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Veterinary Medicines and product data management

EPAR type II variation for Cerenia (EMEA/V/C/0106/II/0018)

International non-proprietary name: Maropitant

Scope: C.I.6.a) Additional indication: Prevention of perioperative nausea and vomiting, and improvement in recovery from general anaesthesia after use of the μ-opiate receptor agonist morphine

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

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Table of contents

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, Zoetis Belgium SA (the applicant), submitted to the European Medicines Agency (the Agency) on 29 November 2012 an application for a type II variation for Cerenia.

1.2 Scope of the variation

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Proposed by the applicant:
Additional claim for the prevention of perioperative nausea and vomiting and improvement in recovery from general anaesthesia after use of full opiate receptor agonists such as morphine (for dogs).

Current	Recommended by CVMP
Cerenia 10 mg/ml Solution for Injection for Dogs and Cats **SPC:** **4.2 Indications for use, specifying the target species** Dogs • For the treatment and prevention of nausea induced by chemotherapy. • For the prevention of vomiting except that induced by motion sickness • For the treatment of vomiting, in combination with other supportive measures Cats:…	Cerenia 10 mg/ml Solution for Injection for Dogs and Cats **SPC:** **4.2 Indications for use, specifying the target species** Dogs • For the treatment and prevention of nausea induced by chemotherapy. • For the prevention of vomiting except that induced by motion sickness • For the treatment of vomiting, in combination with other supportive measures • For prevention of perioperative nausea and vomiting and improvement in recovery from general anesthesia after use of the μ-opiate receptor agonist morphine. Cats:… **The package leaflet is updated accordingly.**

2. Scientific discussion

2.1. Introduction:

Certain surgical procedures and anaesthetic agents (opioids, inhalant agents, α-2-agonists) are known to cause nausea and vomiting in dogs. These emetogenic anaesthetic agents are used frequently for induction and maintenance of anaesthesia, and as analgesics during and after surgery. Preoperative and postoperative vomiting is a significant risk factor for the veterinary surgeon due to the potential

for aspiration pneumonia. The distress and discomfort experienced by dogs with perioperative nausea and vomiting is a concern for the veterinary surgeon since dogs that are nauseous do not return to normal feeding and elimination behaviour as quickly as those without nausea, and may require a longer hospitalisation period.

The applicant applied for a new indication for Cerenia in dogs: Prevention of perioperative nausea and vomiting, and improvement in recovery from general anaesthesia after use of full opiate receptor agonists such as morphine.

In support of the application, two laboratory studies were provided in dogs as presented below.

2.1.1. "Morphine Study"

This study was conducted to demonstrate the efficacy and safety of Cerenia Solution for Injection for prevention of perioperative nausea and vomiting in dogs undergoing routine surgery (premedication: morphine, anaesthesia induction: propofol). Duration of the study: up to 3 hours post-surgery.

Experimental design:

Sixteen male and sixteen female Beagles (7-8 months of age) undergoing routine castration or ovariohysterectomy surgery received Cerenia Solution for Injection or placebo (saline) subcutaneously, 45 minutes prior to administration of the premedication, morphine. After administration of morphine, dogs were continuously observed for nausea and vomiting by a masked study participant, recording observations every 5 minutes for 30 minutes until induction of anesthesia with propofol. Each dog underwent routine spay or neuter surgery under general anesthesia with isoflurane. At the end of the surgical procedure after extubation dogs received subcutaneous carprofen for additional postoperative analgesia. Dogs continued to be observed for nausea and vomiting, every 15 minutes for the first one hour after surgery and then every 30 minutes thereafter for a total of three hours. Also during recovery, dogs were observed for multiple attributes of recovery including speed of recovery, attitude, level of sedation, and food consumption.

Presence of emetic events was observed and was defined as the evidence of retching, vomiting, or vomitus.

Intensity of nausea was assessed using a visual analog scale to subjectively assess and record the severity of nausea experienced by each dog during the perioperative period.

Improvements in speed of recovery from anesthesia were evaluated by measuring differences in time to extubation, time to sternal recumbency, time to standing posture, and time to return to normal feeding.

Efficacy: Cerenia, was significantly better than placebo ($P<0.05$) in preventing vomiting associated with the use of morphine. Only one of 16 Cerenia-treated dogs vomited after receiving morphine and that one dog had received an incomplete dose of Cerenia. Fourteen of 15 placebo-treated dogs vomited post morphine administration and of those 14 vomiting dogs, 9 vomited more than one time.

The intensity of nausea occurring after morphine administration (assessed by visual analog score) was significantly less in dogs receiving Cerenia treatment than in those receiving a placebo at multiple time points in the study. Preoperatively, Cerenia was significantly better than placebo in reducing morphine-induced nausea in both male and female dogs immediately (at the 5 minute time point) after morphine administration. Postoperatively, female dogs treated with Cerenia had significantly less nausea associated with the ovariohysterectomy procedure than did female dogs that were treated with placebo. This difference was evident at extubation and at 30, 45, 60, 90, 120, and 150 minutes in the recovery period.

Results:

Tolerance: For 16 dogs in the study for which food consumption was measured up to 20 hours after surgery, the least squares mean total food consumption (measured in grams) was 204.8 for Cerenia-treated dogs and 39.1 for those treated with placebo. The difference in the mean total food consumption between treatment groups was significant (p= 0.0036). Seventy-five percent of Cerenia-treated dogs had returned to feeding (eaten at least 100 grams of food) by 6 hours post surgery while only 33% of placebo-treated dogs had returned to normal feeding by then. The proportion of dogs that returned to feeding during the study was significantly different between groups (p=0.0272). Pre-operative treatment with Cerenia did not significantly change the speed with which dogs recovered from surgery, their general attitude during the recovery period, or their level of sedation during recovery compared to dogs receiving placebo treatment. However, the quality of recovery (as measured by decreased aimless movement, vocalization and panting) appeared to be better in Cerenia-treated dogs.

Assessment:

The study was well-conducted and in line with GLP, although not fully clear in its aim, indicated by the selection of several primary endpoints and no justification of study size in relation to expected clinical outcome.

It is clearly demonstrated that Cerenia prohibited vomiting in both male and female dogs during the preoperative phase, after administration of morphine. During the postoperative phase, however, vomiting did not occur in any dog, neither test nor control group.

Preoperatively, and after morphine administration, nausea was significantly less intense in Cerenia-treated dogs as compared to placebo at some of the recording occasions before induction of anaesthesia. Reduction in nausea was significantly less intense in Cerenia-treated female dogs during the postoperative phase whereas no corresponding difference was noted for males. This gender difference was attributed to the more invasive surgery applied on female dogs (ovariohysterectomy) where traction on ovarian ligaments in addition to the morphine administration may have caused nausea.

Cerenia-treated dogs, male and female, resumed to appetite more rapidly as compared to placebo-treated animals and ate on average more during the postoperative period. It should be noted that this assessment was made for only some of the animals. This brings indirect support for a nausea inhibiting effect of Cerenia after surgery.

There were no between-group differences with regard to level of sedation postoperatively which is reassuring as it could have biased the assessment of primary endpoints. According to the assessment of quality of recovery there were no differences between the groups, although a numerical difference in favour of Cerenia-treated animals were noted.

Conclusions:

Cerenia treatment before administration of morphine was able to significantly decrease occurrence of emesis and to some extent also nausea before induction of general anaesthesia. The magnitude of effect in this regard appears clinically relevant. No adverse events related to treatment were noted.

2.1.2. “Buprenorphine study”

This study was conducted to demonstrate the efficacy and safety of Cerenia Solution for Injection for prevention of perioperative nausea and vomiting, return to feeding and ease of recovery in female

dogs undergoing routine surgery (premedication: buprenorphine, anaesthesia induction: propofol). Duration of the study: up 15 days post-surgery.

Experimental design:

The same study design is used as in the morphine study , but morphine was substituted with buprenorphine, only female dogs were investigated, and the duration of the study was longer (15 days).

Results:

Tolerance:
Sixteen dogs completed the study except for one dog that was rescued approximately 2.75 hours after extubation due to insufficient pain management. All data from this dog was included in the analysis of effectiveness up to the point of removal. One Cerenia-treated dog appeared to be mildly (5%) dehydrated post operatively (documented as an abnormal health event), which resolved the same day without treatment. Several dogs in both the Cerenia and placebo-treated groups had various degrees of mild bruising and swelling at the incision site.

Efficacy:
Cerenia treatment was significantly better than placebo treatment in improving the quality of surgical recovery 15 minutes post surgery (p=0.0016); however, this finding was not sustained throughout the remaining recovery period.

Cerenia was not significantly better than placebo in reducing the intensity of nausea, improving the rate at which dogs returned to feeding or demonstrating an improvement in total food consumed. Furthermore, the descriptive findings seen from the attributes of surgical recovery which include the level of sedation also failed to show any meaningful differences between treatment groups.

None of the dogs in either treatment group returned to feeding by 6 hours. Two Cerenia-treated dogs returned to feeding at 20 hours. Of the 16 dogs on study, excluding one dog from the Cerenia-treated group that was rescued 2.75 hours post extubation, 4/7 placebo (57%) and 3/8 Cerenia (38%)-treated dogs had satisfied the study criteria of consuming 100 grams of food by the 26 hour observation period. The least squares means total food consumption (measured in grams) for the 15 dogs in the study 26 hours after surgery was 127.6 for Cerenia-treated dogs and 82.6 for those treated with placebo (p=0.3802).

Assessment:

The study was conducted in a relatively small number of dogs undergoing ovariohysterectomy. The only significant changes between treatment and placebo group were an improvement of the quality of recovery at 15 minutes into recovery. However, no significant differences in other parameters were noted.

To explain that lack of difference between groups, the applicant considered that it could be due to insufficient pain control and thus a false positive outcome in the visual analog score assessment due to the detection of signs of pain (which might be difficult to differentiate from signs of nausea). However, the applicant also considered that the dogs had received sufficient pain control through buprenorphine, and also NSAIDs provided post surgery. Another reason for the lack of effect could be a low nausea inducing potential for buprenorphine; however, nausea intensity according to the visual analog score was equally high among Cerenia-treated dogs given buprenorphine, as among the placebo-treated dogs provided morphine in the first study.

The CVMP therefore did not consider that this study would demonstrate the efficacy of Cerenia Solution for Injection for surgery that involves premedication with buprenorphine. Compared to the previous

study, it appears that changing the premedication from morphine to buprenorphine also changed the vomiting and nausea pattern in dogs. Although the mode of action of both compounds is the same (both are acting on the μ-opiate receptor), buprenorphine only acts partly on the μ-opiate receptor, while morphine shows a full inhibition of the μ-opiate receptor.

2.2. Summary and Conclusions

The first study using morphine as premedication, showed efficacy in the proposed new indication "*for prevention of peri-operative nausea and vomiting and improvement in recovery from general anesthesia"*.

However, a second study using buprenorphine as premedication failed to show convincing efficacy in the proposed new indication.

Not all opioids produce nausea and vomiting upon administration. The incidence of vomiting among the opioids is affected by specific characteristics of the opioid including its binding affinity and activity at the various opioid receptors, its lipid solubility profile, the dose, and concomitant drug administration. While morphine, hydromorphone, and oxymorphone are classified as full μ-receptor agonists, other opioids such as buprenorphine and butorphanol are classified as partial agonist-antagonists. The partial μ-receptor binding may contribute to a lack of an emetic affect.

The applicant conceded that neither all opioids nor all opioids that are μ-receptor agonists produce nausea and vomiting, and proposed to restrict the new indications to dogs receiving premedication with a "full opiate receptor agonists such as morphine", e.g. morphine, hydromorphone, oxymorphone.

The CVMP agreed that there are large similarities between the full μ-receptor agonists morphine, hydromorphone, and oxymorphone, and differences to the partial μ-receptor agonist buprenorphine. The Committee also noted that fentanyl and methadone, which are also full μ-receptor agonists and widely used in small animal clinic, however, do not cause emesis. The CVMP considered that Cerenia might possibly also be effective in cases where other full μ-receptor agonists cause vomiting and nausea. However, there are no data to support a claim for full μ-receptor agonists other than the morphine study.

Since no data were presented for dogs that received premedication with other full μ-receptor agonists, the CVMP concluded that insufficient data were provided to consider extrapolation of a similar effect for other opioids working mainly on the μ-receptor, in case these are known to cause vomiting and nausea.

Based on the data provided, the CVMP concluded to restrict the new indication for Cerenia to anesthetic protocols which involve morphine, i.e. "For the prevention of perioperative nausea and vomiting and improvement in recovery from general anesthesia after use of the μ-opiate receptor agonist morphine".

3. Benefit-risk assessment

Certain surgical procedures and anaesthetic agents are known to cause nausea and vomiting in dogs. Pre-operative and post-operative vomiting is a significant risk factor for the veterinary surgeon due to the potential for aspiration pneumonia.

The applicant applied for a new indication for Cerenia in dogs: Prevention of perioperative nausea and vomiting, and improvement in recovery from general anaesthesia after use of full opiate receptor agonists such as morphine.

In support of the application, two laboratory studies were provided in dogs as presented below.

3.1. Benefit assessment

In dogs receiving the full μ-opiate receptor agonist morphine as premedication before undergoing surgery, Cerenia prevented perioperative nausea and vomiting, and showed an improvement in anaesthetic recovery including return to appetite, as compared to placebo-treated animals.

This effect of Cerenia could not be demonstrated in dogs receiving premedication with buprenorphine, which is only a partly acting μ-opiate receptor. The CVMP therefore restricted the proposed new indication (prevention of perioperative nausea and vomiting, and improvement in recovery from general anesthesia) only to dogs that received the μ-opiate receptor agonist morphine as premedication.

3.2. Risk assessment

Cerenia is administered as a single injection. Apart from the known adverse reactions (pain at injection site, in very rare cases, anaphylactic type reactions), which are already adequately described in the SPC no new events have been reported following the use of Cerenia in the proposed new indication.

There is no new risk anticipated for the target animal (dog), the user or the environment.

3.3. Evaluation of the benefit-risk balance

Cerenia has shown to be beneficial in dogs for the prevention of perioperative nausea and vomiting, and improvement in recovery from general anesthesia after use of the μ-opiate receptor agonist morphine. No change to a risk for the target animal (dog), the user or the environment is envisaged.

The benefit-risk balance remains unchanged, when used as recommended in the SPC and product information.

4. Overall conclusions of the evaluation and recommendations

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.

4.1. Changes to the community marketing authorisation

Changes are required in the following annexes of the Community marketing authorisation:

Annexes I and IIIB