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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for a grouped type II variation for Onsior (EMEA/V/C/000127/II/0024/G)

International non-proprietary name: robenacoxib

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

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1. Introduction

1.1. Submission of the variation application

In accordance with Article 7 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, Elanco GmbH (the applicant), submitted to the European Medicines Agency (the Agency) on 29 May 2019 an application for a grouped type II variation for Onsior.

1.2. Scope of the variation

Variations requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II
C.I.4	Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II
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C.I.4	Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

The variation is to introduce the following changes:

- To add a new therapeutic indication: for the treatment of pain and inflammation associated with soft tissue surgery in dogs (tablets);
- To update the product information in order to extend the period of administration for up to 2 days in dogs undergoing soft tissue surgery (solution for injection);
- To update the product information in order to reflect the interchangeable use of tablets and solution for injection in dogs (tablets and solution for injection);
- To update the product information in order to include information in case of accidental intravenous use in dogs (solution for injection);
- To update the product information regarding interactions in case of concurrent use of Onsior with furosemide and benazepril in dogs (tablets and solution for injection).

In addition, the MAH takes the opportunity to include editorial changes to the product information.

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

This application relates to the following sections of the current dossier held by the Agency:

Part 1 and Part 4.

1.4. Scientific advice

Not applicable.

1.5. MUMS/limited market status

Not applicable.

2. Scientific Overview

The product Onsior contains the active substance robenacoxib, a highly selective inhibitor of cyclooxygenase 2 enzyme (COX-2) and is presented as tablets for cats (6 mg), tablets for dogs (5, 10, 20 and 40 mg) and solution for injection for cats and dogs (20 mg/ml).

In dogs, so far, Onsior has been approved for the treatment of:

- pain and inflammation associated with chronic osteoarthritis (tablets);
- pain and inflammation associated with orthopaedic or soft tissue surgery (solution for injection) – one subcutaneous administration before surgery.

This application consists of one C.I.6.a and four C.I.4 Type II variations affecting Onsior tablets for dogs and Onsior solution for injection:

- Type II C.I.6.a – Addition of a new therapeutic indication – proposed new indication: for the treatment of pain and inflammation associated with soft tissue surgery in dogs (tablets);
- Type II C.I.4 – Significant modifications of the SPC – the proposed change is to extend the period of administration for up to 2 days in dogs undergoing soft tissue surgery (solution for injection);
- Type II C.I.4 – Significant modifications of the SPC – the proposed changes relate to the intended interchangeable use of tablets and solution for injection in dogs (tablets and solution for injection);
- Type II C.I.4 – Significant modifications of the SPC – the proposed changes include safety information in case of accidental intravenous use of Onsior in dogs (solution for injection);
- Type II C.I.4 – Significant modifications of the SPC – the proposed changes reflect the interactions in case of concurrent use of Onsior with furosemide and benazepril in dogs (tablets and solution for injection).

New studies as well as studies previously assessed have been submitted in support of this application. Also, literature considered relevant for this application has been included in the dossier.

All confirmatory field trials and key target animal safety trials were conducted with the final formulation of both Onsior solution for injection and tablets for dogs.

2.1. Addition of a new therapeutic indication: for the treatment of pain and inflammation associated with soft tissue surgery in dogs (tablets)

No new studies have been conducted on pharmacodynamics, and no additional dose determination/confirmation studies were performed.

The proposed oral dose of robenacoxib for this new therapeutic indication (treatment of pain and inflammation associated with soft tissue surgery in dogs) is 2 mg/kg bw, which is identical to the dose already approved for solution for injection for the same indication. The dose of 2 mg/kg bw was supported by results of a previously assessed dose finding study. By applying a urate synovitis model, this study demonstrated that, at 3-6 hours following treatment, a dose of approximately 2 mg/kg bw was appropriate for the relief of more severe pain (e.g. peri or post-operative pain; 80-90% of the maximal efficacy (ED80/90)). Also, a single dose of 2 mg/kg bw was already authorised for the solution for injection for the treatment of pain and inflammation associated with orthopaedic or soft tissue surgery in

dogs. Since systemic bioavailability of the solution for injection and the tablets is comparable, this further supports the dose of 2 mg/kg bw.

The pharmaceutical form of the product is an unscored tablet, therefore precise dosing is not possible. As 2 mg/kg bw is considered the minimal effective dose, and the product has a high safety margin, the use of a dose range (2-4 mg/kg bw) is considered appropriate.

The efficacy of Onsior tablets for the proposed indication, treatment of pain and inflammation associated with soft tissue surgery in dogs, was assessed in one new GCP-compliant pivotal field study conducted in various geographic locations within the USA. The primary objective of this study was to evaluate the effectiveness and safety of Onsior tablets administered orally at a target dose of 2 mg robenacoxib/kg bw (with a dose range of 2–4 mg/kg bw) once daily for three days for the control of post-operative pain and inflammation associated with soft tissue surgery in dogs.

This was a randomised, blinded, placebo-controlled, multi-centre confirmatory efficacy field study which included 239 client-owned dogs (intent-to-treat (ITT) population) requiring some form of soft tissue surgery (various abdominal surgeries or major external surgeries). Otherwise, the animals were clinically healthy. The target population is considered sufficiently representative for the field situation. All dogs received a one-time pre-anaesthetic dose of 0.2 mg/kg bw butorphanol as pre-operative treatment administered IM or IV. This is considered appropriate, as performing extensive surgery on dogs that have not received some form of analgesia is considered ethically unacceptable. In addition, the dogs received either a placebo treatment (n=120) or 2 mg/kg bw robenacoxib orally (n=119). This treatment was continued once daily for up to two days following surgery (resulting in a total treatment duration of three days). Efficacy was analysed on a per-protocol (PP) data set (n=231), with 116 dogs in the Onsior-treated group and 115 dogs in the placebo group.

A validated composite scale for assessing pain in dogs in a hospital setting based on observations of behaviour was applied (short-form Glasgow Composite Measure Pain Scale; CMPS-SF). The dogs were evaluated post-surgically using the CMPS-SF at pre-determined intervals to assess the overall response to treatment (1.5h, 3h, 5h, 8h post-extubation on Day 0, and on two post-administration times for the following two days (D1-2)). Dogs showing obvious discomfort or pain or scoring ≥6 on the CMPS-SF were 'Rescued' (additional pain intervention required; 'Failure') and removed from the study. As a safety measure, dogs showing obvious discomfort would also be rescued, regardless of the CMPS-SF score.

Blood samples for haematology and clinical chemistry were taken prior to treatment and upon study completion/withdrawal; also, urinalysis was performed prior to treatment and upon study completion/withdrawal.

The Onsior-treated group was compared to the placebo group on a success/failure basis. The primary efficacy variable (treatment success/failure) was 'Rescue', with superiority established by a statistically significant difference between the proportion of rescues (animals requiring additional pain medication) in the Onsior-treated group compared to the placebo control group. Data for the primary endpoint at all time points (>0-52 hours) were included in the statistical analysis. This analysis was supplemented by time to event analysis (using the Kaplan-Meier method).

Secondary efficacy variables were the Total Pain Scores calculated for each animal at several time points. The Total Pain Score was calculated at each observation time point as the sum of the pain category scores defined on the CMPS-SF. Six CMPS-SF categories were scored: vocalization, attention to wound area/surgical site, mobility, response to touch, demeanour and posture/activity. Formal statistical analyses of the secondary endpoints (subjective scores) were only made for the first 8 hours post-extubation (applying last-observation-carried-forward (LOCF)). The rationale for the exclusion of the secondary endpoints beyond 8 hours post-extubation was the expected higher proportion of cases withdrawn from the placebo group, which would result in a bias.

For the primary efficacy variable, the results obtained in this study showed that 27 dogs (23.28%) in the Onsior-treated group were 'rescued' (i.e. additional pain medication was administered), compared to 41 dogs (35.65%) in the placebo group; that is, only a 12.37% reduction in pain intervention was recorded. Likewise, it is of notice that 64.35% of the placebo-treated dogs (n=74) did not need any pain intervention at all, and robenacoxib treatment only improved the success rate with 12.37% (to 76.72%; n=89). Nonetheless, the study demonstrated a statistically significant reduction (p=0.0188) in the proportion of rescues in the Onsior group compared to the placebo group, i.e. the placebo group required significantly more rescue treatments, compared to the treated group.

For the secondary efficacy variable, overall, the mean Total Pain Scores were lower in the robenacoxib group at all pain assessment time points post-surgery. There was a significant *treatment-by-time* interaction ($p<0.0001$) and therefore all treatment groups were compared at each time point. Significant differences in the least squares mean Total Pain Scores between the robenacoxib group and the placebo control group were recorded at 3, 5 and 8 hours post-extubation, with the robenacoxib group having lower scores. Of the six individual components contributing to Total Pain Score, one component (response to touch) yielded significantly different results between groups, with significantly less sensitivity to touch observed in the treated group at 3, 5 and 8 hours following surgery, whilst a statistically significant overall effect of treatment was observed for posture/activity. The remaining four components (vocalization, attention to wound/surgical site, mobility and demeanour) did not demonstrate significant differences between the treated and the control group.

No dogs with a CMPS-SF score of <6 required rescue, and none were classified as a treatment failure due to an adverse event.

Evaluation of clinical pathology indices showed no biologically significant differences between the robenacoxib and placebo groups.

Safety evaluation showed that oral administration of Onsior at a target dose of 2 mg robenacoxib/kg bw prior to soft tissue surgery and again once daily for up to 2 days after surgery (i.e. a total of three doses) was generally well tolerated.

The main adverse events reported in this study were gastrointestinal disorders (diarrhoea, vomiting), which are addressed in section 4.6 of the SPC. One death occurred in the Onsior-treated group, but this was not considered treatment-related.

The low incidence of adverse events and absence of biologically relevant effect of robenacoxib on clinical chemistry and haematology variables are consistent with results of previous studies, which already demonstrated that Onsior has a relatively high safety margin. Acceptable safety in the short-term (up to three days) oral use of robenacoxib in dogs was demonstrated in this study.

In conclusion, both the primary as well as the secondary efficacy variables support efficacy of the product for the proposed indication. A three day recommendation is supported by the primary efficacy variable (Kaplan-Meier plots), that demonstrated that the frequency of treatment success (dogs which did not require rescue analgesia) was higher in the robenacoxib group compared to the placebo at all time points from >0 to 52 hours. Considering all the data available, this variation concerning the addition of a new therapeutic indication for the treatment of pain and inflammation associated with soft tissue surgery in dogs (Onsior tablets) can be accepted.

2.2. Extension of the period of administration in dogs undergoing soft tissue surgery (solution for injection)

Currently, Onsior solution for injection is indicated in dogs for the treatment of pain and inflammation associated with orthopaedic or soft tissue surgery, as a single subcutaneous administration approximately 30 minutes before the start of surgery, at a dose of 2 mg robenacoxib/kg bw.

The proposed variation is to extend the period of administration for up to 2 days following soft tissue surgery in dogs using the same dose (2 mg/kg bw) as already approved for this indication (single administration before surgery); therefore, the selection of the subcutaneous dose of 2 mg robenacoxib/kg bw is considered appropriate. In support of this variation, the applicant submitted the results of one new GCP-compliant pivotal field study and one pilot field study.

The pivotal study was conducted in various geographic locations within the USA and the primary objective was to evaluate the effectiveness and safety of Onsior solution for injection administered subcutaneously at a dose of 2 mg robenacoxib/kg bw once daily for 3 days for the control of postoperative pain and inflammation associated with soft tissue surgery in dogs.

The pivotal field study was a randomised, blinded, placebo-controlled, multi-centre confirmatory efficacy field study which included 317 client-owned dogs (ITT population) requiring some form of soft tissue surgery (various abdominal surgeries or major external surgeries), but otherwise clinically healthy. The target population is considered sufficiently representative for the field situation. All dogs received a one-time pre-anaesthetic dose of 0.2 mg/kg bw butorphanol as pre-operative treatment administered IM or IV. In addition, approximately 45 minutes prior to surgery, dogs received either a placebo treatment (n=158) or 2 mg/kg bw robenacoxib subcutaneously (n=159) and this treatment was continued once daily for up to two days following surgery (resulting in a total treatment duration of three days). Efficacy was analysed on a per-protocol (PP) data set (n=303), with 151 dogs in the Onsior-treated group and 152 dogs in the placebo group.

The same CMPS-SF validated composite scale for assessing pain in dogs in a hospital setting based on observations of behaviour was applied. The dogs were evaluated post-surgically using the CMPS-SF at pre-determined intervals to assess the overall response to treatment (1.5h, 3h, 5h, 8h post-extubation on Day 0, and on two post-administration times for the following two days). Dogs showing obvious discomfort or pain or scoring ≥6 on the CMPS-SF were 'Rescued' (additional pain intervention required; 'Failure') and removed from the study. As a safety measure, dogs showing obvious discomfort would also be rescued, regardless of the CMPS-SF score.

Blood samples for haematology and clinical chemistry were taken prior to treatment and upon study completion/withdrawal; also, urinalysis was performed prior to treatment and upon study completion/withdrawal.

Onsior-treated group was compared to the placebo group on a success/failure basis. The primary efficacy variable (treatment success/failure) was 'Rescue', with superiority established by a statistically significant difference between the proportion of rescues (animals requiring additional pain medication) in the Onsior-treated group compared to the placebo control group. Data for the primary endpoint at all time points (>0-52 hours) were included in the statistical analysis. This analysis was supplemented by time to event analysis (using the Kaplan-Meier method).

Secondary efficacy variables were the Total Pain Scores calculated for each animal at several time points. The Total Pain Score was calculated at each observation time point as the sum of the pain category scores defined on the CMPS-SF. The same six CMPS-SF categories were scored: vocalization, attention to wound area/surgical site, mobility, response to touch, demeanour and posture/activity. Formal statistical analyses of the secondary endpoints (subjective scores) were only made for the first 8 hours post-

extubation (applying LOCF). The rationale for the exclusion of the secondary endpoints beyond 8 hours post-extubation was the expected higher proportion of cases withdrawn from the placebo group, which would result in a bias.

For the primary efficacy variable, the results obtained in this study showed that 43 dogs (28.48%) in the Onsior-treated group were 'rescued' (i.e. additional pain medication was administered), compared to 67 dogs (44.08%) in the placebo group; 55.92% of the placebo-treated dogs (n=85) did not need additional pain intervention, compared to 71.52% (n=108) of the dogs treated with Onsior. The results showed a statistically significant reduction (p=0.0055) in the proportion of rescues in the Onsior group compared to the placebo control group, i.e. the placebo group required significantly more rescue treatments, compared to the treated group.

For the secondary efficacy variable, there was a significant *treatment-by-time* interaction (p=0.0019). Significant differences in the least squares mean Total Pain Scores between the robenacoxib group and the placebo control group were recorded at 3, 5 and 8 hours post-extubation, with the robenacoxib group having lower scores. Of the six individual components contributing to Total Pain Score, two components of the pain category score yielded significantly different results at 3, 5 and 8 hours post-surgery: response to touch, with significantly less sensitivity to touch observed in the treated group, and posture/activity, with a significantly higher activity/better posture observed in the treated group. The remaining four components (vocalization, attention to wound area/surgical site, mobility and demeanour) did not demonstrate significant differences between the treated and the control group.

No dogs with a CMPS-SF score of <6 required rescue. Evaluation of clinical pathology indices showed no biologically significant differences between the robenacoxib and placebo groups.

Safety evaluation showed that subcutaneous administration of Onsior solution for injection at a dose of 2 mg robenacoxib/kg bw/day for up to 3 days was generally well tolerated.

Gastrointestinal disorders (particularly diarrhoea and vomiting) were the most frequently reported adverse events, and these are already listed in section 4.6 of the SPC. The low incidence of adverse events and absence of biologically relevant effect of robenacoxib on clinical chemistry and haematology variables are consistent with results of previous studies, which already demonstrated that Onsior has a relatively high safety margin. In this study, safety in the short-term (up to three days) subcutaneous use of robenacoxib in dogs was demonstrated.

The pilot study was a randomised, blinded, placebo and positive controlled field study aimed at evaluating the effectiveness and safety of Onsior solution for injection when administered subcutaneously at a dose of 2 mg robenacoxib/kg bw once daily for 3 days for the control of postoperative pain and inflammation associated with soft tissue surgery in dogs. Efficacy was evaluated in 61 dogs (22 in placebo group, 20 in Onsior-treated group and 19 in positive control group). Similar to the pivotal study, all animals required (extensive) soft tissue surgery, and all animals received a single treatment with butorphanol prior to surgery. The primary and secondary efficacy variables are similar to those of the pivotal study. The results showed that there was no statistically significant reduction in the proportion of rescues in the Onsior group compared to the placebo group and the positive control group, probably because the study was not sufficiently powered to detect a statistically significant difference between groups. There were significant differences in the average Total Pain Scores, Response to Touch Scores, and Mobility Scores between the Onsior group and the placebo group at 3, 5 and 8 hours post-treatment, with the Onsior group having lower scores (i.e. experiencing less pain and more ease of mobility). There was also a significant difference in the average Mobility Scores between the Onsior group and the positive control group at 1.5 hours post-treatment. Safety evaluation showed that Onsior treatment was generally well tolerated; digestive tract disorders (diarrhoea, vomiting) were the most frequently reported adverse events.

As in this study only a small group of animals was included (of which 20 were treated with Onsior), and there was no statistically significant reduction in the proportion of rescues (primary efficacy criterion) in the Onsior group compared to the placebo group and the positive control group, the results of this study are merely considered as supportive for the proposed extension of the period of administration and the safety of the product when used according to label.

In conclusion, the current variation concerning the extension of the period of administration in dogs undergoing soft tissue surgery (Onsior solution for injection) is approvable. The results of the pivotal study demonstrate that both the primary as well as the secondary efficacy variables support efficacy of the product for the proposed indication. A three day recommendation is supported by the primary efficacy variable (and Kaplan-Meier plots), which demonstrated that the frequency of treatment success (dogs which did not require rescue analgesia) was higher in the robenacoxib group compared to the placebo at all time points from >0 to 52 hours.

2.3. Interchangeable use of Onsior tablets and solution for injection in dogs (tablets and solution for injection)

To demonstrate the safety of the interchangeable use of the product in dogs, the applicant introduced one pivotal, randomised, blinded (separation of function), placebo controlled, terminal, non-GLP target animal safety study. Although the study was not GLP-compliant, its quality is considered sufficient. The objective of this laboratory study was to establish the safety of interchangeable use of Onsior tablets and solution for injection in 32 4-month old healthy mongrel dogs by alternating between oral tablet and SC injection dosing across doses used in the two indications, postoperative pain and osteoarthritis, at oral dosages of 0, ≥2.0, ≥4.0, and ≥6.0 mg/kg bw for tablets (standard dose), oral dosages of 0, ≥4.1, ≥8.0, and ≥12.0 mg/kg bw for tablets (higher dose) and at 0, 2.0, 4.0 and 6.0 mg/kg bw via SC injection. The treatment was administered in three 20-day periods of oral and SC treatments, separated by a 14-day washout (total: 88 days).

Safety evaluation was based on clinical observations, body weights, food consumption measurements, physical examinations including neurological assessments, injection site scoring, ophthalmological examinations, ECG examinations, buccal mucosal bleeding time, bioanalytical collections, clinical pathology collections, necropsies, macroscopic observations, and tissue processing. Additionally, the qualification of blood robenacoxib concentration under interchangeable use conditions was performed.

The results showed that no clinically relevant Onsior-related effects were noted in body weight, food consumption, physical and neurological examinations, ophthalmic evaluations, ECG parameters, buccal mucosal bleeding time or clinical pathology. At necropsy, no clinically relevant difference in mean organ weight was observed; macroscopic and microscopic abnormalities were present at the injection site (oedema, erythema, thickening of the skin, skin ulceration) and in the intestinal tract (inflammation, congestion or haemorrhage in the duodenum, jejunum and cecum) and these findings are reflected in section 4.10 of the SPC. These effects were considered related to the mechanism of action of robenacoxib (gastrointestinal findings) or a reflection of the injected volume and/or location of the administration site (injection site findings). No findings were attributed to the interchangeable use of Onsior oral and injectable formulations. The study also demonstrated that, when the product is used according to the label, bioaccumulation of robenacoxib is not expected.

In conclusion, as supported by this target animal safety study, interchangeable dosing of robenacoxib appears well tolerated.

With regard to efficacy, an earlier study demonstrated comparable blood pharmacokinetic profiles after oral and subcutaneous administration of Onsior. The newly performed field-efficacy studies demonstrated similar (and sufficiently good) efficacy for the solution for injection and tablets in dogs undergoing soft

tissue surgery. Finally, the safety of administering a single dose of the solution for injection prior to surgery followed by once daily treatment with the tablets for up to 14 days was demonstrated in previously assessed EU field studies for both orthopaedic and soft tissue surgery.

In conclusion, the current variation concerning the interchangeable use of Onsior tablets and Onsior 20 mg/ml solution for injection for dogs is approvable. The proposed amendments to the SPC in relation with the interchangeable use of Onsior tablets and Onsior solution for injection in dogs are accepted. In addition, this study also supports the high safety margin of the product.

2.4. Accidental intravenous use of Onsior in dogs (solution for injection)

Since occasional questions from the veterinary field have been received with regard to the safety of Onsior solution for injection following inadvertent intravenous use, the applicant considers this information to be of benefit for the veterinarian.

The applicant presented one (non-blinded) GLP randomised parallel design comparison study performed in order to assess the safety of Onsior solution for injection after a single IV administration (which is not the recommended route) in dogs. The study was performed on eight healthy beagles (4/sex); each dog was administrated Onsior injectable solution according to a randomised crossover design, with a minimum washout period of 72 hours between the following dosages of robenacoxib: 0 mg/kg bw (IV injection of saline), 2 mg/kg bw (1X SC), 2 mg/kg bw (1X IV), and 4 mg/kg bw (2X IV).

The following parameters were evaluated: clinical observation, physical examination, body weight and food consumption, clinical pathology parameters (haematology, coagulation, clinical chemistry and urinary parameters), buccal mucosal bleeding time. Cardiovascular parameters (blood pressure, heart rate, body temperature and ECG (duration of PR, PQ, QT and QRS in msec)) were recorded up to 8 hours after dosing for telemetered animals (n=4) only.

When comparing IV and SC routes, this study revealed no relevant clinical differences. However, since vomiting was observed in two animals that had received an IV dose of 4 mg/kg, a warning was included in Section 4.10. Under the experimental conditions adopted, IV injection of Onsior at 1X and 2X the recommended therapeutic subcutaneous dose, i.e. 2 and 4 mg/kg bw respectively, had no effect on arterial blood pressure, heart rate, temperature or cardiac conduction times for a period of 8 hours post-dosing in comparison with saline administered IV or Onsior at 2 mg/kg bw administered SC. No marked changes in haematology, coagulation, clinical chemistry and urinary parameters measured 8 hours post dosing were noted based on results of individual values. No clinical signs of intolerance were observed during physical and clinical examinations and, also, no effect on body weight or food consumption was recorded.

In conclusion, in case of accidental intravenous use, this study demonstrated that a single IV administration of Onsior solution for injection at doses of 2.0 and 4.0 mg/kg bw seemed to be well tolerated (in terms of physical and clinical examinations, cardiovascular and clinical pathology parameters, body weight and food consumption) in healthy dogs.

Therefore, this variation concerning the update of the product information in case of accidental intravenous use of Onsior 20 mg/ml solution for injection in dogs is approvable. The proposed amendments to the SPC are considered acceptable.

2.5. Interactions in case of concurrent use of Onsior with furosemide and benazepril in dogs (tablets and solution for injection)

In the absence of specific safety studies at that time, Onsior was first registered with a standard warning text introduced into the SPCs for all formulations, i.e. "*concomitant treatment with medicines displaying*

action on renal flow, e.g. diuretics or angiotensin converting enzyme (ACE) inhibitors, should be subject to clinical monitoring".

The applicant hereby introduced two new safety laboratory studies that studied the pharmacodynamics of the interaction and the tolerance of combined treatment of robenacoxib with an ACE inhibitor (benazepril) in healthy dogs. In one study, furosemide was also administered in order to activate the renin-angiotensin-aldosterone system (RAAS).

Both studies were non-GLP (but can be considered of sufficient quality for the objectives) and applied a non-blinded, randomised, placebo-controlled parallel-group design comparison. In both studies, treatment was given at therapeutic doses for both products in 32 healthy beagle dogs (16/sex) for seven consecutive days. The animals were randomly assigned to four groups: Onsior, benazepril, Onsior + benazepril and negative control. In one study, all four groups were treated with furosemide for 7 days.

Both studies used the glomerular filtration rate (GFR), which was estimated from the plasma clearance of iohexol, as a primary endpoint. Secondary endpoints were clinical parameters (body weight, food consumption, haematology, coagulation, clinical chemistry).

The results demonstrated that the treatment with benazepril and Onsior (separate or combined) did not influence renal function as measured by the GFR in healthy dogs treated for up to 7 days, as no significant changes in iohexol clearance were recorded in all study groups. The GFR, as estimated from the plasma iohexol clearance, was maintained in the benazepril, Onsior and benazepril, and Onsior groups compared to the negative control group. Moreover, one study demonstrated that no significant differences in GFR were present when furosemide was also administered. This indicates that the test item(s) given alone or in combination did not affect the renal excretion function in dogs with activated RAAS.

As for the secondary endpoints, neither relevant nor statistically significant changes in body weight or food consumption were observed during the biological phase of the study and no relevant clinical signs were recorded. Clinical pathology findings suggested that benazepril and robenacoxib given alone or in combination at therapeutic doses for seven consecutive days were well tolerated.

Considering the above, the results from the studies can be used in support of the proposed variation. The combined treatment appeared well tolerated for up to 7 days in healthy dogs.

In conclusion, the current variation concerning drug interaction in case of (short-term) concurrent use of robenacoxib (Onsior tablets and Onsior 20 mg/ml solution for injection in dogs) and benazepril and in case of (short-term) concurrent use of robenacoxib with benazepril and furosemide is approvable.

3. Benefit-risk assessment of the proposed change

This product is authorised:

- for the treatment of pain and inflammation associated with acute or chronic musculoskeletal disorders and for the reduction of moderate pain and inflammation associated with orthopaedic surgery in cats (tablets for cats);
- for the treatment of pain and inflammation associated with chronic osteoarthritis in dogs (tablets for dogs);
- for the treatment of pain and inflammation associated with orthopaedic or soft tissue surgery in cats and dogs (solution for injection for cats and dogs).

The active substance is robenacoxib, a non-steroidal anti-inflammatory drug (NSAID) of the coxib class.

The currently recommended dose of robenacoxib is 1 mg/kg body weight (range 1–2.4 mg/kg) in cats (tablets), 1 mg/kg body weight (range 1–2 mg/kg) in dogs (tablets) and 2 mg/kg body weight in cats and dogs (solution for injection).

The proposed variation is to:

- add a new therapeutic indication: for the treatment of pain and inflammation associated with soft tissue surgery in dogs (tablets);
- update the product information in order to extend the period of administration for up to 2 days in dogs undergoing soft tissue surgery (solution for injection);
- update the product information in order to reflect the interchangeable use of tablets and solution for injection in dogs (tablets and solution for injection);
- update the product information in order to include information in case of accidental intravenous use in dogs (solution for injection);
- update the product information regarding interactions in case of concurrent use of Onsior with furosemide and benazepril in dogs (tablets and solution for injection).

In addition, the MAH takes the opportunity to include editorial changes to the product information.

3.1. Benefit assessment

Direct therapeutic benefit

The active substance, robenacoxib, is a well-known non-steroidal anti-inflammatory drug in veterinary medicine. In dogs, following injection, it is beneficial for the treatment of pain and inflammation following soft tissue or orthopaedic surgery. Following oral administration, it is beneficial for the treatment of pain and inflammation associated with chronic osteoarthritis.

The proposed benefit of Onsior in the context of this variation application is its efficacy in the treatment of pain and inflammation associated with soft tissue surgery following oral administration and subcutaneous injection in dogs for up to two days following surgery.

The data from the two pivotal field studies, that were well-designed and conducted to an acceptable standard, demonstrated an improvement compared to controls. The indication can therefore be approved.

Additional benefits

- **Treatment of pain and inflammation associated with soft tissue surgery in dogs**

Onsior has a high safety margin.

Onsior increases the range of available treatment possibilities for pain and inflammation in dogs undergoing soft tissue surgery.

- **Interchangeable use of tablets and solution for injection (Onsior tablets and Onsior 20 mg/ml solution for injection for dogs)**

A tablet is practical for the pet owner to continue pain relief at home. Therefore, information on interchangeable use of Onsior tablets and Onsior solution for injection is of benefit.

- **Overdose advice in case of accidental intravenous use (Onsior 20 mg/ml solution for injection for dogs)**

In case accidental intravenous use occurs, this information is of benefit for the veterinarian treating the animal.

- **Concurrent use with furosemide and benazepril (Onsior tablets and Onsior 20 mg/ml solution for injection for dogs)**

Additional information on (short-term) concurrent use of Onsior with furosemide and benazepril would be of potential benefit in dogs that have a heart condition and are in need of soft-tissue surgery, which are already receiving one or both of the latter two medications (a fairly common scenario in older dogs).

3.2. Risk assessment

Quality:

Quality remains unaffected by this variation.

Safety:

Risks for the target animal:

The CVMP concluded that target animal safety for this product is acceptable when used according to the SPC recommendations.

Risk for the user:

The CVMP concluded that user safety for this product is acceptable when used according to the SPC recommendations. Standard safety advice is already included in the SPC.

Risk for the environment:

Onsior is not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is already included in the SPC.

3.3. Risk management or mitigation measures

Appropriate information has been included in the SPC and other product information to inform on the potential risks of this product relevant to the target animal.

No additional risk management or mitigation measures are considered necessary.

3.4. Evaluation of the benefit-risk balance

No change to the impact of the product is envisaged on the following aspects: quality, safety, user safety, environmental safety and target animal safety.

The benefit-risk balance remains positive.

4. Conclusion

Based on the original and complementary data presented on target animal safety and efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Onsior can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No. 1234/2008), as follows:

- To add a new therapeutic indication: for the treatment of pain and inflammation associated with soft tissue surgery in dogs (tablets);

- To update the product information in order to extend the period of administration for up to 2 days in dogs undergoing soft tissue surgery (solution for injection);
- To update the product information in order to reflect the interchangeable use of tablets and solution for injection in dogs (tablets and solution for injection);
- To update the product information in order to include information in case of accidental intravenous use in dogs (solution for injection);
- To update the product information regarding interactions in case of concurrent use of Onsior with furosemide and benazepril in dogs (tablets and solution for injection).

In addition, the MAH takes the opportunity to include editorial changes to the product information.

The CVMP considers that the benefit-risk balance remains positive and, therefore, recommends the approval of the variations to the terms of the marketing authorisation for the above-mentioned medicinal product.

Changes are required in the following Annexes to the Community marketing authorisation:

I and IIIB.

As a consequence of these variations, sections 4.2, 4.4, 4.6, 4.8, 4.9, 4.10 and 5.1 of the SPC are updated. The corresponding sections of the package leaflet are updated accordingly.