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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for type II variation for Onsior (EMEA/V/C/000127/II/0018/G)

International non-proprietary name: robenacoxib

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

Rapporteur: Gerrit Johan Schefferlie

Co-rapporteur: Ellen-Margrethe Vestergaard

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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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 Europe Ltd (the applicant), submitted to the European Medicines Agency (the Agency) on 23 June 2017 an application for a grouped type II variation for Onsior.

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
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

The grouped variation is to introduce the following changes:

- Addition of a new therapeutic indication - treatment of pain and inflammation associated with chronic musculo-skeletal disorders in cats (Onsior 6 mg tablets for cats) – type II (C.I.6.a);
- Significant modifications of the Summary of Product Characteristics: Interchangeable use of tablets and solution for injection - interchangeable use of Onsior 6 mg tablets and Onsior 20 mg/ml solution for injection for cats - type II (C.I.4); Drug interaction robenacoxib and benazepril - concurrent use with furosemide and benazepril (Onsior 6 mg tablets and Onsior 20 mg/ml solution for injection in cats) - type II (C.I.4); Intravenous use of Onsior 20 mg/ml solution for injection in cats - overdose advice in case of accidental intravenous use - type II (C.I.4).

In addition, several other amendments are proposed (editorial changes, updates to the Product Information requested by the Agency and updates consequent to the revised Quality Review of Documents (QRD) template).

Current	**Proposed**
C.I.6.a - Addition of a new therapeutic indication - treatment of pain and inflammation associated with chronic musculo-skeletal disorders in cats ***This variation applies to Onsior 6 mg tablets for cats only.***	***C.I.6.a - Addition of a new therapeutic indication - treatment of pain and inflammation associated with chronic musculo-skeletal disorders in cats*** ***This variation applies to Onsior 6 mg tablets for cats only.***
ANNEX 1	**ANNEX 1**
SUMMARY OF PRODUCT CHARACTERISTICS **4.2 Indications for use, specifying the target species**	**SUMMARY OF PRODUCT CHARACTERISTICS** **4.2 Indications for use, specifying the target species**
	AMEND AND ADD TEXT
For the treatment of **acute** pain and inflammation associated with musculo-skeletal disorders in cats.	For the treatment of pain and inflammation associated with acute or chronic musculo-skeletal disorders in cats.

.....	.....
4.6 Adverse reactions (frequency and seriousness)	**4.6 Adverse reactions (frequency and seriousness)**
Mild and transient diarrhoea, soft faeces or vomiting were commonly reported....	AMEND AND ADD TEXT Mild and transient diarrhoea, soft faeces or vomiting were commonly reported in clinical trials with treatment up to 6 days. ..... . Vomiting was very commonly reported, and anorexia, diarrhoea, lethargy and inappropriate defecation were commonly reported in field studies with treatment up to 3 months in cats with chronic musculo-skeletal disorder, with similar frequencies in the Onsior and placebo treated cats.
4.9 Amounts to be administered and administration route	**4.9 Amounts to be administered and administration route**
Acute musculoskeletal disorders treat: for up to 6 days.	AMEND TEXT Acute musculo-skeletal disorders: treat for up to 6 days. ADD TEXT Chronic musculo-skeletal disorders: Treatment duration is unlimited.
	.....
4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary	**4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary** ..... ADD TEXT In healthy young cats aged 7-8 months, oral robenacoxib (Onsior tablets) administered at overdoses of up to 5 times the maximum recommended dose (2.4 mg, 7.2 mg, 12 mg robenacoxib/kg bodyweight) for 6 months was well tolerated. A reduction in body weight gain was observed in treated animals. In the high dose groups kidney weights were decreased and sporadically associated with renal tubular degeneration/regeneration but not correlated with evidence of renal dysfunction on clinical pathology parameters.
5.1 Pharmacodynamic properties ...In clinical trials in cats, robenacoxib tablets reduced pain and inflammation associated with musculoskeletal disorders...	**5.1 Pharmacodynamic properties** AMEND AND ADD TEXT …In clinical trials in cats, robenacoxib tablets reduced pain and inflammation associated with acute musculo-skeletal disorders..In clinical trials in cats with chronic musculo-skeletal disorder, robenacoxib increased the activity and improved subjective scores of activity, behaviour, quality of life, temperament and happiness of the cats. Corresponding sections of the package leaflet are amended accordingly.
C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data - Interchangeable use of tablets and injection - interchangeable use of Onsior 6 mg tablets and Onsior 20 mg/ml injection for cats	***C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data - Interchangeable use of tablets and injection - interchangeable use of Onsior 6 mg tablets and Onsior 20 mg/ml injection for cats***
ANNEX 1	**ANNEX 1**
SUMMARY OF PRODUCT CHARACTERISTICS **4.9 Amounts to be administered and administration**	**SUMMARY OF PRODUCT CHARACTERISTICS** **4.9 Amounts to be administered and administration**

route ..... **4.10 Overdose (symptoms, emergency procedure, antidotes) if necessary** .....ADD TEXT	**route** ..... ADD TEXT The interchangeable use of Onsior tablets and Onsior solution for injection has been tested in a target animal safety study and was shown to be well tolerated by cats. **4.10 Overdose (symptoms, emergency procedure, antidotes) if necessary** .....ADD TEXT The interchangeable use of Onsior tablets and Onsior solution for injection in 4-month old cats at overdoses of up to 3 times the maximum recommended dose (2.4 mg, 4.8 mg, 7.2 mg robenacoxib/kg orally and 2.0 mg, 4.0 mg and 6.0 mg robenacoxib/kg subcutaneously) resulted in a dose-dependent increase of sporadic oedema at the injection site and minimal to mild subacute/chronic inflammation of the subcutaneous tissue. No relevant effects on body weight, bleeding time or evidence of any gastrointestinal, kidney or liver toxicity were observed. Corresponding sections of the package leaflet are amended accordingly.
C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data - concurrent use with furosemide and benazepril (Onsior 6 mg tablets and Onsior 20 mg/ml injection in cats) **ANNEX 1** **SUMMARY OF PRODUCT CHARACTERISTICS** **4.8 Interaction with other medicinal products and other forms of interaction**	***C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data - concurrent use with furosemide and benazepril (Onsior 6 mg tablets and Onsior 20 mg/ml injection in cats)*** **ANNEX 1** **SUMMARY OF PRODUCT CHARACTERISTICS** **4.8 Interaction with other medicinal products and other forms of interaction** .....ADD TEXT In healthy cats treated with and without the diuretic furosemide, concomitant administration of Onsior with the ACE inhibitor benazepril for 7 days was well tolerated and was not associated with any negative effects on renal variables including glomerular filtration rate. Corresponding sections of the package leaflet are amended accordingly.
C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data - Intravenous use of Onsior 20 mg/ml injection in cats - overdose advice in case of accidental intravenous use **ANNEX 1** **SUMMARY OF PRODUCT CHARACTERISTICS** **4.10 Overdose (symptoms, emergency procedures, antidotes) if necessary**	***C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data - Intravenous use of Onsior 20 mg/ml injection in cats - overdose advice in case of accidental intravenous use*** **ANNEX 1** **SUMMARY OF PRODUCT CHARACTERISTICS** **4.10 Overdose (symptoms, emergency procedures, antidotes) if necessary** .....ADD TEXT In healthy cats, single intravenous administration of Onsior solution for injection (robenacoxib doses of 2 or 4 mg/kg) was well tolerated and was not associated with any changes in blood pressure, heart rate or electrocardiogram.

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

The applicant received scientific advice from the CVMP on 07 February 2013 (EMA/CVMP/SAWP/760198/2012). The scientific advice pertained to efficacy issues for the clinical development of the dossier.

The applicant requested scientific advice following efficacy issues for the development of the new indication (*Addition of a new therapeutic indication - treatment of pain and inflammation associated with chronic musculo-skeletal disorders in cats (Onsior 6 mg tablets for cats)*) of this product.

The advice received was followed by the applicant.

1.5. MUMS/limited market status

Not applicable.

2. Scientific Overview

Chronic musculo-skeletal disorders (CMSD) are relatively frequent in older cats and include joint osteoarthritis (OA), spinal disorders, peri-articular fibrosis, calcification, osteochondral fragments, and post-traumatic disorders. Clinical signs in cats that suffer from CMSD vary, and are often not specific. The clinical benefit of treating cats with CMSD-associated clinical signs forms a challenge, due to the nature of the disease and the fact that cats do not manifest signs of pain and inflammation as clearly as some other species, making recognition of this disease and evaluation of treatment challenging at this stage.

Therapeutic strategies for CMSD are directed towards slowing the progression of the disease and controlling pain and inflammation in order to improve the cat's quality of life. NSAIDs are used in treatment.

So far, robenacoxib (Onsior), a highly selective inhibitor of cyclooxygenase 2 enzyme (COX-2), has been approved in cats for:

- the treatment of pain and inflammation associated with orthopaedic or soft tissue surgery (subcutaneous (SC) injection);
- the treatment of acute pain and inflammation associated with musculo-skeletal disorders and for the reduction of moderate pain and inflammation associated with orthopaedic surgery (tablets).

The current application is a variation to the already authorised use of robenacoxib for the cat and the dog. This application concerns one Type II C.I.6.a and three Type II.C.4 variations:

- Type II C.1.6.a – Addition of a new therapeutic indication – proposed new indication: treatment of pain and inflammation associated with chronic musculo-skeletal disorders in cats - change of indication affecting Onsior 6 mg tablets for cats only;
- Type II C.1.4 – Significant modifications of the Summary of Product Characteristics – proposed change: Interchangeable use of tablets and solution for injection - interchangeable use of Onsior 6

mg tablets and Onsior 20 mg/ml solution for injection for cats, i.e. one Type II variation covering both pharmaceutical forms;

- Type II C.1.4 – Significant modifications of the Summary of Product Characteristics – proposed change: Drug interaction robenacoxib and benazepril – concurrent use with furosemide and benazepril (Onsior 6 mg tablets and Onsior 20 mg/ml solution for injection in cats), i.e. one Type II variation covering both pharmaceutical forms;
- Type II.C.4. – Significant modifications of the Summary of Product Characteristics – proposed change: Intravenous use of 20 mg/ml solution for injection in cats - overdose advice in case of accidental intravenous use, i.e. covering Onsior 20 mg/ml solution for injection and use in cats only.

New studies, as well as studies previously assessed, have been submitted for this application. Some of the original studies submitted in 2007 have now been published, and literature considered relevant to this submission in cats has been submitted for information.

All confirmatory field trials and key target animal safety trials were conducted with final formulations of both Onsior 20 mg/ml solution for injection and Onsior 6 mg tablets for cats.

2.1. Addition of a new therapeutic indication: treatment of pain and inflammation associated with chronic musculo-skeletal disorders in cats (Onsior 6 mg tablets for cats)

Dose determination / dose confirmation

The proposed dose of robenacoxib for the treatment of pain and inflammation associated with CMSD in cats is equal to the currently approved dose for treatment of pain and inflammation associated with acute musculo-skeletal disorders and surgery in cats, i.e. 1 mg/kg bw per day with a range of 1 – 2.4 mg/kg bw per day.

This proposed dose is acceptable, considering that the target for therapy for one of the indications (pain and inflammation) has joint characteristics. In addition, chronic use of Onsior is not expected to pose additional risks for cats, because robenacoxib does not accumulate with repeated administration (related to the short terminal half-life in blood (<2 hrs)) and the product has a high safety margin. Also, recommendation of the same dose of robenacoxib for all indications is simple and thus increases owners' compliance. The dosage of 1-2.4 mg/kg bw once daily has already been shown to be well tolerated in cats with CMSD treated for either 28 days or three months). Following results of these studies, the efficacy of this proposed dose has been further assessed in the two pivotal field studies.

No new studies have been conducted on pharmacodynamics. This is acceptable, considering that, for current application, sufficient information was obtained from (previously) submitted studies. New pharmacokinetic data are available from the interchangeable use target animal safety study and from a 6-month target animal safety study. No accumulation of robenacoxib at dosages of 2.4, 7.2 or 12.0 mg/kg bw was observed after once daily dosing for 6 months in a target animal safety study.

In conclusion, based on previous studies and the efficacy results of the (combined) two pivotal efficacy studies, the selection of the dosage of 1-2.4 mg/kg once daily is acceptable.

Target animal safety

In total, three pivotal safety studies were conducted to evaluate the tolerability of the tablets. TAS

assessment is largely based on these existing TAS studies, especially the 6-month TAS study. No additional laboratory studies have been provided. This is considered acceptable.

These previously submitted studies sufficiently supported safety in the short-term (up to 6 days) use of robenacoxib in cats, but were re-evaluated in this submission for the proposed long-term use of Onsior. In short, also for long-term use of the product, these safety studies demonstrated good tolerability of the product.

From a 21 day safety study, it was concluded that the product was well tolerated. However, 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. Also, there were no apparent treatment effects on body weight, feed or water consumption, body temperature, haematology, clinical chemistry, coagulation, or ophthalmology. During the current procedure, questions were raised regarding some of the symptoms observed during this study (decreased "wheelbarrow test", nystagmus, and head tilt). These questions were adequately addressed by the applicant.

Another study performed in December 2006, was assessed during the initial application. It was a 42-day tolerance study using doses of 0, 2, 6 and 10 mg robenacoxib/kg bw, divided over 2 administrations. There was no increase in body weight during the whole study period and weight loss was observed in one group after D13. A considerable difference in food consumption between groups was observed as well. Body weights of male cats did increase during the study. No effect of the administration of the test item was found on all analysed parameters in haematology, clinical chemistry (including the protein fractions), coagulation and urinalysis.

In, a 6-month oral safety study, some adverse events were observed that could possibly be related to the long term medication, resulting in physiological changes as an adaptation to medication. For the current application intended for long term use, the applicant adequately included the observed adverse events in Section 4.10 of the SPC.

For the current application, tolerance was confirmed under field conditions in the target population. Compared to the animals that were used in the pivotal TAS studies, the target population in the field studies consisted of animals of a more advanced age and potentially suffering from concurrent diseases. In total, four field efficacy studies with a total of 267 cats treated are available to confirm safety under field conditions.

From a study, it was concluded that, overall, the product was acceptably tolerated in cats with CMSD. There were no significant differences between groups in the incidence of all adverse events; however, the number of cases of vomiting was higher with robenacoxib versus placebo. There was no indication of differences between treatment groups in haematology and clinical chemistry variables.

From one study, no biologically significant differences were observed between the investigational veterinary product (IVP) and the placebo groups for any clinical pathology variable. In addition, serious adverse effects were not observed following an assessment of enrolled cases with possible pre-existing renal disease. The administration of robenacoxib for up to 28 days appeared to be well tolerated by cats with OA in this study.

Two additional (pivotal) field studies, performed to prove the efficacy benefit versus placebo during long-term treatment, were newly assessed during this procedure.

Both of these new studies were performed in the USA. The formulation used was the marketed formulation. Both studies were conducted in compliance with GCP (VICH GL9) and National / Federal Regulations, where relevant. The studies used client-owned cats that were treated for spontaneously developed CMSD. Both were prospective, randomized, blinded, placebo-controlled, multi-centre,

parallel-group field studies. Both studies included the following safety parameters: haematology and serum chemistry analyses, urinalysis, reporting of adverse events, physical examination (including body weight).

For both field studies, the total maximum duration of treatment was 6 weeks. The treatment period with robenacoxib for both studies was 21 days for the placebo-robenacoxib-placebo (PRP) group, with an additional 21 days for the placebo-robenacoxib-robenacoxib (PRR) group. The duration is considered adequate.

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. Both studies reported no distinct breed, age, gender, or dosage predilections for adverse events. When evaluating clinical pathology indices, both studies showed no overall clinically relevant abnormalities associated with robenacoxib treatment. Cats with evidence of pre-existing (stable) chronic kidney disease (CKD) showed no treatment related effects on clinical chemistry, haematological or urinalysis variables and the frequency of adverse events was similar to placebo treated CKD cats. There were no statistically significant differences in post-treatment body weight, adjusted for initial body weight, among the treatment groups.

During the procedure, following initial questions from the CVMP concerning target animal safety during long-term use of the product, the applicant performed a combined analysis of safety endpoints from all four of these clinical efficacy studies (Thompson, 2017). The analysis revealed that the data provide no indication of clinical relevant differences in haematology, chemistry, and urinalysis variables or frequency of adverse events between robenacoxib and placebo treated cats, both for all cats and the subgroup of cats with evidence of CKD.

Also, the applicant submitted the most recent Period Safety Update Report (PSUR) (Wilson, 2017) for the period 1 Jan 2014 to 31 Dec 2016. The clinical signs reported during this period were similar in type and frequency to those observed in previous PSURs. It was concluded from this PSUR that the benefit - risk ratio remained positive for both formulations.

In conclusion, additional pivotal field studies support the earlier results that the product is well tolerated in client-owned cats when administered at therapeutic dosage for periods ranging from 3 weeks to 3 months.

Field studies

In total, four clinical field studies with a total of 267 cats treated were conducted in client-owned cats with CMSD in order to evaluate the effectiveness of robenacoxib for the proposed new indication, using the marketed formulation of Onsior 6 mg tablets for cats. All studies were conducted in compliance with GCP (VICH GL9) and National / Federal Regulations, where relevant. All studies used client-owned cats that were treated for spontaneously developed CMSD. The studies were performed in comparison with a placebo.

The two initial (non-pivotal) field studies assessed non-validated subjective owner assessments (and, in addition, assessed clinical safety). Both studies were randomized, blinded, placebo-controlled, multi-centre confirmatory efficacy field studies. The primary outcome measures in both studies were non-validated subjective assessment scoring systems. These two initial studies did not succeed in detecting difference in efficacy between the placebo and the tested product.

In addition, the applicant performed two (pivotal) field studies. Both additional field studies were randomized, blinded, placebo-controlled, multi-centre field studies, conducted in the USA. The goal of both studies was to evaluate the effectiveness (and clinical safety) of robenacoxib administered orally

as a tablet at a target dosage of 1 mg/kg bw per day (range 1-2.4 mg/kg bw per day) given once daily, with a duration of treatment of 3 or 6 weeks.

This overview focusses on results of one of the placebo-controlled pivotal efficacy studies and the combined results of the two (pivotal) studies. The number of cats in the second study was too low to serve as a "stand-alone" study.

In both of these (combined) studies, animals were randomized into three sequence groups: placebo-placebo-placebo (PPP), placebo-robenacoxib-robenacoxib (PRR), and placebo-robenacoxib-placebo (PRP). Also, since previous results indicated that there is a (potentially high) care giver placebo-effect, the experimental design involved three arms with three consecutive periods:

- 2 week baseline period (T0), Days -13 to 0;
- First treatment period (T1), Days 1-21;
- Second treatment period (T2), Days 22-42.

The efficacy data were analysed using three pre-planned hypotheses (H1, H2, and H3), which were supplemented by additional (exploratory) hypotheses H4, H5, H6, and H7. Analyses H4-H7 should be considered supportive only. In the opinion of the CVMP, H2 is considered the most important hypothesis since it potentially demonstrates the strongest treatment contrast possible (PPP versus PRR):

- H1: Whether responses in the first treatment period of group PPP and the groups PRR and PRP differed significantly (comparing CP versus IVP for T1);
- H2: Whether responses in the sequence groups PPP and PRR differed significantly (comparing CP versus IVP over T1 and T2);
- H3: Whether response changed and differed between the PRP group compared to the PRR group from period T1 to period T2 (assessing deterioration from period T1 to period T2 after withdrawal of IVP);
    - H4: Whether responses in the groups PRR and PRP differed significantly in period T2 (i.e. to compare CP versus IVP in period T2 after all cats had received IVP in period T1);
    - H5: Whether responses in group PRP differed significantly from period T1 to T2 (i.e. to assess change after switching from IVP in T1 to CP in period T2);
    - H6: Whether responses in group PRR differed significantly from period T1 to T2 (i.e. to assess changes with the IVP from period 1 to 2);
    - H7: Whether responses in combined groups PPP and PRP differed significantly from the PRR in period T2 (i.e. to compare CP versus IVP in period T2).

The primary endpoint of study was the activity of the cats, which was assessed objectively by activity monitors mounted on a neck collar. This device measures changes in acceleration of the animal. Activity data were recorded once each minute, representing the total cumulative activity for that period. It is however not known what activity the cats are undertaking at any time, though it is agreed that it is highly likely that most of the increased activity represents a clinically relevant beneficial effect. The use of an activity monitor to objectively assess activity of a cat as a primary endpoint, has, according to the applicant's expert, previously been validated (Lascelles *et al*., 2007b: *'Both an AM and a CSOM system can detect behaviour associated with pain relief in cats that are arthritic. Objective activity data might allow subjective assessment systems to be validated for use in clinical studies.'*; Lascelles, 2008: *'Acceleration-based activity monitors may allow for objective measurement*

of improved mobility following analgesic treatment for conditions such as osteoarthritis.'). The applicant also summarized several other (independent) studies that have used accelerometers as an important objective outcome measure for assessing the efficacy of new treatments in cats with degenerative joint disease or osteoarthritis (Lascelles *et al*., 2007b; 2010; Benito *et al*., 2013a; Guillot *et al*., 2013; Gruen *et al*., 2015; 2016). The CVMP concluded that, for the purposes of the current submission, sufficient validation of the activity monitors has been provided.

As independently recommended by Gruen *et al*. (2015), the most meaningful test for superiority of robenacoxib versus placebo is within-cat analysis. Given the high inter-animal variability, CVMP indeed accepts that the intra-animal comparison is likely to provide a more precise estimate of the effect of robenacoxib on activity. However, this resulted in a very much reduced dataset (group 3 – PRP; 35 animals as opposed to the original number of 109 animals) for the purpose of demonstrating effectiveness. In the within-cat analyses, based on the PRP group, a higher proportion of cats had higher activity when receiving robenacoxib versus placebo, and differences were significant for non-zero counts (p=0.021) and night-time activity (p=0.035).

Results showed that statistically significant p-values have been reported for activity for 'non-zero counts' and 'night-time' activity in group 3 – PRP. This was however not the case for 'non-zero counts & night-time activity' (or all counts, daytime activity, daytime activity & non-zero counts). Considering the separate analysis of 'non zero-counts', the applicant acknowledges that this additional analysis was unexpected and not pre-planned. It is agreed that the fewer non-hits present, the stronger a potential contrast will be, since non-hits will 'dilute' the true results. Analysis after removal of non-hits is therefore agreed by the CVMP.

Furthermore, based on the between-group comparisons made in H1 and H2 , the relative change from baseline activity over the entire treatment period (the *treatment effect size* of robenacoxib versus placebo) was approximately 5% for total activity (day plus night) and approximately 10% for night-time activity.

Secondary endpoints of study were subjective assessments by the cat owner of the Client Specific Outcomes Measures (CSOM; validated (Lascelles *et al*., 2007b; Gruen *et al*., 2015)), Feline Musculoskeletal Pain Index (FMPI), Quality of Life (QOL), and temperament. Efficacy was assessed using two methods:

1. Conventional parallel-group comparisons, using the hypotheses H1 and H2;
2. The 'deterioration' design to detect possible deterioration in the scores when IVP was withdrawn at D21.

In the parallel-group comparison of group PPP versus PRR over days 1-42 (i.e. periods T1 and T2 combined, H2 analysis), CSOM scores were better during robenacoxib treatment compared to placebo. For H2, in the per protocol population, this difference was significant in both the adjusted and unadjusted population (p=0.0101 and p=0.0435, respectively). For Intent-To-Treat (ITT), this difference was only significant for the unadjusted analysis (p=0.0226).

Considering the secondary endpoints, CVMP acknowledges that statistical significant differences between placebo and robenacoxib treatment were not often found. One reason could be that the analysis is not sufficiently powered. A second likely reason is the fact that cats are nocturnal animals and mostly active when the owner is asleep. Thus, changes in behaviour may not be sufficiently noticed.

The study report of the combined analysis of two (pivotal) studies describes the results of the pre-planned combined analysis of endpoints common to the clinical trials. It included a total number of 140 animals (safety, n=138; efficacy ITT, n=136; and efficacy per protocol, n=129). In one study, the

per protocol and ITT data sets were the same for the within-cat analysis of activity. In this study, cases with major protocol deviations likely to bias the study outcomes were removed from the per protocol data set. No clinically relevant differences between the (efficacy) results from the per protocol and ITT analyses were observed and therefore the per protocol data set can be considered a "full analysis set".

The primary endpoint of the study was the result of the combined analysis of the endpoints CSOM.

Whereas numerically, the analysis for endpoints appeared favourable for robenacoxib, this was statistically significant on only a few occasions. In the comparison of groups PPP versus PRR over days 1-42 (the most important contrast H2), treatment with robenacoxib improved CSOM score significantly ($p=0.0195$) for the per protocol population, but only when unadjusted for baseline.

Secondary endpoints were FMPI, QOL, and temperament data. For the secondary endpoints, in the parallel-group comparison of groups PPP versus PRR over days 1-42 (i.e. periods T1 and T2 combined, hypothesis H2), QOL, temperament, and happiness scores were significantly higher during robenacoxib treatment versus placebo (per protocol and ITT sets, comparison to before the most recent treatment). Differences were not significant for the day 1-21 period (hypothesis H1). For the assessment of deterioration in FMPI after withdrawal of robenacoxib treatment beyond day 21 (PRP versus PRR), differences were not significant for any endpoint for the H3 analyses (but were statistically significant for the H4 and H7 analyses for FMPI (not adjusted for baseline), QOL, temperament (for both QOL and temperament, comparison to before the most recent treatment), and happiness).

In one study, as well as in the combined analysis of two other studies, a number of statistical analyses were conducted. However, for the main contrasts (hypotheses H1-H3), the number of analyses performed is not considered excessive. The additional hypotheses H4-H7 tested should only be considered supportive.

In conclusion, though the proof of efficacy provided by the current studies is not overwhelming, the CVMP is of the opinion that, for cats suffering from CMSD, the clinical relevance of Onsior has been sufficiently demonstrated. Since these data provide valuable information and indicate that Onsior cannot be expected to be efficacious in all treated cats, the SPC adequately summarizes the results of the field studies.

Thus, this variation concerning the addition of a new therapeutic indication: treatment of pain and inflammation associated with chronic musculo-skeletal disorders in cats (Onsior 6 mg tablets for cats) is approvable.

2.2. Variation related to significant modifications of the Summary of Product Characteristics: Interchangeable use of tablets and solution for injection - interchangeable use of Onsior 6 mg tablets and Onsior 20 mg/ml solution for injection for cats

To demonstrate the interchangeable use of the product, one pivotal study and one pilot terminal target animal safety study were conducted in the USA, both with a duration of 37 days.

One study was a masked non-clinical laboratory pilot tolerance study that evaluated the tolerance of the interchangeable use of robenacoxib formulations (Onsior tablets and Onsior solution for injection) in 4 month old kittens at 0X, 1X, and 5X the maximum dose exposure. Each kitten in the test article group was dosed daily with robenacoxib on an alternating schedule of four 7-day tablet dosing rounds and three 3-day SC injection dosing rounds for 37 days.

Tolerance of the interchangeable use of robenacoxib as tablets and solution for injection was evaluated based on the following measured variables: twice daily detailed clinical observations, injection site scoring, physical examinations including neurological assessments, weekly body weights, daily food consumption, bleeding times, electrocardiographic examination, and clinical pathology parameters, followed by necropsy.

Treatment-related changes were noted in injection site scoring, body weights and food consumption data, clinical chemistry parameters (phosphorus and possibly creatinine), electrocardiographic and histopathological (injection sites and kidneys) evaluations. There appears to be no significant bioaccumulation with repeated administration.

Interchangeable dosing of robenacoxib appears well tolerated. Several mild adverse effects observed in the study (such as the dose-related QT prolongation) are included in Section 4.10 of the SPC.

The other study was a masked pivotal target animal safety study that evaluated the tolerance and interchangeable use of the test article, robenacoxib, in 4-month old cats when administered as a 6 mg Onsior tablet and as a 20 mg/ml Onsior solution for injection (final formulations) at 1X, 2X, and 3X the upper limit of the inherent dose band, by alternating between tablet and SC injection dosing, for a total of 37 days of treatment.

There were three treatment groups of four male and four female cats, and one additional control group.

Tolerance was evaluated based on the following measured variables: observations for general health and clinical observations, injection site observations, body weights, food consumption, ophthalmoscopic examinations, physical and neurological examinations, electrocardiographic examinations, buccal mucosal bleed times, blood and urine samples for clinical pathology evaluations, blood samples for determination of robenacoxib and pharmacokinetic (PK) analyses, necropsy examinations, and bone marrow smears.

Treatment-related changes were noted in injection site scoring, electrocardiographic examinations, and histopathological (injection sites) evaluations.

It is concluded that interchangeable dosing of robenacoxib appears acceptably well tolerated. There appears to be no significant bioaccumulation with repeated administration. The observed mild adverse effects are all adequately addressed in the SPC. The SPC is sufficiently clear, indicating that the 'interchangeability' of formulations relates solely to the indication for the treatment of pain and inflammation associated with orthopaedic surgery in cats, which is common to both pharmaceutical forms and for which the first treatment is administered approximately 30 minutes prior to surgery and may be continued post-surgery for up to two days.

In conclusion, the results of these studies are considered to appropriately support the safety of the interchangeable use. Thus, the current variation concerning the interchangeable use of Onsior 6 mg tablets and Onsior 20 mg/ml solution for injection for cats is approvable.

2.3. Variation related to significant modifications of the Summary of Product Characteristics: Drug interaction robenacoxib and benazepril – concurrent use with furosemide and benazepril (Onsior 6 mg tablets and Onsior 20 mg/ml solution for injection in cats)

In the absence of specific safety studies at the 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 now introduced two new safety laboratory studies that studied the pharmacodynamics of the interaction of robenacoxib (Onsior) with benazepril (Fortekor) in healthy cats by combining the administration of the ACE inhibitor benazepril with robenacoxib for 7 days, with or without the diuretic furosemide.

Both studies were non-GLP (but can be considered of sufficient quality for the objectives), and both studies applied a non-blinded, randomized, placebo-controlled parallel-group design comparison. Both studies applied treatment (that was given at therapeutic doses for both products) to healthy cats, during 7 consecutive days. In one study, furosemide was also administered for activation of the renin–angiotensin–aldosterone system (RAAS). Both studies used the glomerular filtration rate (GFR), which was estimated from the plasma clearance of iohexol, as a primary endpoint.

A study demonstrated that Iohexol clearance (assessed per body weight or per body surface area) in females was significantly higher in the Fortekor + Onsior group than in all other groups (by about 50%). Fortekor and Onsior administered alone had no significant effect on iohexol clearance. Iohexol clearance in both sexes pooled was higher in the Fortekor + Onsior group than in the other groups (by about 30%) and it was higher in the Fortekor group than in the control group.

Another study demonstrated that furosemide had a significant diuretic action at the administered dose, observed in all groups. In the Control group there were in addition significant increases in blood cell counts, haematocrit and haemoglobin concentrations and increases in plasma albumin and total protein concentrations, indicating dehydration. Administration of furosemide produced also a significant reduction in GFR and activation of the RAAS.

The results of these two studies, performed in healthy cats, demonstrate that concomitant treatment with these products was well tolerated during the 7 day treatment period. In these healthy cats, there was no indication of worsening of renal function, including GFR. The SPC sufficiently reflects that no studies were performed on possible effects on safety in the target population and efficacy when these products are combined.

In conclusion, current variation concerning drug interaction robenacoxib and benazepril – concurrent use with furosemide and benazepril (Onsior 6 mg tablets and Onsior 20 mg/ml solution for injection in cats) is approvable.

2.4. Variation related to significant modifications of the Summary of Product Characteristics: Intravenous use of Onsior 20 mg/ml solution for injection in cats - overdose advice in case of accidental intravenous use

Since occasional questions from the veterinary field have been received with regards to the safety of Onsior solution for injection following inadvertent intravenous administration, the applicant had considered this information to be of benefit for the veterinarian. The applicant submitted one GLP study to substantiate the proposed claim.

This study was a randomised parallel design comparison study (non-blinded) performed in Switzerland in order to assess the safety of robenacoxib after a single intravenous (IV) administration to 32 cats at 1X and 2X the recommended therapeutic SC dosage.

The following parameters were evaluated: clinical signs, body weights, food consumption, electrocardiography, haematology, clinical chemistry, and coagulation parameters.

When comparing the IV and SC routes, this study revealed no relevant clinical differences. In conclusion, a single IV administration of Onsior solution for injection at dosages of 2.0 and 4.0 mg/kg in cats appeared well tolerated in anaesthetized cats.

Section 4.10 of the SPC has been sufficiently updated.

Therefore, this variation concerning intravenous use of Onsior 20 mg/ml solution for injection in cats - overdose advice in case of accidental intravenous use is approvable.

3. Benefit-risk assessment of the proposed change

This product in the form of tablets is authorised for the treatment of acute pain and inflammation associated with musculo-skeletal disorders in cats, as well as for the reduction of moderate pain and inflammation associated with orthopaedic surgery in cats; the injectable solution is authorised for the treatment of pain and inflammation associated with orthopaedic or soft tissue surgery in cats. The active substance is robenacoxib, a non-steroidal anti-inflammatory drug (NSAID) of the coxib class. The pharmaceutical forms intended for cats are tablets containing 6 mg robenacoxib and solution for injection containing 20 mg robenacoxib/ml. The recommended dose of robenacoxib is 1 mg/kg body weight with a range 1–2.4 mg/kg bw (for tablets); the recommended dose for the injectable solution is 2 mg/kg body weight.

The grouped variation is to introduce the following changes:

- Addition of a new therapeutic indication - treatment of pain and inflammation associated with chronic musculo-skeletal disorders in cats (Onsior 6 mg tablets for cats) – type II (C.I.6.a).
- Significant modifications of the Summary of Product Characteristics: Interchangeable use of tablets and solution for injection - interchangeable use of Onsior 6 mg tablets and Onsior 20 mg/ml solution for injection for cats - type II (C.I.4); Drug interaction robenacoxib and benazepril - concurrent use with furosemide and benazepril (Onsior 6 mg tablets and Onsior 20 mg/ml solution for injection in cats) - type II (C.I.4); Intravenous use of Onsior 20 mg/ml solution for injection in cats - overdose advice in case of accidental intravenous use - type II (C.I.4).

In addition, several other amendments are proposed (editorial changes, updates to the Product Information requested by the Agency and updates consequent to the revised Quality Review of Documents (QRD) template).

3.1. Benefit assessment

Direct therapeutic benefit

The active substance, robenacoxib, is a well-known non-steroidal anti-inflammatory drug in veterinary medicine. It is beneficial in the alleviation of inflammation and pain in acute musculo-skeletal disorders in cats (and dogs).

The proposed benefit of robenacoxib is its efficacy in alleviation of inflammation and pain in case of CMSD, which was investigated in two well-designed field studies conducted to an acceptable standard.

The data from the field studies demonstrated an improvement compared to controls, although the effect size was relatively small and statistical significance for activity could only be reached during active periods and/or at night. However, it was recognised that, due to the nature of the species as

well as the disease, testing the efficacy of therapies for CMSD in cats is expected to be very challenging and a clear trend for superiority of robenacoxib over placebo was demonstrated. In conclusion, the product is considered sufficiently effective for cats with CMSD.

Additional benefits

Additional benefit: Treatment of pain and inflammation associated with chronic musculo-skeletal disorders in cats (Onsior 6 mg tablets for cats)

Onsior has a high safety margin.

Onsior increases the range of available treatment possibilities for CMSD.

Additional benefit: Interchangeable use of tablets and solution for injection (Onsior 6 mg tablets and Onsior 20 mg/ml solution for injection in cats)

For an animal undergoing general anaesthesia, oral medication should not be administrated and an injection is therefore more practical. However, a tablet is more practical for the pet owner to continue pain relief at home. Therefore, information on interchangeable use of the tablets and solution for injection is of benefit in this case.

Additional benefit: Concurrent use with furosemide and benazepril (Onsior 6 mg tablets and Onsior 20 mg/ml solution for injection in cats)

Additional information on concurrent use of Onsior with furosemide and benazepril would be of potential benefit to cats requiring treatment for chronic musculo-skeletal disorders which are already receiving one or both of the latter two medications (a fairly common scenario in older cats).

Additional benefit: Overdose advice in case of accidental intravenous use (Onsior 20 mg/ml solution for injection in cats)

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

3.2. Risk assessment

Quality:

Quality remains unaffected by this variation.

Safety:

Measures to manage the risks identified below are included in the risk management section.

Risks for the target animal:

The CVMP concluded that target animal safety for this product is acceptable when used according to the SPC recommendations. However, in the studies conducted for these variations, some additional risks have been identified.

Risk for the user:

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

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 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

The benefit of Onsior introduced by this variation consists in its efficacy in the treatment of pain and inflammation associated with chronic musculo-skeletal disorders in cats.

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

- Addition of a new therapeutic indication - treatment of pain and inflammation associated with chronic musculo-skeletal disorders in cats (Onsior 6 mg tablets for cats);
- Significant modifications of the Summary of Product Characteristics: Interchangeable use of tablets and solution for injection - interchangeable use of Onsior 6 mg tablets and Onsior 20 mg/ml solution for injection for cats; Drug interaction robenacoxib and benazepril - concurrent use with furosemide and benazepril (Onsior 6 mg tablets and Onsior 20 mg/ml solution for injection in cats); Intravenous use of Onsior 20 mg/ml solution for injection in cats - overdose advice in case of accidental intravenous use.

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.