dose descriptors. Content uniformity data for halved tablets has been presented to show that these tablets break evenly along the break-line.

Critical process parameters were identified; blending time of excipients; lubrication time prior to, and post, roller compaction; operating parameters for the roller compaction and milling; minimum compression dwell times, and these were all optimised.

Foil/foil blister packaging was selected as the primary packaging in order to adequately protect the tablets from moisture uptake, which had been observed in less protective packaging.

Method of Manufacture

The manufacturing formulae for the proposed batch sizes were presented for both the solution for injection and for the tablet formulations.

Solution For Injection

Manufacture of Cerenia solution for injection utilises conventional pharmaceutical equipment and standard processing techniques and terminal sterilisation. The process is well described and controlled. There are no critical steps that require in-process controls for the solution. Development studies have confirmed good product chemical stability and microbiological quality over holding periods of up to 48 hours for the unfiltered solution, and for up to 6 days for a pre-filtered solution, prior to filtration and filling.

Satisfactory process validation data demonstrate the processes to be reliable and robust and a validation protocol for the initial commercial batches was presented for the Solution For Injection.

Tablets

Manufacture of the tablets is a typical dry granulation process involving conventional dilution, blending, screening, roller compaction, milling and compaction processes. Full details of the process are given. There are no critical steps requiring in-process controls, for either the manufacture of the tablet blend or tablet compression. Tablet appearance, average and individual tablet weight, thickness and hardness are routinely monitored during the compression process at regular intervals.

Batch analysis data for both the solution and tablets demonstrates that the respective manufacturing processes consistently produces product that meet the required specifications.

Satisfactory process validation data demonstrate the processes to be reliable and robust and a validation protocol for the initial commercial batches was presented for the tablets.

Control Of Starting Materials

Active substance

Maropitant citrate ($C_{32}H_{40}N_2O \cdot C_6H_8O_7 \cdot H_2O$) is not detailed in any pharmacopoeia and a detailed specification was provided including tests for appearance, identity (chiral), particle size, assay, impurities, total solvents and bacterial endotoxins.

The specification for maropitant citrate contains tests and limits satisfactory to control the active substance. Flow charts of each step of the synthesis of maropitant citrate are provided as well as detailed descriptions of the manufacturing processes including any reprocessing. Detailed specifications for all starting materials are provided. Satisfactory justification for each specification limit for starting materials and isolated intermediate is provided. Satisfactory description of methods and methods validation are presented.

Structural characterisation of maropitant citrate is provided (Mass Spectrometry, Infrared Spectroscopy, X-ray crystallographic studies and Nuclear Magnetic Resonance Spectroscopy) along with a detailed physico-chemical characterisation covering solubility, pKa, logP, logD, crystal properties, thermal analysis, moisture sorption/desorption and UV absorption has been performed. Characterisation, physical stability and preparation of the polymorphic forms identified during polymorph and solvate investigations are detailed. Maropitant citrate monohydrate (Form A) was selected because it is chemically stable, non-hygroscopic and can be reproducibly produced.

The impurities present (one specified at 0.5% level), all comply with VICH-CVMP guidelines for a new drug substance. All other non-recurring impurities are limited as individual unspecified impurities in maropitant citrate to a maximum of 0.2% each. Data provided for batches manufactured using the commercial process, was shown to be consistently within the specification limits.

Stability studies up to and including the 12 month time point demonstrate that maropitant citrate is photochemically stable and shows no degradation in the solid state when exposed to accelerated (40ºC/75% RH), intermediate (30ºC/60% RH), and long term (25ºC/60% RH) VICH storage conditions. Based on the results of these stability studies and additional stress testing, a re-test period for maropitant citrate of 24 months was agreed.

Excipients

Solution For Injection
Conventional pharmaceutical excipients are used and comply with the relevant Ph.Eur. monograph for all excipients listed in a pharmacopoeia. A specification for metacresol, which has been developed to capture all requirements of both the Ph.Eur. and USP monographs, was presented. Detailed specifications including microbiological tests and confirmation of the structure for sulphobutylether-β-cyclodextrin sodium (SBECD) a solubilising agent used in parenteral formulations was presented. The specification includes a limit of 1 ppm for the specified impurity. Certificates of analysis from the suppliers for metacresol and SBECD were provided.

Tablets
Microcrystalline Cellulose, Lactose Monohydrate (spray dried), Croscarmellose Sodium and Magnesium Stearate all comply with the appropriate current monographs of the Ph.Eur. Sunset Yellow FCF (E110, Aluminium Lake) complies with Council Directive 95/45/EC.

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

A declaration is provided stating that all the components used in the manufacture of Cerenia solution for injection and tablets comply with Directive 1999/104/EC and the current TSE guideline (EMEA/410/01 Rev. 2). Certificates from the suppliers of SBECD and metacresol are provided stating

that the materials are of synthetic origin and no product of animal origin has been used in the manufacture. Certificates from the suppliers of all the excipients are also presented.

Control tests on finished product

Solution For Injection
Specifications and details of routine tests for control of the Cerenia solution for injection finished product including appearance, identity of the active, SBECD and preservative, visible particles, content uniformity, pH, sterility, related substances and bacterial endotoxins were provided. Details of all test procedures (suitably validated) were provided. There is no requirement for a formal identity test for the SBECD excipient in the finished product specification although an assay method including an identity check was provided. The assay and identity of metacresol are confirmed by assay. Batch analysis data from batches manufactured with the commercial formulation are presented which support the validity of the manufacturing method and the robustness of the formulation.

Tablets
Release and shelf-life specifications for Cerenia tablets 16 mg, 24 mg, 60 mg and 160 mg include appearance, identity and assay of the active, identity of the colorant (non-routine), content uniformity, water content, related substances and dissolution time. Specification criteria, for individual degradants, of 0.5% at time of release and 1.0% at end of shelf life have been proposed in accordance with VICH GL11 and a limit for total degradation products of 1.0% at time of release and 2.0% at end of shelf life is considered justified. The absence of limits for tablet weight, thickness and hardness in the finished product specification was justified as these parameters are routinely monitored during compression and appropriate limits have been specified. Details of all test procedures suitable validated were provided. Identity testing of Sunset Yellow (E110) will be performed annually on batches selected at random and no identification tests for the remaining excipients are required. Batch analysis data demonstrate batch to batch consistency and that the specifications are met.

Stability Tests on the Finished Product

Solution For Injection
A detailed specification for the solution for Injection shelf life was agreed including tests for appearance, identity (active and preservative), visible particles, active substance, SBECD and preservative content, pH, degradation products, sterility, chiral purity and bacterial endotoxins. The shelf-life specification differs only from the release finished product specification in tests for preservative efficacy and chiral purity and in the limits applied for individual and total degradation products.

Stability programmes under the conditions outlined in VICH GL3 and GL5 were conducted and data following stability studies at 25°C/60% RH and 30°C/60% RH and at 40°C/75% RH are presented in the dossier. The batches demonstrate good stability at all the storage conditions evaluated and no significant degradation or trends were observed. The results from the VICH photostability guideline GL5, (UV and Fluorescence), demonstrate that the solution for injection is stable in the commercial (amber glass) vial and does not require additional protection from light. Vials from one batch were subjected to three temperature cycles (where a cycle consisted of storing the vials both upright and inverted at –20°C for 2 days then at 40°C for 2 days). The results demonstrate that the solution for injection is stable during short-term excursions of temperature.

In-use Stability Tests
In-use stability studies were performed according to guideline EMEA/CVMP/424/01. The results from the in-use studies for the solution for injection at the initial and 12 month stability time point support the maximum 28-day in-use period. A fragmentation study confirmed the acceptability of the stopper for this product.

Based on the presented data, a shelf life of 24 months was accepted for the solution for injection, with a standard maximum in-use period of 28 days.

Tablets

The shelf-life specification for the tablets differs from the release specification only in the limits for assay, individual and total degradation products. The tablet registration stability programme has been conducted in accordance with VICH guidelines GL3 and GL5. A justified bracketing strategy was applied as all tablet strengths are manufactured from a common blend.

Accelerated stability studies and long term and intermediate studies for the tablets have been provided. In addition, data from VICH photostability conditions are presented. Based on the data provided, a 24 month shelf life is justified. Stress testing results showed that very few degradation products were formed under these extreme thermal and oxidative conditions.

In-use Stability Tests

The stability of halved tablets over a two-day period was investigated. The design of the study and the parameters evaluated, showed that once halved, the half tablets are stable for at least 2 days.

Based on the presented data, a shelf life of 2 years was accepted for the tablets, with an in-use period of 2 days for halved tablets.

OVERALL CONCLUSION ON QUALITY

The data provided are satisfactory and adheres to current guidelines. The compositions of both formulations (solution for injection and tablets) are well described and the container/closure systems are suitable. Detailed information regarding the novel active substance maropitant and the formulations and packaging of lots used in specific clinical studies has also been provided, for both the parenteral product and the tablets. Both finished products are manufactured using conventional pharmaceutical equipment and standard processing techniques. There are no critical steps, which require in-process controls, so all the critical parameters are tested at the final product stage. Suitable control tests on the finished products are conducted using validated methods where appropriate. Batch data show that the finished product is within the specifications.

Satisfactory stability studies have been presented and both formulations demonstrated good stability. The shelf-life of 24 months for the solution for injection and an in-use shelf-life of 28 days are supported by data. The shelf-life for the tablets is 24 months and halved tablets were shown to be stable for at least 2 days.

3. SAFETY ASSESSMENT

PHARMACOKINETICS

Absorption

In dogs, maropitant is rapidly absorbed after both oral and subcutaneous administration with plasma concentration peaks (T_{max}) between 1 and 2 hours. Mean maximum plasma concentrations (C_{max}) were 81 ng/ml and 776 ng/ml (2 and 8 mg/kg, oral use) and 92 ng/ml (1 mg/kg, subcutaneous use).

Similar systemic exposure, terminal half lives and time to reach maximum plasma concentrations were observed in fed or fasted dogs following oral administration of maropitant at 2 mg/kg. It was therefore concluded that feeding does not affect the bioavailability of maropitant. However, the data showed large inter animal variations up to 70 CV% for AUC in animals kept under similar conditions (breed, age, bodyweight, health status, husbandry etc.), which was attributed to the saturable metabolism.

No clinically significant pharmacokinetic differences were observed between sexes.

Distribution

The volume of distribution at steady-state (Vss) determined after intravenous administration at 1-2 mg/kg ranged from approximately 4.4 to 7.0 l/kg. Penetration of maropitant into the CNS was demonstrated in gerbils. Subcutaneous administration of maropitant at 1 mg/kg resulted in behavioural changes (inhibition of tachykinin-induced foot tapping) two hours (100% inhibition) and 8 hours (50% inhibition) post dose. Mean brain-to-plasma ratios of maropitant were approximately 1.8, 1.5, and 3.6 at 2, 4, and 8 hours post dose, respectively.

Metabolism

The bioavailability of maropitant is 24% after administration of 2 mg/kg orally and 37% after 8 mg/kg orally, suggesting first pass metabolism, which becomes saturated at the high dose. AUC_{inf} was 561± 322 and 7840 ± 5600 ng.h/ml (mean ± SD) for the 2 and 8 mg/kg dose, respectively; indicating that the total body clearance is saturable. Following subcutaneous administration of 1 mg/kg, bioavailability is 91% with an AUC_{inf} of 860 ± 137 ng.h/ml, indicating that the relative bioavailability of the 1 mg/kg subcutaneous dose is about twice that of an 2 mg/kg oral dose. This was confirmed during dose confirmation studies in dogs, where a dosage of 1 mg maropitant/kg bodyweight administered subcutaneously corresponded to 2 mg/kg bodyweight orally administered.

When administered orally, the pharmacokinetics of maropitant was approximately linear in the dose range 20-50 mg/kg but non-linear in the dose range 2-16 mg/kg. Following repeated oral administration for five consecutive days at a daily dose of 2 mg/kg, accumulation was 151%. Following repeated oral administration for two consecutive days at a daily dose of 8 mg/kg, accumulation was 218%. The CVMP noted this considerable accumulation of maropitant after repeated oral administration; however, since tolerance in dogs had been confirmed in doses of up to 3 times the recommended dose of 8 mg/kg, for 3 times longer than the proposed maximum duration of treatment, this was considered acceptable. However, in view of the large interanimal pharmacokinetic variation and the occurrence of vomiting as a side effect more frequent at the 8 mg/kg dose, it was recommended that lower doses could be used for some individuals and in case of repeated administration.

Hepatic metabolism of maropitant involves two cytochrome P450 enzymes: CYP2D15, being a low capacity, high affinity system, and CYP3A12 with low affinity and high capacity. The non-linear kinetics observed at doses 2-16 mg/kg may be linked to saturation of the low capacity CYP2D15, with increasing involvement of CYP3A12 in metabolism with increasing doses.

Twenty-one metabolites were identified with the major (pharmacologically active) metabolite being CJ-18,518, a product of hydroxylation.

After repeated oral administration to mice, serum concentrations of the parent compound were on average, 6 times and 3 times greater than those measured for the metabolite in males and females, respectively. In rats, following repeated oral administration of 5 mg or 150 mg maropitant, plasma concentrations at 5 mg/kg/day were about 2 times higher for the main metabolite than the parent in both genders; however, in the 150 mg/kg/day group, AUC values for the metabolite were, on average, lower than those for the parent compound. In rabbits (150 mg/kg/day), exposure to the metabolite, as assessed by mean C_{max} and AUC values, was 1.6 times greater than that of the parent compound. In dogs, oral doses of 5 mg/kg/day resulted in metabolite plasma concentrations about 2 times greater than the parent compound, while a higher dose of 20 mg/kg/day resulted in C_{max} and AUC values 6 times greater for the parent compound.

Excretion

Maropitant is mainly eliminated through the liver. Urinary excretion of maropitant and its major metabolite is less than 1%.

No particular risk for hepatically impaired dogs was observed in clinical trials which included a small (3%) proportion of dogs with hepatic disease / neoplasia, or in the overdose studies. However, since maropitant is mainly eliminated through the liver, a warning to use the product with caution in patients with hepatic disease was included in the SPC and product literature.

TOXICOLOGICAL STUDIES

Single dose toxicity

Single dose toxicity was studied in mice and rats after oral and intravenous administration. The clinical signs in mice and rats were similar and independent from the route of administration and included decreased activity, irregular or laboured respiration, ataxia and tremors. Salivation, nasal discharge and “raspy” breathing were also noted in rats after oral dosing, while the excretion of reddish urine was observed in some mice and rats following intravenous administration. The no observed adverse effect level (NOAEL) after **oral** administration was 30 mg/kg and 100mg/kg for mice and rats, respectively. The NOEL after **intravenous** application was 6.5 mg/kg and 2.5 mg/kg for mice and rats, respectively.

Repeated dose toxicity

In **rats**, repeated oral doses of 5, 30 and 150 mg/kg over 93-days toxicity was investigated in a GLP compliant study.

At 30 and 150 mg/kg/day, effects included salivation and raspy breathing, decreased body weight gain , secondary microscopic pulmonary lesions and increased liver weights with correlating hepatocellular hypertrophy and induction of hepatic microsomal enzymes (150 mg/kg/day only). Changes to the upper respiratory tract were possibly initiated by topical irritant effects of orally administered maropitant. Changes in clinical pathology parameters were generally limited to the 150 mg/kg/day dose group and consisted of slightly elevated serum hepatic enzymes, alterations in serum lipids and proteins and slightly higher neutrophil counts when compared to controls. Adrenal weights were slightly higher at 150 mg/kg/day in females. No treatment-related changes in sperm count or motility were apparent. In general, serum exposure was generally higher in females than in males.

Another GLP compliant study was provided in **dogs** with repeated oral doses of 1, 5 and 20 mg/kg administered by oral gavage over 93-days.

Clinical signs were assessed daily, body weights were recorded once per week. Ophthalmoscopic and physical examinations were performed, and ECD, blood pressure measurements, haematology, serum chemistry and urinalysis parameters were monitored. Serum drug concentrations were also measured

on days 1, 31 and 92. At the conclusion of the dosing period, all dogs were necropsied. Selected organs were weighed and a comprehensive set of tissues was collected for microscopic examination.

No effects were noted in the group with dogs dosed with 1 or 5 mg maropitant/kg/day. In the 20 mg/kg/day, effects included emesis in two females on day 1, body weights losses of 8 - 15% when compared to those at start of study, ECG changes (slight increases in P-R interval, P wave duration and QRS amplitude were noted over the course of treatment), slightly lower serum albumin and slightly higher adrenal weights (females) at 20 mg/kg/day in both sexes. Serum drug exposure was supraproportional with increasing dose with no observed sex differences in exposure.

Based upon these data, a dose of 5 mg/kg bodyweight/day was identified as a "no observed adverse effect level" (NOAEL) in rats (oral) and dogs (oral).

Reproductive toxicity, including teratogenicity

The applicant provided the results of a non-GLP complaint study investigating the effects of oral doses of 15, 75 or 150 mg maropitant/kg/day in pregnant Sprague-Dawley rats over 12 days. No treatment related clinical signs or findings at necropsy were noted in any of the treated animals. No embryotoxic/foetotoxic effect of maropitant was observed at 15 mg/kg, but mean maternal body weights and food consumption were reduced at 75 and 150 mg/kg. However, due to the limited number of animals in this study, no definitive conclusion on embryo/foetotoxicity could be made.

The CVMP concluded, therefore, that the reproductive and embryo/foetal toxicity studies in laboratory animals were not conclusive. In the absence of any other data in the target species, the Committee concluded that Cerenia should only be used in pregnant or lactating bitches following a benefit/risk assessment by the responsible veterinarian.

Mutagenicity

The potential for maropitant to produce genetic injury was assessed in a series of GLP regulated genetic toxicity assays (bacterial reverse mutagenicity test, chromosomal effects in Human peripheral lymphocytes cells, gene mutation in Chinese hamster ovary (CHO) cells and Mouse Micronucleus Assays) using the methanesulphonate salt. All studies were according to VICH GL23 guidelines and no genotoxic activity was recorded in any of the assays.

Carcinogenicity

No carcinogenicity data were presented. However, *in vitro* and *in vivo* genotoxicity tests sufficiently demonstrated that maropitant is not genotoxic; therefore the lack of *in vivo* carcinogenicity studies was considered acceptable. The CVMP concluded that the use of maropitant would not be associated with an increased carcinogenic risk.

Metabolites

Twenty-one metabolites were identified. Oral toxicokinetic studies with the main metabolite were conducted in mice, rats, rabbits and dogs, indicating that the metabolite was well tolerated.

Excipients, impurities

All excipients used in the maropitant tablet formulation and most of the excipients used in the maropitant solution for injection formulation do not cause any human user safety concern or a concern for the target animal, the dog.

The solution for injection contains two substances, sulphobutylether-β-Cyclodextrin (SBECD) as excipient and its impurity 1,4-butane sultone, which are pharmacologically active. SBECD is an excipient used in two authorised human parenteral formulations. The CVMP assessed data submitted for these substances and concluded that the toxicological profiles of SBECD and the genotoxic

impurity 1,4-butane sultone were well characterised and that at the maximum clinical dose (for a 60 kg dog), accidental human exposure to SBECD or 1,4-butane sultone would not present an unacceptable risk.

Eye irritation

A single application of maropitant to the non-irrigated eye of one rabbit produced areas of opalescent cornea1 opacity, iridial inflammation, severe conjunctival irritation and sloughing of the cornea. White test material adhered to the corneal, nictitating and conjunctival membranes were also noted. The animal was killed for humane reasons five hours after treatment.

Maropitant was considered irritant according to EU labelling regulations Commission Directive 93/21/EEC. An appropriate warning has been included in the SPCs that if accidental eye exposure occurs, the user will be advised to flush the eyes immediately with water and to seek medical attention.

Dermal irritation / sensitisation

Acute dermal irritation studies in rabbits produced no evidence of skin irritation. The acute dermal toxicity of maropitant in rats produced no evidence of dermal toxicity.

A skin sensitisation study was performed to assess the contact sensitisation potential of maropitant in albino guinea pigs. Under the conditions of the test maropitant was classified as a non-sensitizer to guinea pig skin. However, in a local lymph node assay in the mouse, the highest concentration tested (10% w/v) was positive. Therefore, maropitant was considered to be a sensitizer.

USER SAFETY

Cerenia is available for use in dogs as tablets or solution for injection. Tablets are to be administered by veterinary professional or the animal owner once daily for up to 5 days. Possible human exposure is limited to dermal contact or accidental ingestion. The solution for injection is to be administered to individual dogs by a professional user (veterinarian, veterinary nurse) as a single subcutaneous injection using a needle and syringe. Possible human exposure is limited to accidental self-injection or dermal contact after accidental spillage at a single occasion.

Self-injection

In the case of accidental self-injection of 6 ml, the largest volume likely to be routinely administered (1 mg/10 kg bw for a 60 kg dog) would amount to 1 mg/kg bodyweight (assuming a 60 kg person). The maximum asymptomatic dose (NOAEL) following intravenous injection in male rats was considered 2.5 mg/kg, i.e. 2.5 times higher.

Therefore, the CVMP concluded that under normal operating conditions, accidental injection of the maximum dose of 6 ml would not be anticipated to represent a human safety risk. In addition, a professional operator would administer the subcutaneous formulation.

Accidental oral administration

Following oral administration of 100 mg of maropitant, mild adverse events such as nausea, dizziness and somnolence have been observed in adult humans. QTc-prolongation was observed at doses of 300 mg (about 4 mg/kg bodyweight) causing a mild QTc-prolongation of 20 milliseconds, which did not appear to increase with higher dosages.

Results from *in vitro* assays, *in vivo* QT studies in the dog and clinical data indicate that the mild degree of QT prolongation observed in humans is caused by the active metabolite, inhibiting hERG channels (i.e. a potassium ion channel). Blocking hERG channels can prolong the QT-interval and could lead to potentially fatal arrhythmias, including *Torsade de pointes.* However, inhibition by the

active metabolite was less than 10 %. The modest increase in the QT-interval combined with the lack of a dose-response suggest that Ca^{2+}-channel blocking properties of maropitant is counteracting the QTc-prolongation and preventing episodes of *Torsade de Pointes*.

If a 60 kg person were to accidentally ingest a single tablet of the largest strength (160 mg), he/she would be exposed to a dose of about 2.7 mg/kg, i.e. 11 times lower than the minimum asymptomatic dose of 30 mg/kg observed in single-dose oral studies in male mice. Accidental ingestion of a single 160 mg tablet would, therefore, not be expected to present a serious safety concern in adults, although some persons may experience nausea, dizziness and somnolence at this dose. However, ingestion of three 160 mg tablets (i.e. 480 mg, the maximum dose for a 60 kg dog at 8 mg/kg) could be expected to result in more severe adverse events.

In the scenario of a 15 kg toddler ingesting half a 160 mg tablet (i.e. 5.3 mg/kg), the exposure would be high enough to induce QTc-prolongation, however the increase could be regarded as modest and an increased dose would not increase the QT-interval further. The CVMP, therefore, concluded that accidental ingestion of half a 160 mg tablet of maropitant by a child would represent a low risk. In addition, the child proof packaging and warnings on the label and package leaflet would provide additional safety measures.

Dermal exposure

In the local lymph node assay, maropitant was considered to be a sensitizer. In the worse-case scenario of an operator's skin coming in contact with the maximum oral clinical dose of 480 mg for a 60 kg dog, the amount the operator would be exposed to (8 mg/kg for a 60 kg person) is 25 times lower than the dose, which was positive as a sensitizer in mice. In addition, the product literature includes user warnings, which should adequately control the minimum hazard, presented by handling the oral tablet formulation.

Conclusions on user safety

Accidental exposure of the human operator to the maximum clinical subcutaneous dose of 1 mg/kg by parenteral or dermal exposure and to the maximum clinical oral dose of 8 mg/kg by oral or dermal exposure in a worst-case scenario would not be anticipated to represent a human safety risk. In addition, the subcutaneous formulation will be administered by a professional user (veterinarian, veterinary nurse). Given the label/package leaflet instructions and the adequate safety margins for parenteral, oral and dermal exposures of humans to maropitant, the user should be adequately protected.

ECOTOXICITY

A phase I assessment was prepared in accordance with VICH Topic Guideline 06 on Environmental Impact Assessment (EIAs) for Veterinary Medicinal Products - Phase I (CVMP/VICH/592/98-Final). Maropitant citrate will only be used in non-food producing animals and so a Phase II assessment was not requested.

A summary of studies on the effects of maropitant on aquatic species was presented, demonstrating that maropitant is very toxic to aquatic organisms. The log $_{Kow}$ value of 7.75 indicated that maropitant has bioaccumulative potential. The biodegradation rate is not known, but an EPI-Win calculation predicts maropitant not to be readily biodegraded.

These properties make maropitant a potential persistent bioaccumulative and toxic (PBT) substance and environmental exposure should be avoided. However, due to the limited use of Cerenia in individual dogs, maropitant residues are not expected to released into the environment at levels expected to exert negative effects on non-target environmental species.

CONCLUSION ON SAFETY

In dogs, maropitant is rapidly absorbed after both oral and subcutaneous administration with plasma concentration peaks (T_{max}) between 1 and 2 hours. Plasma protein binding of maropitant is high. After repeated oral administration, considerable accumulation of maropitant was noted. In view of the large pharmacokinetic variation, lower doses than recommended might, therefore, be sufficient in some individuals when repeating the dose. Feeding status does not affect bioavailability. Maropitant is mainly eliminated through the liver, urinary excretion of maropitant and its major metabolite is less than 1%.

Single oral dose studies identified a no observed adverse effect level (NOAEL) of 30 mg/kg and 100mg/kg for mice and rats, respectively. Following intravenous application, the respective NOAEL was 6.5 mg/kg and 2.5 mg/kg for mice and rats. Repeated dose toxicity studies identified a NOAEL of 5 mg/kg/day in both rats and dogs.

Developmental toxicity studies revealed no embryotoxic/foetotoxic effect of maropitant at 15 mg/kg but mean maternal body weights and food consumption were reduced at 75 and 150 mg/kg. Due to the limited number of animals in this study no definitive conclusion on embryo/foetotoxicity can be made. No generational reproductive toxicity studies were presented. In the absence of any other data in the target species, Cerenia should only be used in pregnant or lactating bitches following a benefit/risk assessment by the responsible veterinarian.

No mutagenic activity was recorded in a series of *in vitro* and *in vivo* genetic toxicity assays according to VICH GL23 guidelines. No carcinogenicity data were presented.

Maropitant citrate was not a dermal irritant or skin sensitizer but did produce acute eye irritation and is considered to be a sensitizer in the local lymph node assay.

Accidental human exposure via parenteral, dermal or oral routes was not considered to represent a risk. In addition, the subcutaneous formulation will be administered by a professional user (veterinarian, veterinary nurse). Accidental ingestion of half a 160 mg tablet of maropitant by a child was assessed and considered to present a low risk. In addition, the child proof packaging and warnings on the label and package leaflet would provide additional safety measures.

Maropitant is very toxic to aquatic organisms and the $\log_{Kow}$ value of 7.75 indicates that maropitant has bioaccumulative potential. However, due to the use of Cerenia being limited to dogs, maropitant residues are unlikely to be released into the environment at levels expected to exert negative effects on non-target environmental species.

4. EFFICACY ASSESSMENT

Pharmacodynamics

Maropitant is a potent and selective neurokinin-1 (NK_1) receptor antagonist, which acts in a dose-dependant manner as an anti-emetic by inhibiting the binding of substance P, a neuropeptide of the tachykinin family in the CNS. Substance P is found in significant concentrations in the nuclei comprising the emetic centre and is considered the key neurotransmitter involved in vomiting. By inhibiting the binding of substance P within the emetic centre, maropitant is effective against neural and humoral (central and peripheral) causes of vomiting.

A variety of *in vitro* and *in vivo* studies demonstrated that maropitant binds selectively at the neurokinin-1 (NK_1) receptor using the following models with known NK_1 receptors, i.e. inhibition of substance P-induced phosphotidylinositol turnover, relaxation of dog carotid artery and tachykinin-induced contraction of guinea pig trachea.

Selective binding at the NK_1 receptor results in a dose-dependent functional antagonism of substance P activity as demonstrated in several animal models (gerbil foot tapping test; plasma extravasation in guinea pig skin or ureter).

The anti-emetic efficacy of maropitant against central and peripheral emetics including apomorphine, cisplatin and syrup of ipecac was demonstrated in a number of *in vivo* studies in dogs (see dose determination studies).

Intracellular levels of vincristine have been shown in other research to increase to toxic levels in the presence of verapamil (a Ca^{2+}-channel blocker). Maropitant is a potential anti-emetic for use in chemotherapy protocols with affinity towards ion channels, and vincristine is one of the most widely used drugs in canine chemotherapy. However, in view of possible interactions with vincristine, the Applicant explained that maropitant is only a weak Ca^{2+}-channel blocker (IC_{50} for calcium channels 110 nM) and therapeutic levels are considerably lower than those needed for ion-channel blockage. As more than 99% of the maropitant is protein bound in plasma, it seems unlikely that free plasma drug concentrations should reach the level for activity on the calcium channels. Furthermore, it was suggested that the reported vincristine-verapamil interaction may have more to do with competition for the P-gp transporter than ion-channel effects and there is no reason to believe that maropitant is a P-gp substrate (as evidenced by the good penetration of the blood-brain barrier).

The CVMP accepted these explanations and concluded that no further warning would be needed in the SPCs.

Tolerance in the target animal

Solution for injection:
The recommended dose for the solution for injection is 1 mg/kg bodyweight (0.1 ml/kg bodyweight), once daily for up to 5 days, subcutaneously.

The Applicant provided two GLP compliant studies, investigating the tolerance of 0, 1, 3 and 5 mg maropitant/kg bodyweight (i.e. up to 5 times the recommended dose) in young beagle dogs (aged about 2-4 months) administered once daily for 15 days, i.e. 3 times the recommended duration. Tests parameters included general health and clinical observations, body weight, feed intake, clinical assessment of the injection sites pre-and post-dosing, haematology and clinical chemistry analyses, faecal analysis, urine analysis. On Day 15, dogs were euthanased and subjected to necropsy and histopathological examination.

Study results demonstrated the safety in dogs at up to 5 times the recommended subcutaneous dose of 1 mg/kg for up to 3 times the recommended maximum duration of treatment.

In a few dogs (less than 2%) treated with maropitant solution for injection, in both laboratory and field studies responses at the time/site of injection (pain, head tilt, vocalisation, etc) were reported.
However, these numbers are lower than the incidence of injection reactions recorded for saline treated dogs (2.5%) and were attributed to reactions to the surroundings (e.g. stress at being in a veterinary practice), the mild pain as the needle is inserted or poor injection technique by inexperienced dispensers, all of which are not product-related.

An additional GCP-compliant study was provided demonstrating that accidental administration of maropitant intravenously at up to 2 mg/kg for two consecutive days is well tolerated in dogs.

Tablets:
The recommended daily dose for the tablet formulation is 8 mg/kg bodyweight once daily for up to 2 days for the prevention of motion sickness or 2 mg/kg bodyweight once daily for up to 5 days (treatment and prevention of vomiting other than prevention of motion sickness).

The Applicant provided four GLP studies conducted in 2000-2004, investigating the tolerance of up to 50 mg maropitant/kg bodyweight (i.e. approximately 6 times the maximum dose of 8 mg/kg) in dogs. Tablets were administered for up to 6 or 15 days (i.e. 3 times the recommended duration of the higher dose or 5 times the recommended duration of the lower dose). Some studies were not conducted in accordance with the Commission guideline "Evaluation of the safety of veterinary medicinal products for the target animals" and could only be considered as supportive. Tests parameters included general health and clinical observations, body weight, clinical pathology (blood, urine, faeces) and post-mortem gross and histopathological evaluation.

In general, maropitant tablets were well tolerated when administered for 6 days to dogs above 16 weeks of age at dosages up to 5 times the recommended dose of 2 mg/kg (for treatment and prevention of emesis other than motion sickness). Since no studies were undertaken in very young dogs, maropitant should only be used in dogs of less than 16 weeks following a benefit/risk assessment by the responsible veterinarian.

Administration of a higher oral doses of 24 mg/kg (i.e. three times the recommended dose of 8 mg/kg for prevention of motion sickness) for 6 days (3 times the recommended maximum duration of treatment of 2 days) resulted in decreased food intake and loss of body weight. Since these effects appeared reversible after cessation of treatment, it was concluded that they were not of concern.

A common side effect in the pre-clinical and clinical studies was **post-treatment vomiting,** noted at a dosage of 8 mg/kg of maropitant (vomiting post-treatment was also seen at 2 mg/kg but at a frequency similar to that seen in dogs dosed with placebo tablets). In most cases a single, isolated emetic event was observed within 2 hours of dosing and the animals were otherwise healthy. None of the dogs required any therapy. The CVMP noted that the incidence of emesis was reduced in dogs that were relaxed and fed a small amount of food at least 1 hour prior to treatment. In addition, an additional study was provided demonstrating that feeding the dogs a small meal or snack one hour before tablet administration significantly reduced this post-dose emesis. It was, therefore, concluded to include "vomiting" as a common side effect at 8 mg/kg in the SPC and product literature together with a recommendation to feed the dog prior to treatment and to avoid prolonged fasting before administration.

ECG monitoring was not routinely performed in the tolerance studies. However, one study indicated minor decreases in heart rate and increased QT_c intervals in dogs treated with 20 mg/kg/day or more for seven days. Since similar effects had also been reported in human trials, the Applicant therefore provided a specific study on the **cardiac safety** in dogs investigating electrocardiographic parameters in conscious, unrestrained radiotelemetry-implanted adult beagle dogs; following single dose exposure to maropitant at doses of 0, 8, and 24 mg/kg. Statistically significant differences in P-wave and QRS duration, prolongation of PR and QT_c-intervals were observed at both 8 and 24 mg/kg. However, the changes recorded were small and not considered to be toxicologically or clinically significant. All observed changes in QT_c-interval were less than 10 %.

The Applicant also provided results from *in vitro* assays, *in vivo* QT studies in the dog and clinical data indicating that the mild degree of QT prolongation observed in humans is caused by the active metabolite, CJ-18,518 inhibiting hERG channels (i.e. a potassium ion channel). Blocking hERG channels can prolong the QT interval and could lead to potentially fatal arrhythmias, including *Torsade de pointes.* However, inhibition by the active metabolite, CJ-18,518 was less than 10 %.

The CVMP, therefore, concluded that the risk of cardiac related adverse reactions is unlikely to be of clinical significance in healthy dogs. However, a warning to use caution when treating dogs with manifest cardiac dysfunction or known genetic predisposition for cardiac diseases was included in the SPCs and product literature.

In some supportive studies performed in young dogs (about 8 weeks), pathological changes in **bone marrow** were noted. However, such pathological changes can be caused by a combination of factors, particularly in young animals and these studies were not conducted in healthy and sufficiently acclimatised animals, but in very young dogs affected by other factors (parvoviral infection, coccidiosis, ongoing acclimatisation). Other tolerance studies in older dogs (16 weeks) did not indicate any bone marrow changes. The CVMP, therefore, concluded that maropitant would not have immuno-suppressive effects especially since the product is not authorised for use in dogs less than 16 weeks of age.

Dose determination and confirmation

Cerenia is indicated for

- The prevention and treatment of emesis including that induced by chemotherapy (except motion sickness) at a dosage of 1 mg/kg (subcutaneous injection) or 2 mg/kg (oral tablets) for up to 5 days.
- The prevention of vomiting induced by motion sickness at a dosage of 8 mg/kg (oral tablets) for up to 2 days

Prevention and treatment of emesis (except motion sickness)

The Applicant provided a number of laboratory studies to demonstrate the efficacy of maropitant administered subcutaneously or orally in the prevention and treatment of emesis in dogs. Most of the studies were in compliance with GCP and conducted between 2001 – 2003, using three different emetics (apomorphine, syrup of Ipecac and cisplatin) with different modes of action (central, peripheral, mixed).

In the pivotal, GCP-compliant dose **determination study**, beagle dogs between 9 months and 3 years of age received a single **oral dose** of maropitant (1, 2 or 3 mg/kg bodyweight) to **prevent emesis** induced by cisplatin. Maropitant was administered 19 hours prior to the administration of the emetogen, which would have normally resulted in severe vomiting from 20 to 24 hours post-treatment. The results showed that doses of 2 and 3 mg/kg maropitant were statistically more effective in controlling vomiting (1 – 5 hours after administering the emetogen) than 1 mg/kg. Since no further effect was gained from a dose of 3 mg/kg as compared to 2 mg/kg, it was concluded that a dose of 2 mg/kg bodyweight would be effective in the prevention of emesis.
Preliminary work in a pilot dose selection study with a very similar design was predictive of a similar result not only for cisplatin but also for apomorphine. The cisplatin model was selected for the final dose selection as it was shown to be the most robust and reliable model for emesis.

In a pivotal **dose confirmation study** for the **treatment of emesis**, nausea and vomiting was induced by cisplatin in beagle dogs, aged more than 7 months. A single **subcutaneous** dosage of either 1 mg maropitant/kg bodyweight or a placebo was administered after the first cisplatin-induced emetic event was experienced by the animal. The results showed that maropitant administered at 1 mg/kg subcutaneously was rapidly effective in the treatment of cisplatin-induced emesis (after 30 min).

A series of **dose confirmation studies** demonstrating the **prevention of emesis** investigated the anti-emetic effect of a single dose of either 2 mg/kg maropitant administered orally or 1 mg/kg

administered subcutaneously to dogs (2 – 8 years) approximately one hour prior to the administration of syrup of Ipecac or apomorphine. The results showed that maropitant was effective in reducing apomorphine or syrup of Ipecac-induced emesis in dogs when administered 1 hour before emetic challenge.

The CVMP concluded that the laboratory data (supported by clinical data) demonstrated the anti-emetic efficacy of maropitant (subcutaneously at 1 mg/kg or orally at 2 mg/kg) when used in the prevention and treatment of emesis other than that caused by motion sickness. Cerenia has also been demonstrated to be effective in preventing emesis induced by chemotherapeutic agents. To maximise its effectiveness in these situations, it is recommended to administer, Cerenia prior to administration of the chemotherapeutic agent.

Prevention of motion sickness

The Applicant provided one study demonstrating the efficacy of 2 mg/kg maropitant (oral) in the prevention of vomiting and nausea (motion sickness) caused by transportation. However, this study was performed with young motion-naïve laboratory dogs. Efficacy in this study was considerably better than that achieved in subsequent field studies, which were performed using dogs with a history of motion sickness.

The CVMP noted these complex factors and the absence of a reliable laboratory model for canine motion sickness. The Committee, therefore, concluded to base the effective dose for prevention of motion sickness on the results of field studies rather than on a classical dose-titration study.

FIELD TRIALS

Prevention and treatment of emesis (except motion sickness)

Solution for injection
The Applicant provided two European randomised, multi-centre, GCP-compliant field studies from 2002- 2004 demonstrating the efficacy of 1 mg/kg bw maropitant **subcutaneously** in the treatment of emesis in dogs presented in veterinary clinics in Europe (Italy, France, UK, Slovakia). The most frequently diagnosed cause of vomiting was gastritis followed by gastroenteritis and dietary indiscretion' although other non-gastrointestinal diagnosis were made (urogenital, hepatic, endocrine, pancreatic and viral diseases among them)..

The dogs were from various breeds and different age groups (2 months to 17 years) and were either treated with 1 mg/kg maropitant administered subcutaneously once daily for up to five days or with an authorised positive control (metoclopramide). Some animals also received concomitant medications, however, treatment with other anti-emetics immediately prior to or during the studies was an exclusion criteria. End-points were the number of animals vomiting and the total number of emetic events per dog during the first 24 hours of treatment. Pregnant or lactating animals were not included in the studies. In both studies, maropitant treated dogs vomited significantly less than metoclopramide treated dogs.

The results demonstrated that maropitant is effective in the treatment of ongoing emesis when administered subcutaneously at 1 mg/kg daily to a representative population of canine patients with emesis.

A third study conducted in the USA was also submitted demonstrating the efficacy of the injectable formulation as an initial dose with injectable or oral as follow-up therapy thereafter, for up to a total period of 5 days.

Tablets

The Applicant provided a GCP-compliant, placebo-controlled study involving dogs from 29 US veterinary hospitals with a history of recent emesis. The most frequent diagnoses in both treatment groups were parvoviral enteritis, gastroenteritis and acute pancreatitis. Animals were treated with maropitant once daily for up to 5 days **subcutaneously**. Initial treatment was with the injectable formulation (1mg/kg sc) with follow up therapy delivered using either the injectable (1mg/kg **subcutaneously**) or the oral tablets (2 mg/kg oral) at the discretion of the examining veterinarian. The results demonstrated that maropitant is effective in the treatment of ongoing emesis when administered subcutaneously at 1 mg/kg or orally at 2 mg/kg daily to a representative population of canine patients with emesis.

The CVMP considered that 2 mg/kg of maropitant administered as oral tablets provides similar exposure to that provided by 1 mg/kg administered by subcutaneous injection, leading to equivalent efficacy. The injectable formulation of maropitant is effective approximately 30 minutes after administration and the oral tablets within one hour of ingestion. Both are effective for up to 24 hours after administration.

The Committee expressed concerns that animals with ongoing emesis might vomit up **tablets** before the onset of efficacy, if dosed orally. Use of Cerenia tablets is therefore only recommended for the **prevention of emesis** or as a **follow-up treatment** following subcutaneous administration of Cerenia solution for injection. The sequential use of the two formulations to treat the vomiting patient was demonstrated in the field.

The CVMP noted that vomiting due to gastrointestinal disturbances and not related to foreign bodies, often ceases once food is withdrawn and intravenous fluid supplementation is given. For the **treatment of emesis,** Cerenia (tablets or solution for injection) should therefore only be used in combination with other supportive measures such as fasting, dietary regimen or rehydration whilst addressing the underlying causes of the vomiting. A warning that vomiting can be associated with serious, severely debilitating conditions including gastrointestinal obstructions; requiring appropriate diagnostic evaluations is also provided in the SPC's.

During clinical trials, only a small proportion of patients required four to **five days** of treatment to adequately control their emesis. The CVMP considered that the dogs used in the clinical studies were reflective of the typical the patient population presented to a veterinarian. Since the target animal safety studies demonstrated the tolerance of repeated administration, the Committee agreed on a maximum duration of 5 days for the treatment and prevention of emesis other than motion sickness at a dose of 1mg/kg (s.c.) or 2 mg/kg (oral).

No major adverse effects have been observed at the relevant doses. However, as the pharmacokinetic variation is large and maropitant accumulates after once daily repeated administration, dose dependent side effects might occur in individual dogs. An appropriate recommendation was, therefore, included in section 4.9 (amounts to be administered) of the SPC that **lower doses** than the recommended one might be sufficient in some individuals and when repeating the dose.

Emesis induced by chemotherapy (cisplatin)

The Applicant provided two GCP-compliant studies demonstrating the efficacy of maropitant (subcutaneously or orally) in the prevention of cisplatin-induced emesis in canine cancer patients.

A multicentre GCP compliant study performed in 2003/4 in the USA was presented, comparing the efficacy of 1 mg/kg maropitant subcutaneously with a negative (placebo) control in the prevention and control of cisplatin-induced emesis in canine cancer patients**.** In this study, maropitant effectively prevented cisplatin-induced emesis when given 1 hour before cisplatin administration. However, it was much less effective when given after cisplatin treatment, i.e. after the first emetic event had occurred.

In another randomised multi-centre GCP compliant study performed in 2002/3 in the USA, canine cancer patients received either 2 mg/kg maropitant (tablets) or a negative (placebo) control approximately 1 hour before cisplatin infusion. Following cisplatin-therapy, dogs were observed continuously for 4 hours for emetic events, more than 4 emetic events were considered as treatment failure. No significant adverse effects associated with maropitant-treatment were observed. The results indicated that a single preventive oral treatment of maropitant (2 mg/kg) was effective in significantly reducing the number of emetic events following cisplatin therapy in dogs.

The CVMP concluded that maropitant (1 mg/kg subcutaneously or 2 mg/kg, oral) is effective in the prevention and treatment of emesis induced by chemotherapy. However, it was stressed that good veterinary practice would suggest administering Cerenia prior to the chemotherapeutic agent in situations where emesis would otherwise be expected.

Motion sickness:

The Applicant provided five GCP-compliant, placebo-controlled multi-centre studies conducted in Europe (France, Italy, UK) and USA investigating the efficacy of an oral dose of 8 mg maropitant/kg bodyweight on one or on two consecutive days in dogs with a history of travel-induced emesis. No motion sickness studies were undertaken with the solution for injection as the Applicant did not wish to pursue a motion sickness claim for this pharmaceutical form as it is not considered practical for this indication.

The studies involved a sufficient number of dogs of various breeds and ages. Pregnant and lactating bitches were excluded from the studies. Maropitant was administered as a single dose 1 to 10 hours before a car journey lasting from 30 minutes to several hours.

The results demonstrated that Cerenia tablets significantly reduced the occurrence of emesis during car transportation in dogs with a history of motion sickness at the proposed oral dosage of 8 mg/kg. The occurrence of emesis during transportation was reduced from a mean of 58.8% in placebo-treated dogs to a mean of 11.3% in maropitant-treated dogs. This represents a reduction of 5.2 fold in the likelihood of vomiting in dogs predisposed to motion sickness.

The **choice of a dose** level of 8 mg/kg for prevention of emesis caused by motion sickness was founded on safety data and the results from the field trials not on traditional dose-titration studies as the laboratory model of motion sickness using motion naïve pups (2 mg/kg) was not predictive of field efficacy. Target animal safety data indicated that 8 mg/kg was the highest nominal dose which could be safely supported.

During the studies, a limited number of short-lasting and self-limiting **adverse events** were recorded, the most frequent being pre-journey (post-dose) emesis (not connected to the journey), decreased activity levels and lethargy. The observed frequencies of adverse effects in the field studies were 6-10%.
In a single laboratory study specifically designed to investigate post-dose emesis, 49% of fasted (for 24 hours) dogs treated orally with maropitant 8 mg/kg had a least one episode of vomiting on one of the two occasions they were treated. Only 15.6% of dogs showed post-dose emesis on both occasions that they were treated. In this same study feeding a small meal or snack significantly reduced post-dose emesis (5.8% of dogs vomited)

The Committee noted that the frequency of pre-journey emesis was reduced in dogs that had been fed a small amount of food before administration of the tablets and that dogs dosed on an empty stomach (e.g. prolonged fasting of 24 hours) may occasionally vomit. The CVMP concluded that such adverse reactions might be reduced when dogs are relaxed and fed a small amount of food at least an hour before administration of the tablets. An appropriate recommendation was, therefore, made in the SPC.

The finding of undissolved tablets in the vomit of two dogs, that were administered maropitant tablets embedded in snacks led to another recommendation in the SPC, that to ensure optimum efficacy in the

prevention of motion sickness, tablets should not be administered wrapped or embedded in food/snacks as this may delay dissolution and consequently onset of efficacy.

Conclusions

Maropitant is a potent and selective neurokinin-1 (NK_1) receptor antagonist, which acts in a dose-dependant manner as an anti-emetic by inhibiting the binding of substance P, a neuropeptide of the tachykinin family in the CNS. Substance P is found in significant concentrations in the nuclei comprising the emetic centre and is considered the key neurotransmitter involved in vomiting. By inhibiting the binding of substance P within the emetic centre, maropitant is effective against neural and humoral (central and peripheral) causes of vomiting.

Maropitant injected subcutaneously is generally well tolerated when administered daily to dogs older than 16 weeks of age at dosages up to 5 mg/kg (5 times the recommended dose of 1 mg/kg) for 15 days (3 times the recommended maximum duration of treatment of 5 days). Some animals showed mild reactions at the injection sites; however, these were no more frequent than those seen in the saline placebo group and not considered of clinical concern.

Maropitant tablets were well tolerated when administered for 5 days to dogs older than 16 weeks at dosages up to 10 mg/kg (5 times the recommended dose of 2 mg/kg). Administration of higher oral doses of 24 mg/kg (i.e. three times the recommended dose of 8 mg/kg for prevention of motion sickness) for 6 days (3 times the recommended maximum duration of treatment of 2 days) resulted in decreased feed intake and body weight loss. These effects were spontaneously reversible after cessation of treatment.

Since no studies were undertaken in very young dogs, a recommendation is made in the SPC and product literature to use maropitant in dogs of less than 16 weeks of age only following a benefit/risk assessment by the responsible veterinarian.

A common side effect in the field studies following the administration of 8 mg/kg of maropitant was post-treatment (but pre-travelling) vomiting. The incidence of emesis was reduced in dogs that were relaxed and fed at least 1 hour prior to treatment and appropriate information has been included in the SPC and product literature.

A study investigating electrocardiographic parameters was performed in beagle dogs following single oral administration of maropitant at dosages of 0, 8, and 24 mg/kg. Statistical significant differences in P-wave and QRS duration, prolongation of PR and QT_c intervals were observed at both 8 and 24 mg/kg. However, the recorded changes were small and not considered to be clinically significant. All observed changes in QT_c interval were less than 10 %.

Laboratory studies using three different emetics (apomorphine, syrup of Ipecac and cisplatin) with different modes of action (central, peripheral, mixed) demonstrated efficacy of maropitant in the prevention and treatment of emesis in dogs. The clinical data demonstrated the anti-emetic efficacy of maropitant administered as a subcutaneous injection at 1 mg/kg or orally at 2 mg/kg when used in the prevention and treatment of emesis other than that caused by motion sickness (e.g. gastrointestinal, hepatic, endocrine, renal, pancreatic disorders and viral infestations, among others). For optimal efficacy against chemotherapy induced vomiting it is good clinical practice to administer the antiemetic prior to the chemotherapeutic agent. No major adverse effects have been observed at the relevant doses. In one field study, the combination of subcutaneous and oral administration was safely used.

Maropitant has been shown to significantly reduce the occurrence of emesis during car transportation in dogs with a history of motion sickness at the proposed oral dosage of 8 mg/kg. The occurrence of emesis during transportation was reduced from 52-68% in placebo-treated dogs with a history of motion sickness, to 7-16% in maropitant-treated dogs. The choice of 8 mg/kg as the dosage level for prevention of emesis caused by motion sickness was not founded on traditional dose-titration studies

as the laboratory model of motion sickness was not predictive of field efficacy. Instead, based on safety data a dose of 8 mg/kg was used in the field trials for efficacy testing.

During the field studies of motion sickness a limited number of adverse events were recorded, the most frequent being pre-journey emesis, decreased activity levels and lethargy. The observed frequencies of adverse effects in the field studies was 6-10%. In a single laboratory study investigating the effect of feeding status on post-dose emesis, approximately 50% of fasted (for 24 hours) dogs treated orally with maropitant (8 mg/kg) vomited following administration. Feeding the dogs an hour before dosing reduced the frequency of post-dosing emesis to 5.8% and an appropriate recommendation was therefore included in the SPC and product literature.

The finding of undissolved tablets in the vomit from two dogs experiencing motion sickness, that were administered maropitant tablets embedded in snacks leads to a recommendation in the SPC, that to ensure optimum efficacy in the prevention of motion sickness, tablets should not be administered wrapped or embedded in food/snacks, as this may delay dissolution.

Data on the duration of efficacy is sparse. The onset of efficacy is confirmed to be fast (maropitant is active from 30 minutes post-treatment) for the injectable formulation, which would be the right choice for treatment of a dog showing ongoing emesis. However, the duration end of the efficacy period of Cerenia was found to be at least 24 hours but it could be considerably longer. The recommendation to treat daily for up to 2 days (8 mg/kg orally) or 5 days (2 mg/kg orally or 1 mg/kg subcutaneously) is based on tolerance data only. However, there is no reason to suspect reduced efficacy after repeated administration. Information about the possibility to reduce the doses is given in the SPC, as dose dependent side effects exist and accumulation is substantial,

5. RISK BENEFIT ASSESSMENT

The quality aspects of the product have been well documented and comply with current guidelines. The novel active substance (maropitant citrate) and both finished product types (tablets and solution for injection) are manufactured and controlled in the appropriate manner, in compliance with current EU and VICH guidelines. Detailed specifications for the novel excipient sulphobutylether-β-cyclodextrin sodium (SBECD) a solubilising agent, in veterinary medicine, have been provided. Satisfactory information has been provided to demonstrate that the manufacture and control processes for both the solution for injection and tablets routinely and consistently generate product of uniform quality.

The starting materials of animal origin used in the production of both of the final products have all been declared in compliance with the current regulatory texts related to the TSE Note for Guidance (EMEA/410/01-Rev.2) and Council Directive 2001/82/EC, as amended.

Pharmacokinetic/pharmacodynamic data demonstrated that 2 mg/kg of maropitant administered as oral tablets provides similar exposure to that provided by 1 mg/kg administered by subcutaneous injection, leading to equivalent efficacy. The injectable formulation of maropitant is effective approximately 30 minutes after administration and the oral tablets within one hour of ingestion. Both are effective for up to 24 hours after administration. Plasma protein binding of maropitant is high in dogs (>99%), which might lead to interactions with other highly bound products. This has been adequately addressed in the SPC. Maropitant is metabolised in the liver and, although no clinical signs have been reported in any of the laboratory or clinical studies, it is recommended that the product should be used with caution in dogs with hepatic disease.

No reproduction studies were provided in dogs; though maternal body weights were reduced in rats receiving high oral doses (75 mg/kg) of maropitant. However, due to the limited number of animals in this study, no definitive conclusion on embryo/foetotoxicity could be made. The CVMP concluded, therefore, that the reproductive and embryo/foetal toxicity studies in laboratory animals were not conclusive and that Cerenia should only be used in pregnant or lactating bitches following a benefit/risk assessment by the responsible veterinarian. An appropriate recommendation was introduced in the SPC and product literature.

Accidental exposure of the human operator via parenteral, dermal or oral routes does not represent a human safety risk. However, maropitant produced acute eye irritation and a warning has therefore been introduced into the product literature of the solution for injection.

Maropitant is very toxic to aquatic organisms and has bioaccumulative potential. However, due to the limited use of Cerenia in dogs, maropitant residues are unlikely to be released into the environment at levels of concern and the Committee therefore concluded that no additional warning is necessary.

Maropitant is a selective neurokinin-1 receptor antagonist, which acts in the CNS by inhibiting the binding of substance P, the key neurotransmitter involved in vomiting. By inhibiting substance P within the emetic centre, maropitant is effective against neural and humoral (central and peripheral) causes of vomiting. Laboratory studies using three different emetics (apomorphine, syrup of Ipecac and cisplatin) with different modes of action (central, peripheral, mixed) demonstrated the efficacy of maropitant in the prevention and treatment of emesis in dogs.

Maropitant and its active metabolite have affinity to Ca- and K-ion channels. Small increases in the QT interval of the electrocardiogram were reported in humans and observed in healthy beagle dogs administered 8 mg/kg, but these increases were small and were not considered of clinical relevance. Also, no clinical signs concerning cardiac effects were observed in any laboratory or field study. However, a warning has been included in the product literature to use Cerenia with caution in dogs suffering from or with predisposition for cardiac diseases.

Cerenia was generally well tolerated when administered daily at dosages up to 5 times the recommended doses for an extended period of time (up to 3 times the recommended maximum duration of treatment). However, a common side effect following the administration of 8 mg/kg of maropitant was post-treatment vomiting. The incidence of emesis is reduced in dogs that are relaxed and fed a light meal prior to administration of the medicine. An appropriate recommendation has been included in the SPC and product literature. A limited number of other adverse events were recorded when the product was used for the prevention of motion sickness; the most frequent were decreased activity levels and lethargy.

The Applicant provided a number of clinical studies conducted in Europe and USA demonstrating the efficacy of maropitant as subcutaneous injection at 1 mg/kg or tablets at 2 mg/kg when used in the prevention and treatment of emesis other than that caused by motion sickness. However, it was noted that animals with ongoing emesis might not retain the tablets until the onset of the effect. Use of Cerenia tablets for treatment is therefore only recommended following an initial treatment with the solution for injection. When used to prevent emesis associated with chemotherapy, it is recommended to administer the product prior to the chemotherapeutic agent.

The CVMP stressed that especially in the treatment of emesis due to gastrointestinal disturbances, Cerenia should only be used in conjunction with other supportive measure such as fasting or rehydration therapy while addressing the underlying causes of the vomiting. Appropriate recommendations have, therefore, been introduced into the SPC and product literature.

Accurate dosing of small dogs (less than 3 kg bodyweight) in the lower oral dose of 2 mg/kg bodyweight is not possible. Since no studies were undertaken in very young dogs, maropitant should only be used in dogs less than 16 weeks of age following a benefit/risk assessment by the responsible veterinarian.

At an oral dosage of 8 mg/kg, maropitant has been shown to significantly reduce the occurrence of emesis during car transportation in dogs with a history of motion sickness. The finding of undissolved tablets in the vomit from two dogs experiencing motion sickness, that were administered maropitant tablets embedded in snacks leads to a recommendation in the SPC, that to ensure optimum efficacy in the prevention of motion sickness, tablets should not be administered wrapped or embedded in food/snacks as this may delay dissolution.

Based on the original and complementary data presented, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the quality, safety and efficacy of Cerenia were considered to be in accordance with the requirements of Council Directive 2004/28/EC, as amended.