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Veterinary Medicines and Product Data Management

EPAR for Onsior

Grouping of type II variations (EMEA/V/C/000127/II/0006/G)
Scope of the variation:

Type II - C.I.6.a) New indication – solution for injection ("treatment of pain and inflammation associated with orthopaedic surgery in cats (including repeated use post surgery)") and consequent changes in SPC and product literature.

Type II - C.I.6.a) New indication – tablets ("treatment of pain and inflammation associated with orthopaedic surgery in cats") and consequent changes in SPC and product literature.

Type IB - C.I.3.a) - Additional warnings following PSUR assessment.

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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, Novartis Animal Health (UK) Ltd. (applicant), submitted to the European Medicines Agency (the Agency) on 7 October 2011 an application for a grouping of two type II and one type IB variations for Onsior.

1.1.1. Scope of the variations

Type II - C.I.6.a) New indication – solution for injection ("treatment of pain and inflammation associated with orthopaedic surgery in cats (including repeated post surgery use)") and consequent changes in SPC and product literature.

Type II - C.I.6.a) New indication – tablets ("treatment of pain and inflammation associated with orthopaedic surgery in cats") and consequent changes in SPC and product literature.

Type IB - C.I.3.a) - Additional warnings following PSUR assessment (covering the period 01/07/2010 to 31/12/2010).

1.1.2. Background information on the variation:

Onsior is currently authorised for dogs for the treatment of pain and inflammation associated with chronic osteoarthritis (tablets) and orthopaedic or soft tissue surgery (solution for injection), respectively. In cats, Onsior is currently authorised for treatment/relief of (acute) pain and inflammation associated with musculo-skeletal disorders (tablets) and soft tissue surgery (solution for injection).

The scope of this variation was to widen the indications for cats, by adding the treatment of pain and inflammation associated with orthopaedic (tablet and solution for injection) surgery to the existing indications. In addition, following the assessment of PSURs, some changes in section 4.6 (special warnings) were proposed for both species and formulations.

In July 2012 the CVMP by consensus considered that this 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, was acceptable concerning the solution for injection ("treatment of pain and inflammation associated with orthopaedic surgery in cats (excluding the repeated post surgery use)") and the additional warnings following PSUR assessment. However, the CVMP by majority recommended the refusal of the variation to the terms of the marketing authorisation, concerning the new tablet indication ("treatment of pain and inflammation associated with orthopaedic surgery in cats")

Following the receipt of a composite opinion by the CVMP for this variation (12 June 2012), the applicant requested a re-examination of the CVMP opinion. An ad-hoc expert group (AHEG) was involved in this re-examination, consisting of experts in veterinary surgery, analgesia (pain management) and statistics.

Based on the re-assessment of the data submitted in the dossier and the recommendations given by the AHEG, the CVMP adopted in November 2012 a final opinion, recommending the new indications for the Onsior solution for injection ("treatment of pain and inflammation associated with orthopaedic surgery in cats (including the repeated post surgery use)") and for the Onsior tablets ("for the reduction of moderate pain and inflammation associated with orthopaedic surgery in cats"), respectively. The inclusion of additional warnings following the PSUR assessment was also recommended.

2. Scientific discussion

Robenacoxib is a highly selective cyclooxygenase -2 (COX-2) inhibitor in cats, and at recommended dosages both the injection and tablet will produce marked inhibition of COX-2 with limited effect on COX-1 in cats (and dogs). Robenacoxib has been shown to have analgesic, anti-inflammatory and antipyretic properties in cats. The present variation is to add new indications, and to modify the posology and safety warnings.

The applicant provided two new tolerance studies in support of the safety of the tablet in cats, and four new clinical studies in support of the proposed change to the use of the product for the cat. In addition, a PSUR in support of the proposed safety changes was submitted.

The applicant also included a number of publications on robenacoxib, based on actual study data. As these data have been evaluated in relation to the initial application, they have not been re-assessed.

3. Tolerance

Two new tolerance studies with the tablets and a PSUR covering the period from 1 July 2010 to 31 December 2010 were provided.

No tolerance data on the use of the solution followed by administration of the tablets (vice versa) was submitted.

3.1. A tolerance study of robenacoxib tablets in cats

A randomized, blinded study was provided, investigating the safety of robenacoxib tablets following daily oral administration at 0 or 24 mg/kg robenacoxib (10 x the maximum recommended therapeutic dose (RTD) of 2.4 mg/kg bw) to fasted young cats (8-months) over a 21-day period.

Differences in clinical pathology parameters and organ weights between controls and treated cats were occasionally observed. There were no treatment-related effects in either gross necropsy or histopathology evaluations. There were no apparent treatment effects in body weight, feed or water consumption, body temperature, haematology, clinical chemistry, coagulation or ophthalmology.

In conclusion, administration of 10X the RTD of robenacoxib tablets to male and female cats for 21 days produced only minor changes in some of the parameters examined, and is overall well tolerated.

3.2. 6-month oral safety study of robenacoxib tablets for cats.

In this study, 32 young cats (8-month) were given daily doses of 0, 2.4, 7.2 and 12 mg robenacoxib/kg bw/day (i.e. 1X, 3X, or 5X RTD) as whole tablets in gelatine capsules for 6 months.

In the robenacoxib treated cats reduced body weight and food consumption (after approx. 3 weeks), dose related and possibly time related increase of heart QTc interval (at D41 and D175), reduced kidney weight, mild kidney lesions (degenerative/regenerative lesions, with or without chronic inflammation and/or papillary necrosis) and mild liver lesions (increased Kupffer cell pigmentation) were observed.

Such findings were not noted in other studies, and it was concluded that these were non-serious adverse reactions due to their mild severity, and uncertain toxicological relevance, and probably due to reduction in food consumption.

The CVMP considered, however, that a relationship between robenacoxib and the observed effects could not be excluded. However, as the current application was only relating to short-term use, the Committee acknowledged that the results of this long-term study would have no direct relevance to the proposed changes to the marketing authorisation, and therefore this issue needed no further discussion.

3.3. PSUR for Onsior, covering the period from July 2010 to December 2010 (6-months)

During this period, 15 reports were received for Onsior 20 mg/ml solution for injection (11 dogs and 6 cats) and 32 reports for Onsior tablets (27 dogs and 5 cats).

Data revealed that in very rare cases lethargy can be observed, and that pain at injection was more commonly observed than anticipated. The CVMP concluded that except for lethargy, no new adverse reactions were observed for the tablets, and agreed with the changes proposed by the applicant adding an appropriate warning to section 4.6 of the SPC. With respect to pain at injection, the observed frequency for the dog is higher than anticipated and the Applicant proposes to amend the text of section 4.6 of the SPC as follows: "Pain at injection site was commonly reported". A similar change is made to section 5.1 of the SPC.

3.4. Overall conclusion on tolerance

The tolerance of a single injection followed by tablets for up to 11 days was studied in clinical trials in cats undergoing soft tissue and orthopaedic surgery, and was assessed previously.

The results from a new overdose study using the tablet formulation (21-day tolerance study) were in agreement with those presented before, concluded that overall robenacoxib tablets were well tolerated in cats. It was pointed out that the study population, consisting of young healthy cats, may not be representative for the target population. Vomiting was the major treatment related adverse effect.

Data from the PSUR did not reveal unexpected adverse effects, except for lethargy in very rare cases. The applicant added an appropriate warning to section 4.6 of the SPC (warnings).

The tolerance of robenacoxib solution for injection followed by administration of tablets, or vice versa, was not studied in tolerance studies. However, these data were not considered necessary, in view of the lack of persistence of robenacoxib in blood at 24 hours after dosing with either the injection or tablets, and the reasonably wide margin of safety in healthy cats. Even if accumulation would occur when used at the recommended dose rates, this would not immediately lead to adverse events.

Overall, the conclusions made previously on the tolerance of the cat for robenacoxib tablets when used at the recommended dose rate of up to 2.4 mg/kg bw by the oral route and for up to 6 consecutive days remained valid.

4. Clinical studies

Data from four new clinical trials were submitted, as well as a pilot study that was already submitted with the initial application. The pilot study was not re-assessed.

In all four new studies, the final formulations of the injection and tablet were used, and all the studies were conducted in compliance with GCP (VICH GL9) and national / federal regulations, where relevant. The four clinical studies were carried out to demonstrate the efficacy of robenacoxib injection and tablets when used peri-operatively in case of orthopaedic surgery to control pain and inflammation. Dosages were the same as already authorised for the solution for injection / tablets, i.e. solution for injection: 2 mg/kg via the subcutaneous route, tablet: 1-2.4 mg/kg bw.

4.1. Confirmatory efficacy field study of robenacoxib administered by subcutaneous injection and tablets for peri-operative pain and inflammation after orthopaedic surgery in cats

The pivotal study was a multi-centre, positive and negative-controlled, randomized and blinded comparison of 2 treatment groups, carried out in the EU (France and the United Kingdom (UK)) between 2005 and 2009. The surgery involved a number of cats and included conditions that are known to induce pain over a short period of time, e.g. fractures, hip and joint surgery, amputations and other types of surgery. Inclusion and exclusion criteria were provided.

The treatment routine was a single pre-operative subcutaneous injection with 2 mg/kg robenacoxib or a positive control (meloxicam) administered by the veterinarian, and follow-up treatment with robenacoxib tablets (test) or placebo (control) administered by the animal owner at a dose rate of 1-2 mg/kg for 9 ± 2 days.

In the UK, the use of butorphanol within the 24 hours up to and including premedication was permitted via amendment, because of ethical concerns, reflecting standard UK practice for feline surgery.

Clinical examinations were performed by the clinician before surgery and approximately 3, 8 and 22 hours after surgery/return of the palpebral reflex, 2 to 6 hours after the first oral administration of the test treatment, and at the final visit at day 10. Efficacy was assessed by the clinician based on a multidimensional rating scale taking into account the posture and behaviour of the cat in the recovery cage and pain on palpation/manipulation at all visits (primary endpoint). As a secondary endpoint, overall pain control, sedation and inflammation intensity of the wound) at final visit were assessed by the clinician, and the cat's activity, behaviour, appetite and sociability were assessed by the animal owner (daily when cats at home). In addition, blood samples for haematology and blood chemistry were taken (France only) pre-surgery, approximately 4 hours after the first oral dose, and at day 10.

Efficacy:
In regard to the solution for injection, non-inferiority of robenacoxib as compared to the positive control meloxicam was shown. The efficacy of a single subcutaneous dose of 2 mg/kg bw to achieve peri-operative pain control in connection with orthopaedic surgery in cats was therefore shown.

However, for the tablet formulation, no differences in effect between robenacoxib and placebo tablets were observed. A non-inferiority design was chosen by the applicant, but for this type of comparison (robenacoxib versus placebo) a superiority design would have been more appropriate. The study design was similar to that of a previously already submitted study, in which it was also concluded that the results did not demonstrate the efficacy of the tablet, i.e. the efficacy of the tablet formulation as follow-up treatment after surgery was not demonstrated.

Tolerance:
There were no significant differences between the two treatment groups in the frequency of adverse events. The tolerability in both groups was considered as acceptable for this class of drugs. Analysis of the hepatic enzymes did not reveal significant differences between robenacoxib and positive or negative control groups. Assessment of the local tolerability of the injectable did not reveal significant differences between robenacoxib and meloxicam.

In addition to the pivotal European field study, the applicant also submitted clinical data from one trial undertaken in Japan and in two the USA. The US studies were undertaken by the applicant following advice given by the FDA.

4.2. Clinical study of the efficacy and safety of robenacoxib for peri- and post-operative pain and inflammation in cats

The objective of this clinical trial was to investigate the efficacy and safety of robenacoxib for peri- and post-operative pain and inflammation associated with orthopaedic or soft tissue surgery in cats. The study was carried out in Japan in compliance with GCP for veterinary medicinal products. Robenacoxib (2 mg/kg) and meloxicam (0.3 mg/kg) were injected pre-operatively only. Butorphanol was allowed additionally as pre-operative treatment.

However, the number of cases concerning orthopaedic surgery was too low to allow evaluation of a treatment effect, and the study was not further considered in the assessment of the current application.

4.3. Field effectiveness and safety of robenacoxib (injectable) for the control of postoperative pain and inflammation associated with ovariohysterectomy, castration and onychectomy in cats

This was a randomized, blinded, placebo controlled, multi centre GCP compliant field study involving a number of cats. The study was conducted in the USA, comparing the effect of robenacoxib as a single pre-operative subcutaneous injection (2.0 mg/kg), and post-operative for 2 additional days at the same dosage, to that of a placebo (0.9% NaCl), using the same administration scheme.

Cats received surgery for declawing on the fore-paws in combination with ovariohysterectomy or castration, and were allocated to one of the 2 groups in a 2:1 ratio of robenacoxib to placebo. All cats were treated with butorphanol pre-operative. Observations were made after surgery up to 52 hours. The primary efficacy parameter was the need for rescue treatment with butorphanol or any analgesics except other NSAIDs, secondary efficacy parameters included animal behaviour (posture, behaviour from a distance or following social interaction) and pain (elicited on palpation, and overall pain control).

The trial design followed a superiority design with regards to the primary variable (need for rescue treatment). Secondary endpoint variables were evaluated on Day 1 until 8 hours after surgery and were only descriptive beyond 8 hours. Over the whole treatment period, a lower proportion of rescues were observed in the robenacoxib group compared to placebo group (20.63% versus 37.29%).

The Kaplan-Meier plots and Cox-Tarone test and Gehan-Breslow tests indicated significantly less frequent need for rescue analgesia with the robenacoxib injection up to the last time point at 52 hours, thereby supporting the 3 day indication.

With regards to the primary endpoint (need for rescue therapy), the CVMP agreed that it was an appropriate primary clinical endpoint. The primary endpoint analysis allowed a clear demonstration of

efficacy. It was also considered that declawing could be used as a model for moderate orthopaedic pain evaluation in cats in the context of this procedure.

The CVMP also concluded that since all animals (verum and placebo group) received butorphanol as a standard of care, the groups could be comparable concerning the issue of concomitant medication. This was not considered problematic, as it is now adequately reflected in the product literature.

Finally the CVMP confirmed that there was a lack of data with regards to the treatment of inflammation related to surgery. However, the mode of action of NSAIDs and their role in the peri-operative use for the treatment of pain and inflammation was acknowledged. Therefore, the CVMP accepted the inclusion of "inflammation" in the indication.

As a result of the above it was agreed that this study confirmed the efficacy of the repeated post surgery use up to 3 days of the Onsior solution for injection.

4.4. Field effectiveness and safety of robenacoxib (Tablet) for the control of postoperative pain and inflammation associated with ovariohsterectomy, castration and onychectomy in cats

The efficacy of the tablets was investigated in a randomized, blinded, placebo controlled, multi centre field study involving a number of cats. The study was conducted in the USA, comparing the effect of robenacoxib tablets (once daily, 1-2.4 mg/kg bw) with a placebo tablet, administered pre-operative and post-operative for 2 additional days at the same dosage. All cats received butorphanol and a forelimb metacarpal block as part of the pre-operative therapy. The first treatment was given approximately 30 minutes prior to surgery at the same time as the pre-anaesthetic was given.

The same efficacy parameters were chosen as in the study above, i.e. primary efficacy parameter was the need for rescue treatment; secondary efficacy parameters included animal behaviour and pain. As mentioned in the previous study the need for rescue treatment was considered an appropriate clinical endpoint.

A statistically significant difference was shown between the robenacoxib and the placebo group with regards to the primary endpoint (in the robenacoxib group (14.91%) versus the placebo (45.57%).

Also a statistically significant difference in the efficacy of the tablet group versus the placebo was demonstrated for the following endpoints: posture score, social interaction behaviour score and soft tissue incision site pain score. In some cases (distance behaviour, paw assessment pain and overall pain control) the statistical model (ProcGLIMMIX) did not converge and therefore prevented statistical analysis.

As in the previous study it was considered that declawing could be used as a model for moderate orthopaedic pain evaluation in cats in the context of this procedure. Although it is not representative of all orthopaedic surgical procedures, the difficulties associated with conducting a study representing all orthopaedic procedures regarding the different level of pain were acknowledged. The addition of a soft tissue surgical procedure increased the level of overall pain although it did not represent a more severe orthopaedic surgical procedure. The applied combination of orthopaedic and soft tissue procedures did not allow a clear differentiation of the pain source.

The issues of concomitant medication and the inclusion of inflammation in the tablet indication for orthopaedic surgery were also relevant for this trial. The CVMP comments made on these issues in the previous study were also applicable for this one.

Finally based on the time to peak concentration (Tmax) of the oral formulation it was considered that the time of oral administration should be 30 minutes prior to surgery. However, tablets should be administered to a conscious animal. The wording in section 4.9 of the SPC was therefore amended accordingly.

On the basis of this study it was concluded that the efficacy of an oral dose (tablets) of Onsior of 1-2.4 mg robenacoxib/kg bw to achieve pain control following orthopaedic surgery associated with moderate pain in cats was demonstrated. As a result the recommended indication was as follows: "For the reduction of moderate pain and inflammation associated with orthopaedic surgery in cats".

4.5. Overall conclusions on efficacy in case of orthopaedic surgery

In support of the new indication for pain control following orthopaedic surgery, the CVMP considered the results of a European and two US field studies.

Efficacy of a single subcutaneous injection of 2 mg/kg bw to achieve peri-operative pain control in connection with orthopaedic surgery in cats was demonstrated in a GCP-compliant European field trial where non-inferiority of robenacoxib was shown to a positive control (meloxicam). Efficacy of repeated injections post surgery was confirmed in a randomised placebo-controlled clinical field study under US field conditions.

Efficacy of an oral dose of 1-2 mg robenacoxib/kg bw to achieve pain control following orthopaedic surgery in cats was demonstrated in a randomised placebo-controlled clinical field study for orthopaedic procedures associated with moderate pain. The proposed indication was revised accordingly. The timing for administration should be approximately 30 minutes before surgery, but not before general anaesthesia.

5. Benefit-risk assessment

5.1. Benefit assessment

Onsior solution for injection is currently authorised in cats for the treatment of pain and inflammation associated with soft tissue surgery. The new indication to widen the use of the product also for other types of surgery, i.e. orthopaedic surgery was considered as demonstrated. The efficacy of repeated injections post surgery was confirmed in a randomised placebo-controlled clinical field study under US field conditions.

Onsior tablets are currently authorised in cats for the treatment of pain and inflammation associated with musculoskeletal disorders. The efficacy for the proposed new indication to widen the indication for orthopaedic surgery was demonstrated in a randomised placebo-controlled clinical field study for orthopaedic procedures associated with moderate pain. The proposed indication was revised accordingly. The timing for administration should be approximately 30 minutes before surgery, but not before general anaesthesia. The wording in section 4.9 of the SPC and corresponding information in the product literature has been revised accordingly.

5.2. Risk assessment

Data provided during the PSUR assessment revealed that in very rare cases lethargy can be observed in dogs as in cats, and the SPC for both the tablet and solution for injection was amended accordingly.

Also, the frequency and intensity of pain experienced by cats at the injection site was clarified in the SPC.

As the variation does not result in major changes to the current posology, no additional risks can be identified and the risk profile of the product remains unchanged. Therefore it is not necessary to change the current PSUR cycle.

5.3. Evaluation of the benefit-risk balance

No change to the impact on the environment is envisaged.

Since efficacy has been demonstrated with regard to the new indications, the benefit-risk balance of the product is considered positive.

6. Final overall conclusions of the evaluation and recommendations

The CVMP considers by consensus that this 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 acceptable concerning the following change(s):

- Type II - C.I.6.a) New indication – solution for injection ("treatment of pain and inflammation associated with orthopaedic surgery in cats", (including the repeated use of the solution for injection post surgery)) and consequent changes in SPC and product literature.
- Type IB - C.I.3.a) - Additional warnings following PSUR assessment.
- Type II - C.I.6.a) New indication – tablet ("For the reduction of moderate pain and inflammation associated with orthopaedic surgery in cats") and consequent changes in SPC and product literature.