EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines and product data management

CVMP type II variation assessment report
Cerenia (EMEA/V/C/0106/II/0013)

International non-proprietary name: Maropitant

Scope: C.I.6.a) Addition of a new target species (cats)

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

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1. Background information on the variation

1.1. Submission of the variation application

In accordance with Article 16 of Commission Regulation (EC) No. 1234/2008, the marketing authorisation holder, Pfizer Limited, submitted to the European Medicines Agency (the Agency) on 9 June 2011 an application for a type II variation for Cerenia.

1.1.1. Scope of the variation

Current	CVMP recommendation
SPC: 1. Name of the veterinary medicinal product Cerenia 10 mg/ml solution for injection for dogs.	SPC: 1. Name of the veterinary medicinal product Cerenia 10 mg/ml solution for injection for dogs **and cats**
4.1 Target species Dogs	4.1 Target species Dogs, **Cats**
4.2 Indications for use, specifying the target species Dogs • […]	4.2 Indications for use, specifying the target species Dogs • […] **Cats** • **For the prevention of vomiting and the reduction of nausea, except that induced by motion sickness.** • **For the treatment of vomiting, in combination with other supportive measures.**
4.4 Special warnings Dogs […]	4.4 Special warnings Dogs […] **Cats** **The efficacy of Cerenia in reduction of nausea was demonstrated in studies using a model (xylazine-induced nausea).**

Current	CVMP recommendation
4.5 Special precautions for use Special precautions for use in animals The safety of the veterinary medicinal product has not been established in dogs less than 8 weeks of age and in pregnant or lactating bitches. Use only according to the benefit/risk assessment by the responsible veterinarian. […]	4.5 Special precautions for use Special precautions for use in animals The safety of the veterinary medicinal product has not been established in dogs less than 8 weeks of age, **or in cats less than 16 weeks of age,** and in pregnant or lactating ~~bitches~~ **dogs and cats.** Use only according to the benefit/risk assessment by the responsible veterinarian. **Injecting the product at refrigerated temperature may reduce pain at injection.** […] **Due to the frequent occurrence of transient pain during the injection, appropriate animal restraining measures may have to be applied.**
4.6 Adverse reactions (frequency and seriousness) Pain at injection site may occur. […]	4.6 Adverse reactions (frequency and seriousness) Pain at injection site may occur. **In cats, moderate to severe response to injection is very commonly observed (in approximately one third of cats).** […]
4.9 Amounts to be administered and administration route For subcutaneous use. Cerenia solution for injection should be injected subcutaneously, once daily, at a dose of 1 mg/kg bw (1 ml/10 kg bw). Cerenia can be used to treat or prevent vomiting either as tablets or as solution for injection once daily for up to five days.	4.9 Amounts to be administered and administration route For subcutaneous use **in dogs and cats.** Cerenia solution for injection should be injected subcutaneously, once daily, at a dose of 1 mg/kg bw (1 ml/10 kg bw) **for up to 5 consecutive days.** **In dogs**, Cerenia can be used to treat or prevent vomiting either as tablets or as solution for injection once daily for up to five days.
4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary Cerenia solution for injection was well tolerated in dogs injected daily with up to 5 mg/kg bw (5 times the use dose) for 15 consecutive days (3-times the recommended duration of administration).	4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary **Apart from transient reactions at the injection site,** Cerenia solution for injection was well tolerated in dogs **and young cats** injected daily with up to 5 mg/kg bw (5 times the ~~use~~ **recommended** dose) for 15 consecutive days (3-times the recommended duration of administration). **No data have been presented on overdoses in adult cats.**

Current	CVMP recommendation
5.1 Pharmacodynamic properties *In vivo* studies in dogs demonstrated the anti-emetic efficacy of maropitant against central and peripheral emetics including apomorphine, cisplatin and syrup of ipecac. Maropitant is effective against vomiting. Signs of nausea including excessive salivation and lethargy might remain after treatment.	5.1 Pharmacodynamic properties **Maropitant is effective against vomiting**. ~~*In vivo* studies in dogs demonstrated~~ The anti-emetic efficacy of maropitant against central and peripheral emetics **was demonstrated in experimental studies** including apomorphine, cisplatin and syrup of ipecac **(dogs) and xylazine (cats).** ~~Maropitant is effective against vomiting~~ Signs of nausea **in dogs** including excessive salivation and lethargy might remain after treatment.
5.2 Pharmacokinetic particulars […]	5.2 Pharmacokinetic particulars **Dogs** […] **Cats** **The pharmacokinetic profile of maropitant when administered as a single subcutaneous dose of 1 mg/kg bw to cats was characterised by a maximum concentration (C_{max}) in plasma of approximately 165 ng/ml; this was achieved on average 0.32 hours (19 min) post-dosing (T_{max}). Peak concentrations were followed by a decline in systemic exposure with an apparent elimination half-life (t1/2) of 16.8 hours.** **There appears to be an age-related effect on the pharmacokinetics of maropitant in cats with kittens having higher clearance than adults.** **During clinical studies maropitant plasma levels conferred efficacy from 1 hour after administration.** **The bioavailability of maropitant after subcutaneous administration in cats was 91.3%. The volume of distribution at steady-state (Vss) determined after intravenous administration at 0.25 mg/kg bw ranged from 2.27 to 3.80 L/kg. Maropitant displays linear kinetics when administered subcutaneously within the 0.25 – 3 mg/kg bw dose range.** **Following repeated subcutaneous administration of once-daily doses of 1 mg/kg bw for five consecutive days, accumulation was 250%. Maropitant undergoes cytochrome P450 (CYP) metabolism in the liver. CYP1A and CYP3A-related enzymes were identified as the feline isoforms involved in the hepatic biotransformation of maropitant.** **Renal and faecal clearances are minor routes of elimination for maropitant, with less than 1% of a 1 mg/kg subcutaneous dose appearing in the urine or faeces as maropitant. For the major metabolite 10.4% of the maropitant dose was recovered in urine and 9.3% in faeces. Plasma protein binding of maropitant in cats was estimated to be 99.1%.**

1.1.2. Documentation submitted

In accordance with the requirements laid down in Article 16 of Commission Regulation (EC) No. 1234/2008, the marketing authorisation holder submitted the following documentation:

- Administrative data (application form, amended product literature)
- Efficacy detailed and critical report, environmental risk assessment
- Associated study reports and references

1.1.3. Changes to the dossier held by the European Medicines Agency

This variation relates to the following parts of the current dossier held by the Agency:

- Parts 3 and 4

1.2. Steps taken for the assessment of this variation

- The dossier was submitted on 09 June 2011.
- The procedure started on 18 June 2011.
- A list of questions (LoQ) was adopted on 15 September 2011.
- Responses to the LoQ from the applicant were received on 17 October 2011.
- A list of outstanding issues (LoOI) was adopted on 8 December 2011.
- Responses to the LoOI/Oral explanation from the applicant were received on 8 February 2012.
- The CVMP opinion was adopted on 8 March 2012.

2. Scientific discussion

Maropitant is a selective antagonist of Substance P at the neurokinin (NK)-1 receptor and a novel class of anti-emetic for use in dogs. Its antiemetic actions are broad spectrum, inhibiting the final common pathway involved in activating the vomiting reflex in the central nervous system and showing efficacy versus both central and peripherally acting emetics. Clinical use of this product has proved safe and effective in the dog over the last 4 years throughout Europe.

2.1. Pharmacology of maropitant in cats

2.1.1. Pharmacodynamics

The applicant provided a number of published references supporting the concept that NK-1 receptors are involved in the vomiting reflex, and that their antagonism will result in anti-emetic actions in the cat as in other species. However, no pharmacological data supporting an anti-emetic effect of maropitant in the cat were provided. There is a lack of specific studies in the cat demonstrating the affinity of maropitant to the NK-1 receptor and thus inhibitory concentrations have not been estimated *in vitro*. Thus, anti-emetic efficacy demonstration for the active substance relies mainly on the outcome of the clinical studies.

2.1.2. Pharmacokinetics

A number of pharmacokinetic studies have been performed in cats.

2.1.2.1. Bioavailability

Objective: The objectives of this study were to determine plasma pharmacokinetic parameters for maropitant citrate and its primary metabolite (CJ-18518) in cats, and to assess the absolute bioavailability following one subcutaneous injection of Cerenia solution for injection at 1 mg/kg bw and one intravenous injection at 0.25 mg/kg bw as the reference.

Methods: In this two-treatment crossover-designed study, group T01 received a 1 mg/kg bw subcutaneous dose, while group T02 received a 0.25 mg/kg bw intravenous dose. In period 2, group T01 received a 0.25 mg/kg bw intravenously and group T02 received 1 mg/kg bw subcutaneously.

Blood samples were collected at 0 (prior to the first dose), 3 minutes, 15 minutes, then 0.5, 1, 3, 8, 24, 32, 48, 72, 120, 168, and 240 hours post-dose in each period. The samples were processed to plasma, then analysed for concentration of maropitant and the primary metabolite, CJ-18518, using a validated LC-MS/MS method. Non-compartmental pharmacokinetic analysis was performed on the plasma concentration data for each analyte. The intravenous (0.25 mg/kg bw) AUC data were dose-normalized to a 1.0 mg/kg bw dose.

Conclusion: The absolute bioavailability of maropitant citrate after subcutaneous injection was 91.3% (90% Cl: 84.3, 98.8%) based on $AUC_{0-\infty}$. For the active metabolite CJ-18518 the ratio of subcutaneous:intravenous was 95.8% (87.6, 1.05%) based on $AUC_{0-\infty}$. Following intravenous administration clearance (Cl) was estimated to be 274 (184, 365) ml/kg/h and Vss was 3.04 (2.72, 3.35) l/kg.

The CVMP concluded that this well conducted study showed almost 100% bioavailability of maropitant after subcutaneous administration.

2.1.2.2. Dose linearity

Objective: The objectives of this study were to determine plasma pharmacokinetic parameters for maropitant and its metabolite (CJ-18518), and to assess dose proportionality following single-dose subcutaneous administration of Cerenia solution for injection to cats at doses of 0.25, 0.5, 1 and 3 mg/kg bw.

Methods: Cats aged 2 to 7 years old (2.9 to 7.8 kg bw) were enrolled in this parallel-designed study. Group T01 received a 0.25 mg/kg bw dose, Group T02 received a 0.5 mg/kg bw dose, Group T03 received the recommended dose of 1 mg/kg bw, and Group T04 received a 3 mg/kg bw dose.

Blood samples were collected at 0.5 to 168 hours post-dose. The samples were processed to plasma, then analysed for concentration of maropitant and the primary metabolite, CJ-18518, using a validated LC-MS/MS method. Non-compartmental pharmacokinetic analysis was performed on the plasma concentration data for each analyte.

Results: Maropitant and CJ-18518 exhibited dose proportional pharmacokinetics in cats dosed subcutaneously over the dose range of 0.25 – 3 mg/kg bw for C_{max} and $AUC_{0-\infty}$. C_{max}, $AUC_{0-t(last)}$, and $AUC_{0-\infty}$ were log transformed and $t_{1/2,z}$ was reciprocally transformed prior to analysis and back-transformed values are reported.

This study demonstrated dose linearity of kinetics for both maropitant and its major metabolite over the dose range 0.25 to 3 mg/kg bw, both in terms of C_{max} and AUC. There was considerable variability within this group of cats in terms of the pharmacokinetic parameters seen at each dose rate.

The statistical method applied to assess dose linearity is appropriately robust. It is noted that doses as high as in the dog (8 mg/kg bw) have not been tested. The highest dose in this study was 3 times the recommended dose.

2.1.2.3. Repeated administration

Objective: The objective of this study was to determine plasma pharmacokinetic parameters for maropitant citrate and its primary metabolite (CJ-18518) in cats following once daily subcutaneous administration of Cerenia solution for injection to cats at 1 mg/kg bw for five consecutive days.

Methods: Cats aged 5 - 7 years (4.8-6.1 kg bw) were enrolled in this study. All animals received the recommended treatment dose of 1 mg/kg bw subcutaneous, daily for 5 consecutive days. Animal response to injection was monitored with 32 of 40 injections (80%) noted as normal responses while 8 of 40 injections (20%) elicited a moderate response. No animals had a marked response.

Blood samples were collected at 0 (prior to the first dose), then 0.5, 1, 3, 6 and 24 hours after the first dose, then at 1 and 24 hours after each of the second, third, and fourth doses, then at 0.5, 1, 3, 6, 24, 48, 72, 120, 168, and 240 hours post-dose 5. The samples were processed to plasma, then analysed for concentration of maropitant and the primary metabolite, CJ-18518, using a validated LC-MS/MS method. Non-compartmental pharmacokinetic analysis was performed on the plasma concentration data for each analyte.

Steady state trough concentrations appear to be demonstrated after the third dose for maropitant and after the 4th dose for CJ-18518. The maropitant citrate AUC_{0-24} after the fifth dose was 2.50 (95% CI: 1.65, 3.79) times higher than after the first dose and for CJ-18518 was 5.22 (4.25, 6.42) times higher after the fifth dose as compared to the first.

Urine and faeces samples were collected daily and assayed for maropitant and CJ-18518. Maropitant urine concentration increased with each dose, then decreased rapidly after dosing ceased with 5 of 8 samples below the limit of quantification at 264h, and all samples below the limit of quantification by 288 h post-first administration. CJ-18518 appeared to plateau after the third dose, then decreased with time after dosing ceased. The least squares (LS) mean for faeces was not reported at 24, 120, or 288 h as the quantity of samples collected was considered inadequate to report the statistical analysis. The concentration of maropitant and CJ-18518 in faeces increased through the dosing period, then declined with time after dosing ceased. Less than 1% of the maropitant dose was eliminated in urine and faeces as parent drug (maropitant) while 10.3 and 9.31% of the maropitant dose was recovered in urine and faeces respectively as CJ-18518.

Conclusion: Steady state trough concentrations appear to be demonstrated after the third dose for maropitant citrate and after the fourth dose for CJ-18518. The AUC_{0-24} on day 5 was 2.5 and 5 times larger than on day 1 of dosing for maropitant and its metabolite, respectively.

Less than 1% of the maropitant dose was eliminated in urine and faeces as parent drug (maropitant citrate) while 10.3 and 9.31% of the maropitant dose was recovered in urine and faeces respectively as CJ-18518. However, as the analytical method used for measuring maropitant and its major metabolite in urine and faeces has not been validated, the results can only be considered as supportive.

2.1.3. Metabolism

Objective: This study was to examine the *in vitro* hepatic metabolism of maropitant in cat liver microsomes.

Methods: Pooled, mixed gender feline liver microsomes were incubated with maropitant using NADPH and UDPGA as cofactors. LC/MS-MS methods were used to characterize the metabolites. Inhibition of maropitant metabolism using substrates or inhibitors of human P450s were used to identify the feline P450 isoenzymes involved.

Results: A total of eight distinct metabolites of maropitant (M1 – M8) were observed in *in vitro* liver microsome incubations. Seven metabolites were likely formed through oxidation by cytochromes P450. No modifications to the diphenyl group were observed. One metabolite was a glucuronide of an oxidative metabolite. Though metabolite standards were not available, the most intense MS signal came from maropitant that had been hydroxylated on one of three equivalent t-butyl carbons (M6). In general, the types of feline microsome modifications were similar to those produced by canine hepatocytes.

Formation of two of the major metabolites formed *in vitro* by feline microsomes appeared to be catalyzed by CYP_{1A} and CYP_{3A}-related enzymes according to reactions conducted with various known P450 substrates or inhibitors. A CYP_{2D} component to maropitant metabolism was not detected using the CYP_{2D} inhibitor quinidine. This differs from the metabolism of maropitant in dogs. Maropitant did moderately inhibit the hydroxylation of bufuralol suggesting maropitant could still bind and inhibit feline CYP_{2D} enzyme(s). However, the degree of CYP_{2D} inhibition-demonstrated-binding is an order of magnitude weaker in cats than it is in dogs (IC_{50} approximately 0.2 µM).

Conclusion: In general, the pattern of feline microsome metabolism was similar to that observed in canine hepatocytes with t-butyl carbons (M6); CJ-18518 as the major metabolite. However, pooled, mixed gender feline liver microsomes are a very crude tool to study the hepatic metabolism and can only be used to identify major metabolic pathways. The use of human probes to test metabolic

pathways may also be questionable. These experiments do not add much to the pharmacokinetic experiments and can only be considered supportive.

2.1.4. Protein binding

In vitro data in cats showed that the mean fraction bound (±SD) of maropitant in cat plasma was 99.1 ± 2.19% at concentrations ranging from 100 to 1000 ng/ml. The unbound fraction measured in the buffer at 100 ng/ml was close to or at the limit of detection of the analytical assay (0.1 ng/ml after refinement of the assay to improve its sensitivity) making the accuracy of this experiment questionable. This technical limitation also meant lower concentrations which would be relevant therapeutically could not be examined. However, the study indicates that maropitant and its metabolite is highly protein bound in plasma although the volume of distribution is rather large (>3 l/kg).

2.2. Dose

The proposed dose is 1 mg/kg bw (1 ml/10 kg bw) subcutaneously, once daily for up to 5 consecutive days. In support of this dose, the applicant submitted a dose determination and a dose confirmation study.

2.2.1. Dose determination

Objective: This study was designed to characterize the effective dose of Cerenia in cats for prevention of xylazine-induced nausea and vomiting through recording of emetic events and assessment and quantification of nausea by visual analogue scale (VAS) scoring.

Methods: Cats 6 months of age or older were allocated to one of five treatment groups. Cerenia solution for injection was administered at 14°C subcutaneously to cats at dosages of 0 (T01), 0.1 (T02), 0.5 (T03), 1.0 (T04), and 2.0 (T05) mg/kg bw. One hour after Cerenia injection, xylazine was administered by intramuscular injection of 0.44 mg/kg. Immediately after the xylazine challenge cats were observed continuously for one hour and the number and time of emetic events recorded. Also, cats were observed for nine one-minute intervals (at -3, 3, 6, 9, 12, 15, 30, 60 minutes ± 30 seconds post-xylazine challenge) for nausea assessed by a VAS scoring method. For consistency, the same observer did all of the emesis counting and a second observer did all of the nausea VAS evaluations for each cat.

In addition, cats were observed for general health 20 minutes after the Cerenia injection and approximately every 30 minutes starting at 90 minutes after the xylazine injection for at least 4 hours until they had recovered from the xylazine-induced sedation. One cat, that vomited six or more times, was "rescued" and it recovered uneventfully. No further data were collected for that cat.

The primary efficacy variable, number of emetic events, was analysed using a general linear model and least squares (LS) mean contrasts since the treatment effect was significant. The secondary variable, nausea VAS score, measured in mm on a 100 mm scale, was analysed with a mixed linear model for repeated measures. LS mean contrasts were not performed since the treatment effect and treatment by time point effect were not significant. Abnormal clinical observations were summarised, including injection reaction at dosing and injection site reactions 25 hours post-dosing.

Maropitant blood concentrations were determined pre-treatment and at 135 minutes post-treatment.

Results: Cerenia treatment at dosages of 0.5 (T03), 1.0 (T04) and 2.0 (T05) mg/kg bw significantly reduced emesis ($P<0.0001$) to < 0.2 LS mean emetic events per cat (range 0 to 2 emetic events per cat) from LS mean >2.4 emetic events per cat (range 1 to 6 emetic events per cat) for placebo (T01)

and the 0.1 (T02) mg/kg bw dose groups. The anti-emetic response to the 0.1 mg/kg Cerenia dosage was significantly less than the higher dosages (treatment contrast: T02 vs T03+T04+T05) at the 0.05 level (P<0.0001) while the anti-emetic response to the 0.5 mg/kg bw dosage was not different from the 1 and 2 mg/kg bw Cerenia dosages (treatment contrast: T03 vs T04 + T05).

Cerenia did not significantly reduce the LS mean nausea VAS score after the xylazine challenge. By 9 minutes the VAS scores were <5 mm on a 100 mm scale suggesting that the cats were sedated from the xylazine and nausea was not possible to assess any longer, although cats would still arouse to vomit.

Local adverse events were generally mild in nature and transient. Cerenia dosages above 0.5 mg/kg bw were associated with moderate to marked injection dosing reactions observed in 50% (T03) to 75% (T04 and T05) of cats. One day post-treatment, four cats treated with Cerenia had mild injection site swellings that were not associated with heat, redness or pain and not related to dosage. The injection site swelling was still present the second day post-treatment for one (T02) cat.

Mild to moderate hypersalivation observed in a dose dependant manner (at dosage of 0.5, 1 and 2 mg/kg bw increased in incidence and severity with dose) was considered to be related to fear due to pain caused by injection.

Conclusion:

The CVMP agreed that a dose of 0.5 mg/kg bw of Cerenia is efficacious for the reduction of xylazine induced emesis in cats, when challenge is administered 1 hour after Cerenia treatment, whereas higher doses appear not to provide a better effect. Whether Cerenia given at this dose is efficacious for the treatment of emesis when challenge precedes the treatment is not clarified from this study. Also, the study was unable to confirm an effect on nausea.

Local adverse events (pain at injection site, and hypersalivation) were generally mild in nature and transient. Information on pain reactions is included in the SPC.

2.2.2. Dose confirmation

Objective: The objective of this study was to confirm the effective daily dose of Cerenia solution for injection when administered subcutaneously to cats at 0 (saline), 0.5 and 1.0 mg/kg bw for prevention of nausea and vomiting induced by administration of an emetogen, xylazine, 23 hours after Cerenia administration.

Methods: Cerenia Solution for injection was administered subcutaneously to cats at dosages of 0 (T01), 0.5 (T02), and 1 (T03) mg/kg bw and 23 hours later, an emetogen, xylazine, was administered by intramuscular injection of 0.44 mg/kg bw. Immediately after the xylazine challenge cats were observed for signs of emesis, nausea and general health.

The primary efficacy variable, number of emetic events, was analysed using a general linear model and LS mean contrasts since the treatment effect was significant. The secondary variable, nausea VAS score, measured in mm on a 100 mm scale, was analysed with a mixed linear model for repeated measures. LS mean contrasts were not performed since the treatment effect and treatment by time point effect were not significant. Abnormal clinical observations were summarized, including injection reaction at dosing and injection site reactions 22 hours post-dosing.

Results: Cerenia administered at either 0.5 or 1.0 mg/kg bw was significantly better than placebo (P<0.0001) at preventing xylazine-induced emesis at 23 hours post-Cerenia administration. Although

both dosages were efficacious, the total number of emetic events per treatment, the number of cats that vomited in each treatment group and the number of emetic events per cat was greater for the 0.5 mg/kg dose group than the 1.0 mg/kg group.

For nausea VAS observations, a significant treatment, time, and treatment by time effect ($P<0.05$) was observed compared to placebo (T01) at 0.5 mg/kg bw (T02) continuously for five 15-second evaluations ($P\leq0.0163$), and at 1.0 mg/kg bw (T03) continuously for seven 15-second evaluations ($P\leq0.0390$) starting from 2 minutes 15 seconds; and for T02 15-second evaluations starting from 4 minutes 45 seconds ($P\leq0.0448$). Cerenia at 0.5 mg/kg bw was different from 1.0 mg/kg bw only at 3 minutes 30 seconds ($P=0.0067$).

The number and percentage of cats with moderate to marked injection reactions appeared greater in the Cerenia treatment groups than for placebo (saline) but the Cerenia dosage groups (T02 and T03) appeared similar to one another with respect to injection reactions at dosing. No cat died or needed rescue treatment. One day after administration, no reactions at the injection site (swelling, redness, pain or heat) were observed. One cat receiving 0.5 mg/kg bw vomited once at 2.5 hours after the administration of the emetogen, and one cat receiving 1.0 mg/kg bw had hypersalivation one time 2 hours after administration of the emetogen. Four placebo cats vomited in the post-emetic observation period.

Conclusions:

The study was well conducted with a similar design as the dose finding study, apart from the nausea assessment and the time of administration of the emetic challenge (23 h after Cerenia administration, to confirm 24 hours effect duration).

Similar to the dose-finding study, pain caused by injection of Cerenia was common and two cats required two attempts to administer the full dose. Hypersalivation among Cerenia-treated animals was less evident in this study as compared to the dose-finding study.

Signs of nausea were recorded for 6 minutes following xylazine administration. A significant reduction of such signs as compared to placebo was only noted at one time of the many evaluation time points for T01, and two times for T02 (for a duration of 1 minute and 15 seconds for the 0.5 mg/kg bw group and 2 minutes and 15 seconds for the 1.0 mg/kg bw group). Therefore, a preventive effect regarding nausea has not been satisfactorily demonstrated.

Regarding emesis, a significant preventive effect as compared to placebo was noted for both dose group (0.5 mg/kg bw and 1.0 mg/kg bw). Although the difference between the two treatment groups did not reach statistical significance, two out of 12 cats in the 0.5 mg/kg bw group were in effect non-responders (vomiting 2 and 3 times respectively, similar to most of the cats in the saline control group), while all cats in the 1 mg/kg bw group seemed to respond to treatment (as none of them vomited more than once). It was therefore concluded that the higher dose of 1 mg/kg bw subcutaneous would be a more effective dose for the prevention of emesis, and also that the claimed effect duration of 24 hours is supported. However, a preventive effect regarding nausea is not sufficiently demonstrated. Reactions to the injection seen at time of administration were common even at the 1 mg/kg bw dose level, and are thus a tolerance concern.

2.3. Tolerance in cats

Tolerance was investigated as part of the dose determination/confirmation studies, as well as in field studies. In addition, the applicant provided two target animal safety studies.

2.3.1. Target animal safety study

Objective: To demonstrate the margin of safety of Cerenia solution for injection administered subcutaneously to cats at 1, 3, and 5 times the recommended therapeutic dose (RTD) of 1 mg/kg bw once daily for 15 days (i.e. up to 3 times the intended duration) in young cats.

Methods: Cats aged 16 weeks of age were administered Cerenia solution for injection subcutaneously at doses of 1 (1 x RTD), 3 (3x), or 5 (5x) mg/kg bw for 15 days, and compared to placebo cats, which received sterile saline for injection. Behavioural response to injection and method of restraint during injection were evaluated daily. Injection sites were examined multiple times on Day 0, then twice daily on subsequent days until the end of the study. In addition, bodyweight and food consumption were measured, and veterinary clinical observations conducted up to 14 days post treatment. Clinical pathology samples were collected twice prior to Day 0, and on Days 7 and 14.

Pharmacokinetic (PK) sampling was conducted on Days 1 and 7 for trough plasma concentrations, and sampling was conducted on Days 14-15 to obtain a limited plasma concentration profile. Necropsies were performed on Day 15; a complete set of tissues was collected from each animal for microscopic pathology evaluation.

Results: The most significant finding in this study was dose related reactions during the injection, likely an expression of pain/discomfort. Among the young cats in this study administered the recommended dose (1 mg/kg bw) moderate or marked behavioural responses were noted at 33% (40/120) of all injection occasions, and moderate restraint or protective restraint was necessary in 49% of the administration occasions in this group. For the 3 mg/kg bw group the corresponding figures were 71% and 71%, and for the 5 mg/kg bw group they were 72% and 76%, respectively. In addition, in the recommended dose group persistent response to treatment was noted at 12.5% of the injection occasions. The data suggest that injection of the recommended dose is connected to a high risk for pain/discomfort, which is of concern.

In addition to apparent pain reactions, short lasting firmness at site of injection was quite commonly noted in the recommended dose group, but these changes were not associated with pain and thus of less importance. Necropsy demonstrated that changes at the injection site were less in the recommended dose group.

2.3.2. Overdose - Target animal safety study

In response to concerns about the tolerance of an overdose of Cerenia in cats, the applicant provided another parallel designed tolerance study in line with the requirements of the VICH GL 43 (target animal safety) in 16 weeks old cats using a dose of 4 mg/kg bw, twice daily for 5 days.

Objective: To evaluate the tolerance of maropitant citrate in 16-week old cats at a dosage predicted to be equivalent to a 3X RTD exposure in adult cats.

Methods: Young cats aged 16 weeks were enrolled in this two-treatment parallel-designed study. Group T01(control) received 0.4 ml/kg bw sterile saline and Group T02 received a 4 mg/kg bw dose subcutaneously. Doses were administered every 12 hours for 10 consecutive doses.

Animals were observed for behavioural response to injection, reactions at sites of injection, bodyweight, food consumption, and veterinary clinical observations. Blood samples for toxicokinetic evaluation were collected at regular interval from prior to first dose up to 72h after the last administration.

Results: The dosage (4 mg/kg bw twice daily for 5 days) was intended to provide systemic exposure approximately 3-fold higher than the exposures observed in adult cats at 1 mg/kg/day. Actual achieved exposures were approximately 2.3 times higher than exposures observed at 1 mg/kg bw in adult cats when considering AUC after the first dose, and 3.3 times higher when considering AUC over the full observation period 0-9 days. In addition to injection site swelling, abnormal clinical signs of diarrhoea and dehydration were observed in a few cats. These observations occurred following cessation of treatment. These signs were entirely reversible.

Conclusions on systemic tolerance

Overall, doses of 4 mg/kg bw twice daily over 5 day, or 1, 2 or 3 mg/kg bw once daily over 15 days were well tolerated in 16-week old cats. However, no tolerance data of an overdose in adult cats were provided.

The CVMP expressed concern about this, since maropitant levels obtained from both target animal safety (overdose) studies only corresponded to between 1.4 and 2.3 times the recommended dose for adult cats (and not the standard requirement of 3x and 5x RTD), and maximum exposure time was between 5 and 14 days (approximately 1-3 x duration) in the two studies.

Although the applicant considered that at these exposures the study would still provide reasonable overdose data applicable in adult cats, the CVMP expressed concern about extrapolations from young cats to conclusions on overdoses in adult animals due to difference in pharmacokinetics, as maropitant is cleared more rapidly in 16 weeks old animals than in animals older than 5 years (with AUC of 738 vs 3370), and an accumulation of parent drug and metabolite during multiple dosing. However, the CVMP acknowledged that studies were undertaken in line with VICH GL 43 (target animal safety), which recommends to use "healthy young mature animals" in such studies, and that a new tolerance study in older cats might be of animal welfare concerns, taking into consideration that higher doses of Cerenia solution for injection have been shown to very painful to cats. Furthermore, tolerance of the recommended dose was confirmed by the pivotal field study which involved a large number of adult cats. No significant treatment related adverse events were noted in that study apart from very commonly occurring injection reactions.

The CVMP therefore concluded that although there were deficiencies in the tolerance studies submitted, all safety data taken together would demonstrate acceptable systemic tolerance for the recommended dose (1 mg/kg bw of maropitant for up to 5 days).

2.3.3. Pain at injection (RTD)

In pre-clinical and field studies, quite a high proportion of cats experienced moderate to marked pain during injection of the recommended dose, and CVMP raised concerns about this reaction. Pain was expressed by behavioural changes, but also by hypersalivation (in anticipation of pain after repeated injections), and resulted in some cases in the need for a second injection (to ensure the full dose of Cerenia was administered). Pain reactions were noted to increase in severity and incidence with increasing doses.

This pain is caused by the active substance, maropitant citrate. One of the excipients in the formulation (cyclodextrin) can bind to maropitant, and pain can be somehow reduced by reducing the amount of free maropitant. As the extent of cyclodextrin binding of active substance is temperature

sensitive, a recommendation is therefore made in the SPC to administer the product at low temperatures ("Injecting the product at refrigerated temperature may reduce pain at injection").

Some cats experiencing pain during injection may require different forms of restraint measures, and a user warning has been added to the SPC: "Due to the frequent occurrence of transient pain during the injection, appropriate animal restraining measures may have to be applied".

2.4. Efficacy

The indications proposed by the applicant for the new target species cats, are the prevention of vomiting and reduction of nausea (except that induced by motion sickness), and treatment of vomiting (in combination with other supportive measures).

2.4.1. Prevention of vomiting / reduction of nausea

The claims "prevention of vomiting", and "reduction of nausea" were supported by the dose determination and dose confirmation studies with Cerenia given at 1 or 23 hours prior to the administration of an emetogen, xylazine (for details see section 2.2.2 above). A dose of 1 mg/kg bw (subcutaneously) was considered effective in the prevention of vomiting.

Regarding nausea, no preventive effect was detected at any dose level in the dose finding study, and only a short lasting preventive effect with questionable clinical relevance was noted in the dose confirmation study. However, based on the mechanism of the vomiting reflex and the relationship between nausea and vomiting, substances that inhibit the vomiting reflex would also be expected to have anti-nausea properties. Furthermore, evaluation of nausea in cats is problematic as it is based on behavioural changes (rather than reports of the sensation itself as is possible in human medicine). Because vomiting is an all or nothing threshold event, it is possible that vomiting can be completely eliminated by some substances while nausea, being a graded phenomenon, is only partially reduced. The multiple inputs to the brain stem that contribute to stimulating the motor events that give rise to the vomiting reflex (and the sensation of nausea) explain why nausea may be more difficult to control than vomiting.

To provide justification for the claim for prevention of nausea in cats, further studies were submitted. Two studies in cats investigating the preventive effect of Cerenia against vomiting and nausea were similar in design to the dose determination and confirmation studies; and indicated that xylazine-induced nausea could be effectively prevented by doses of 0.5 mg/kg bw and 1 mg/kg bw (subcutaneously) of Cerenia.

The CVMP acknowledged that the xylazine model could be used to investigate preventative efficacy. The use of this model was justified by the lack of other, better models, and by extrapolating the same effect on nausea would also be expected for other compounds.

The CVMP agreed that it would be difficult to objectively measure nausea in cats under clinical conditions, and that the xylazine model – although not ideal – could be accepted to support this claim. Taking also into account nausea as a precursor of emesis, and the accepted efficacy of maropitant on emesis, the CVMP agreed to accept the indication "reduction of nausea" in cats.

2.4.2. Treatment of vomiting

Objective: To demonstrate the effectiveness of Cerenia solution for injection when administered subcutaneously once daily for up to 5 consecutive days at a dosage of 1.0 mg/kg, for treatment of vomiting in cats presented as veterinary patients. The study was also intended to demonstrate safety when administered to cats under field conditions.

Methods: The study was a blinded, placebo controlled multi-centre study (ratio treated:placebo animals was 2:1), conducted at various veterinary hospitals in the USA (2009–2010) and enrolling cats of different breeds, ages and gender and with a variety of medical conditions and co-medications. Cats were selected with a history of vomiting in the past 48 hours with at least one episode within the last 24 hours. Cats enrolled in the study were hospitalized for at least 24 hours after Cerenia or placebo treatment to ensure appropriate observation to detect vomiting during that period. Thus, the primary efficacy assessment was based on treatment success as defined as the absence of vomiting in the first 24 hours following treatment. Cats could continue to be treated with the test article for up to *five c*onsecutive days at the discretion of the examining veterinarian.

Cerenia (1.0 mg/kg bw subcutaneous) was administered to 133 cats, and placebo was administered to 62 cats and treatment was allocated in a ratio of two Cerenia-treated to one placebo-treated cat. Study participants were masked to treatment allocation except for a Treatment Administrator who was responsible for dispensing the test article. Upon administration of the test article, the cat's reaction to the injection was recorded and at 24-hours post treatment the injection site was checked for the presence of pain, swelling, redness, discharge, or hair loss. During the first 24-hours of hospitalization, cats were observed for vomiting or the presence of emesis in their cage during four specific time intervals (1 hour, 3-6 hours, 9-21 hours, and 24 hours) after treatment administration.

Cats were hospitalised for at least the first 24 hours, then could be re-treated for up to five consecutive days. Continuous treatment was based on a clinical examination including continued vomiting, food and water consumption in the previous 24-h period at the discretion of a study veterinarian.

Results: In the first 24 hours post treatment, two Cerenia-treated cats vomited (1 time each) while 12 placebo-treated cats vomited a combined total of 20 times. The difference in proportions of treatment failure between treatment groups was significant (p=0.0042). For cats continuing antiemetic treatment, 23.8% of the placebo-treated cats but only 2.9% of Cerenia-treated cats vomited during the second 24 hour period. A larger percentage of placebo-treated cats received two or more treatments (35.6%) compared to Cerenia-treated cats (28.5%). Cats (per protocol set) withdrawn from the study for lack of efficacy or inadequate improvement included 8 (13.6%) of the placebo-treated cats and only 1 (0.8%) Cerenia treated cat.

Diarrhea and fever were observed in cats receiving placebo and cats receiving Cerenia; additionally lethargy, dehydration, and conjunctivitis were observed in Cerenia-treated cats. Clinical pathology laboratory values that changed after administration of the test article were considered to be due to the clinical conditions for which cats were presented and treated and not associated with administration of the test article since these changes occurred for both treatment groups. 67.5% of Cerenia injections elicited no response or mild response from the cats compared to 98% of the injections of placebo. Of 288 total injection sites evaluated by masked study participants 24 hours post treatment, a single cat receiving placebo treatment demonstrated swelling at the injection site after the first injection. None of the Cerenia injections resulted in a reaction at the site of injection 24 hours post treatment.

Conclusions
This was a well conducted placebo-controlled clinical study including cats with emesis due to a variety of acute and chronic medical conditions where antiemetic treatment had been deemed not to be contraindicated. A significant (p=0.0042) reduction in the number of cats vomiting during the first 24 hours after treatment was noted in the Cerenia group (2 cats vomited 1 time each) as compared to the placebo group (12 cats vomited in total 20 times). The proportion of cats that continued to vomit to 24 - 48 hours after treatment was also lower in the Cerenia group (2.9 %) as compared to the placebo group (23.8%). It might be that the inclusion criteria allowed the inclusion of some cats with a clinical condition that was self limiting. However, the data set appears to be reasonably balanced regarding clinical diagnoses and since a placebo group was included the study is regarded conclusive.

The clinical signs and changes in clinical pathology parameters noted were likely due to the underlying disease. There were no apparent treatment related adverse event noted.

It was concluded that the results would support efficacy of 1 mg/kg subcutaneously for the indication "treatment of emesis" in cats.

3. Benefit-risk assessment

3.1. Benefit assessment

The benefit of Cerenia solution for injection for cats, is the treatment and prevention of vomiting (in combination with other supportive measures), and the reduction of nausea in cats.

3.2. Risk assessment

Experimental and clinical data demonstrated that moderate to severe pain reactions during the injection are very common (i.e. in about 30% of cats treated), and in doses above the recommended dose more pronounced.

Overdose data have only been presented in young cats that tolerated the product well (apart from local reactions at the injection site). No overdose studies were presented in the main target population (adult cats); however, the applicant provided some reassurance on the tolerance of an approximately 3x overdose, extrapolating data from overdose studies in young cats to adult animals based on PK-modelling.

3.3. Evaluation of the benefit risk balance

The benefit of the medicinal product in terms of reducing emetic events has been sufficiently demonstrated through experimental and clinical studies in cats at a dose of 1 mg/kg bw once daily for a maximum duration of 5 days.

Whilst efficacy in the reduction of nausea did not gain sufficient support from clinical data provided, it was established based on experimental studies using xylazine as a model to trigger nausea.

Dose finding/dose confirmation data and clinical data suggest an acceptable safety profile at the recommended dose level, apart from very commonly occurring painful injection reactions. However, the pain reactions are transient, and a recommendation has been included in the SPC to inject the product at low temperatures (as this may reduce pain at injection). Also, a warning was added to apply appropriate animal restraining methods to minimise the risk of injury to persons, and to avoid repeated injections.

No overdose studies were presented in adult cats, but the CVMP considered that adult cats were included in the field studies without increased signs of intolerance. In addition, the PSUR cycle of the product will be restarted taken into account this new target species.

The risk management measures included in the SPC are considered appropriate. The variation is not expected to have any impact on the environment.

3.3.1. PSUR cycle

Cerenia is currently on a 3-yearly periodic safety update report (PSUR) cycle. It is proposed to reset the PSUR cycle for Cerenia. PSURs covering all authorised presentations of the product would be required at 6 monthly intervals for the next two years, followed by yearly for the subsequent two years and thereafter at 3 yearly intervals. The DLP for the next PSUR would be 30 June 2012. This is considered necessary in view of the use of the product in a new target species (cats).

4. Overall conclusions

The CVMP considers that the variation, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met, is approvable.

It is recommended to reset the periodic safety update report (PSUR) cycle for Cerenia.

Changes are required in the following annexes of the Community marketing authorisation:
Annexes I (SPC), II, IIIA and IIIB (labelling and package leaflet).