

SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Onsior (as published in December 2008). For information on changes after this date please refer to module 8 (Steps taken after authorisation).

1. INTRODUCTION

The active substance of Onsior is robenacoxib, a non-steroidal anti-inflammatory drug (NSAID) of the coxib class which selectively inhibits the cyclooxygenase 2 enzyme (COX-2). The active substance, robenacoxib is a structural analogue to diclofenac.

Onsior is available as tablets in five different strengths (6 mg for cats, and 5 mg, 10 mg, 20 mg and 40 mg for dogs) and as a solution for injection (20 mg/ml for dogs and cats).

The benefits of Onsior are its efficacy in the treatment of pain and inflammation in dogs and cats.

The most common side effects are gastrointestinal adverse events (vomiting, soft faeces) in cats and dogs; in dogs following long-term oral treatment, an increase in liver enzyme activities was noted. The solution for injection might cause pain on injection.

The approved indications are:

Tablets

Cats: Treatment of acute pain and inflammation associated with musculo-skeletal disorders at a once daily dose of 1 mg/kg body weight up to six days.

Dogs: Treatment of pain and inflammation associated with chronic osteoarthritis at a once daily dose of 1 mg/kg body weight as long as required (as directed by the veterinarian).

Solution for injection:

Cats: Treatment of pain and inflammation associated with soft tissue surgery.

Dogs: Treatment of pain and inflammation associated with orthopaedic or soft tissue surgery in dogs.

2. QUALITY ASSESSMENT

COMPOSITION

The tablets are biconvex, round, beige to brown, imprinted on one side with the company logo “NA” and on the other side referring to the dosage strength (AK, BE, CD, BCK for dogs and AK for cats). Tablets of 6 mg robenacoxib are presented for cats, and tablets with a strength of 5, 10, 20, 40 mg robenacoxib for dogs. Conventional pharmaceutical excipients for tablets are used and full details are included in the SPC. In order to facilitate palatability, tablets for cats contain yeast powder and tablets for dogs contain yeast powder and artificial beef flavour.

The solution for injection for cats and dogs is a clear, colourless to slightly coloured (pink) liquid containing 20 mg/ml robenacoxib as active substance. Other substances are Macrogol 400, ethanol, anhydrous Poloxamer 188, citric acid monohydrate, sodium metabisulphite, sodium hydroxide and water for injections.

CONTAINER

The tablets are packaged into aluminium / aluminium foil blisters, each containing 7 tablets. One cardboard box contains one, two, four (dogs only) or ten blisters.

The solution for injection is presented in a 20 ml multidose amber glass vial, closed with a gray rubber stopper, sealed by an aluminium cap.

CLINICAL TRIAL FORMULAE

All clinical trial formulae have been provided.

Tablets for dogs which did not contain any flavour were initially developed and used in most of the pivotal pre-clinical and clinical trials. However, in order to increase the palatability of the tablets, yeast and artificial beef flavour were added. Pivotal studies conducted with the final formulation (containing yeast and artificial beef flavour) confirmed bioequivalence between the flavoured and non-flavoured formulations.

The initially developed tablets for cats contained yeast and vanillin; however, vanillin was subsequently removed because of incompatibility with the active substance. The final tablet formulation was used for most pivotal trials in cats.

For the solution for injection, preliminary formulations are qualitatively identical to the final commercial formulation. However, some studies were undertaken using a solution which differed quantitatively with regard to active substance, macrogol 400 and ethanol. The preparations containing different amounts of ethanol were shown to be bioequivalent, in addition, an additional target animal safety trial was conducted with the final preparation.

DEVELOPMENT PHARMACEUTICS

Robenacoxib is a free acid. It is freely soluble in aqueous solution at alkaline pH values above 8, and in most organic solvents tested. At acidic pH values robenacoxib is practically insoluble in aqueous solution; solubility in pure water is poor. In acid solutions the active substance readily degrades to form a lactam. Robenacoxib exists in different polymorphic forms. The more stable form at room temperature was chosen and was shown to be chemically and physically stable under registration stability conditions.

The excipients used for the tablets are standard substances in tablet formulations for use in dogs and cats. In both, tablets for dogs and cats, yeast, microcrystalline cellulose, crospovidone, povidone, anhydrous colloidal silica and magnesium stearate are used. The tablets for dogs also contain powdered cellulose and artificial beef flavour as a flavour.

The excipients selected for the solution for injection are well accepted for use in injection formulations and are standard ingredients and their choice was based on the properties of the active substance. In the solution for injection, water for injection is used as solvent, macrogol 400 and ethanol as co-

solvent, poloxamer 188 as solubiliser, citric acid monohydrate and sodium hydroxide for pH control, and sodium metabisulphite as antioxidant. Compatibility of the various excipients was established.

CONTAINER

Because of absorptive properties of the yeast and in order to avoid water uptake, a non moisture-permeable (Al/Al) blister was selected. The suitability of the primary packaging was shown in the stability studies. No incompatibility of the formulation with the primary packaging material in contact with the product was noticed.

The solution for injection is presented in a 20 ml amber Type I glass vial, with a closure comprising a chlorobutyl stopper with aluminium crimp seal. The use of amber coloured vials to prevent photostability of the finished product is justified, since solutions of robenacoxib in various solvents proved to be very sensitive to light resulting in an increase of degradation products.

FORMULATION DEVELOPMENT

Tablets

The development of the tablet formulations took place in two steps. During the initial development phase, the formula was modified several times to adapt tablet size and dosage strength to the final dosage regime and marketing requirements. Initially the tablet weight was identical (160 mg) for all dosage strengths. However, in order to visually differentiate the tablets appearance according to their respective strengths, different weights per strength were introduced i.e. the tablet weights for the 5 mg, 10 mg, 20 mg and 40 mg dosage strengths are respectively 80 mg, 160 mg, 320 mg and 640 mg. All tablets contain the same concentrations of active substance (6.25%) and of excipients.

Initial formulations contained lactose; however, in order to enhance the palatability, this ingredient was later replaced by yeast (dog, cat) and artificial beef flavour (dogs only). Since yeast is not suitable for a direct dry compression process, a wet granulation step was introduced.

The preparation of a granulate common for both dog and cat tablets was developed. In the granulate yeast acts as a water management system and favourably interacts with the equilibrium between robenacoxib and its lactam degradant. Artificial beef flavour is only contained in the dog formulation and therefore only added in the extragranular phase. Since robenacoxib is practically insoluble in water, a phosphate buffer pH 7.4 is used to ensure sufficient dissolution of the active substance in the medium at that pH.

The dissolution test parameters have been selected according to Ph.Eur. procedure to ensure sink conditions. Tablets for dogs dissolve faster than the tablet for cats due to the presence of artificial beef flavour in dog tablets which acts as a hygroscopic agent and allows a faster disintegration. Dissolution was not significantly affected by formulation, dosage strength or size of the tablets.

Solution for injection

As robenacoxib is poorly soluble in water, co-solvents such as macrogol 400 and ethanol were added, and poloxamer 188 was selected as a potential solubiliser for the active substance.

During stability studies at 40°C for three months the preliminary solution for injection containing 1.0% robenacoxib discoloured to a pink colour whilst there was no significant deterioration of the active substance due to oxidation. Therefore, sodium metabisulphite was added as an antioxidant.

The solution for injection was initially developed with a lower 1% (w/v) concentration; however, for clinical reasons the concentration was subsequently increased to a 2% (w/v) or 20 mg/ml of robenacoxib. When increasing the concentration of the active substance, it was found that the same vehicle can be used; however, to reach the desired pH more base was added, and the concentrations of sodium metabisulphite and macrogol 400 increased. No antimicrobial preservative is added to this injectable multidose preparation as the product has adequate inherent antimicrobial activity on the grounds of the

significant non-aqueous solvent loading. However, in order to enhance the preservative efficacy, ethanol was added. Stability data confirmed adequate stability of this formulation. Other relevant tests performed during development included syringeability and closure integrity tests.

MANUFACTURING PROCESS DEVELOPMENT

The manufacturing process of the tablets consists of mixing the active substance with part of the excipients (inner phase), wetting with the aqueous solution, drying and sieving the obtained granulate, then blending with the remaining excipients (external phase) and compression of the final mixture into tablets of the desired tablet weight. The granulation process as well as the compression process was investigated to show adequate batch homogeneity and flow behaviour during compression. A one pot granulation process was selected where mixing, high-shear granulation and drying steps are performed in the same closed equipment.

The amounts of water delivered for the granulation and the drying conditions were optimised. A loss on drying test with a limit of not more than 6% was established as an in-process control to indicate the end point of the drying step. A range of compression force was used to evaluate the impact of the compression force on hardness, friability, thickness, disintegration time, dissolution and uniformity of weight. Results obtained show that there is a good correlation between the compression force applied, the resulting hardness of the tablet and its disintegration time. Crospovidone showed good performance as a disintegrant. Friability and weight uniformity were always well within limits. Content uniformity results confirm the good flowability properties of the tableting mixture and the homogeneous distribution of the active substance.

The manufacture of the solution for injection is essentially dissolution of the active substance in a co-solvent system and the dissolution is facilitated by ensuring that the pH of the solution is in a range where the active substance is fully ionised. The most critical issue of the process is to ensure that the manufacture is conducted in an atmosphere free of oxygen since the substance in solution is prone to oxidation. Terminal sterilisation with moist heat is not possible due to the increase in total degradation products level it produces. Instead, a combination of aseptic filtration and aseptic processing has to be used. Final full scale batches showed full compliance with the finished product specifications.

METHOD OF PREPARATION

The manufacturing formulae for the proposed batch sizes were presented for both the solution for injection and for the tablet formulations.

The manufacturing process for the tablets is a standard process consisting of the following steps: blending of the majority of the excipients with the active substance, wet granulation and drying, screening, addition of the remaining excipients and compression into tablets. The manufacturing process has been described in sufficient detail. Details of the in-process controls including loss on drying, appearance, weight, hardness and friability along with the specifications set were provided.

The manufacturing process for the solution for injection is a standard process consisting of a solution preparation followed by a sterilisation by filtration and filling into vials in an aseptic processing zone. The sterilisation methods of equipment and primary packaging are considered appropriate. The manufacturing process has been described in sufficient detail. Details of the in-process controls including pH, clarity, bioburden level, filter integrity, fill volume/weight, oxygen headspace and vial defects along with the specifications set were provided.

Batch analysis data for both the tablets and the solution for injection demonstrate that the respective manufacturing processes consistently produces product that meet the required specifications.

Satisfactory process validation data demonstrate the processes to be reliable and robust and a validation protocol for the initial commercial batches were presented.

CONTROL OF STARTING MATERIALS

Active substance

Robenacoxib is not described in any pharmacopoeia and in-house specifications are provided in the dossier. A detailed specification for the active substance including tests for appearance, particle size, identification, total viable aerobic count, combined yeast and moulds, specified microorganisms, related substances, residual solvents, loss on drying, sulphated ash, heavy metals, clarity and colour of solution and assay was provided. The test protocol is considered appropriate. Parameters that are not stability indicating are only tested at release.

A detailed description of the manufacture of robenacoxib is provided. The specifications of the starting materials, solvents and catalyst are provided and well controlled by specified limits. The control of the raw materials is considered satisfactory. Key intermediate products are tested and the control procedures on the key intermediates are considered appropriate to control the manufacturing process.

Experimental evidence supporting the structure for robenacoxib has been obtained through elemental analysis, MS, ¹H NMR, ¹³C NMR, IR and X-Ray diffraction. There is no chiral centre in the chemical structure of robenacoxib. Therefore, neither an enantiomer nor diastereo-isomers exist and no optical rotation occurs. Cis-trans isomerism is theoretically not possible.

Physico-chemical characteristics including physical form, solubility, melting point, polymorphism, particle size, pKa and pH values and light stability have been presented.

During drug development all necessary analytical methods to assess the quality of the substance were developed and have been adequately described. Where applicable, validation reports of the test methods have been included. The test methods for the assay, impurities and residual solvents were discussed in detail. Robenacoxib content is determined by a binary gradient HPLC with UV detection. The method has been validated with regard to analytical range of 80-120%, specificity, precision, linearity, accuracy and robustness.

The content of by- and degradation products is assayed with the binary HPLC method. The method has been validated and is stability indicating. The final material is regularly assayed during release. The validated method used is headspace gas chromatography with flame ionisation detection. All tests included in the current active substance specification have been adequately validated and allow an appropriate assessment of the quality of the active substance. A table of potential impurities was presented including by-products and degradation products, solvent, general and catalyst impurities with appropriate limits for each.

The stability data provided support a re-test period of 4 years without special storage instructions. Impurities found after 48 months are included as individual unknown related substances and within the specification limit of 0.2%. Their sum justifies the present specification limit of 0.5%. The residual solvents ethanol, isopropanol and toluene are regularly determined, found below 10% of the VICH limits and considered acceptable.

Analysis results of 5 industrial batches and 4 pilot batches show full compliance with the requirements set.

The active is packaged in a double polyethylene liner (double layers of low density PE) in drums. Routine tests and specifications for identity, appearance and dimensions of the double LDPE layer have been provided. Furthermore, material sheets and certificates of analysis for the primary packaging materials have been provided. All materials used for primary packagings are standard packaging materials for food and pharmaceutical products and comply with the respective Regulations of the European Community, the Ph.Eur. and/or the US Food and Drug Administration.

Excipients

Tablets:

Cellulose, microcrystalline, Cellulose, powdered, Povidone (K-30), Crospovidone, Silica, colloidal anhydrous, Magnesium stearate, Water purified comply with the appropriate current monographs of the Ph.Eur.. Detailed specifications for yeast powder, and a certificate of analysis for artificial beef flavour have been provided. The analysis results show compliance with the requirements set.

Solution for injection

Macrogol 400, Ethanol, anhydrous, Poloxamer 188, Citric acid monohydrate, Sodium metabisulphite, Sodium hydroxide, 5M solution, Water for injections, Nitrogen comply with the appropriate current monographs of the Ph.Eur.. The excipients are tested for microbial bioburden in compliance with the Ph.Eur. method.

PACKAGING MATERIAL (IMMEDIATE PACKAGING)

Tablets

The cold-formed tablet blister consists of 2 foils: an aluminium lidding foil (push-through foil) and an aluminium forming foil containing 7 tablets per blister. The bulk container consists of a multi-layer compound bag (two polyethylene layer) in a metal container. Routine tests and specifications for identity, appearance and dimensions of the aluminium lidding foil, the aluminium forming foil and double polyethylene layer have been provided. Furthermore, material sheets and certificates of analysis of these primary packaging materials have been provided. IR spectra of the plastic components coming into contact with the tablets have also been included.

Solution for injection

20 ml Amber glass vial, type I (Ph.Eur.) with a stopper of Chlorobutyl rubber, type I (Ph.Eur.). Routine tests and specifications for identity, appearance and dimensions and quality according to Ph.Eur. of the vials and rubber stoppers have been provided. Furthermore, certificates of analysis of these primary packaging materials have been provided.

SPECIFIC MEASURES CONCERNING TSE

A declaration is provided stating that all the components used in the manufacture of Onsior tablets and solution for injection comply with Directive 1999/104/EC and the current TSE guideline (EMA/410/01 Rev. 2). Robenacoxib is entirely synthetic and free of any bovine or ruminant material. Yeast does not contain any substance of animal origin and the whole production process is free from contamination with products of animal origin. Artificial beef flavour is sourced from desiccated pork liver powder is of animal origin but not of ruminant origin. Therefore, the beef flavour does not fall within the scope of the Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy. The other excipients are not of animal origin and no animal-derived materials are used during the manufacturing process of these excipients.

CONTROL TESTS ON THE FINISHED PRODUCT

Tablets

Detailed specifications for both release and end-of-shelf-life testing including tests for; Appearance (visual); Identification (TLC and HPLC), Water content (KF, USP), Dissolution (HPLC), Microbial counts (Ph.Eur.), Uniformity of dosage units (HPLC), Assay of robenacoxib (HPLC), Degradation products (HPLC) were provided. Tests on microbial purity are carried out on the first 5 production lots. The control of the tablets is considered sufficient.

All control methods are fully described. The validation of the analytical procedures is found acceptable and in accordance with the VICH validation guidelines. Forced degradation studies (temperature, pH, oxidation, light) showed that most of degradation products were known by- and degradation products of the active substance. The chromatograms showed that the degradation products were well separated from the active substance and mostly from each other. These data provide evidence for the stability indicating capabilities of the analytical method.

Analysis results were provided of pilot scale batches of each strengths for the dog and cat tablets. Three certificates of analysis for each tablet strength are included in the dossier. All samples passed the release criteria.

Solution for injection - Specifications of the finished product

Detailed specifications for both release and end-of-shelf-life testing including tests for; Appearance (visual); Identification (HPLC); Fill volume; pH (potentiometric); Sterility (plate count method, Ph.Eur.); Bacterial endotoxins (turbidimetric evaluation, Ph.Eur.); Assay of sodium metabisulphite (differential pulse polarography); Assay of robenacoxib (HPLC); Degradation products (HPLC) were provided. Tests on microbial purity are carried out on the first 5 production lots. If the requirements are met, testing frequency may be reduced to every tenth lot. At least one lot must be tested in each calendar year in which the product is manufactured.

The control of the solution for injection is considered sufficient. Identification of robenacoxib is performed by HPLC. The proposed limits for NAP 542-01 and total degradation products at shelf-life seem high compared to the levels seen in the stability studies (max. 2.5% and 2.7%, respectively, after 6 months at 40°C/75% RH). The limits were reconsidered ($\leq 0.3\%$ (release) and $\leq 4.0\%$ (stability)) with respect to the actual levels seen and the proposed 36 month shelf life. Also the lower limit for assay (% of declared content) at shelf-life was re-evaluated in connection with the lower impurity levels. Total degradation products specification is $\leq 1.0\%$ (release) and $\leq 5.0\%$ (stability).

All control methods are fully described. Relevant test methods have been validated according to VICH requirements. The differential pulse polarography method used for the assay of sodium metabisulphite has been sufficiently validated with respect to specificity, accuracy, repeatability and intermediate precision, linearity and range, LOQ and robustness. The HPLC method has been sufficiently validated with respect to specificity, accuracy, repeatability and intermediate precision, linearity and range, LOQ and robustness.

Forced degradation studies (temperature, pH, oxidation, no light as this was already done with the active substances) showed that most of degradation products were known by- and degradation products of the active substance. The chromatograms showed that the degradation products were well separated from the active substance and mostly from each other. These data provides evidence for the stability indicating capabilities of the analytical method.

The test for bacterial endotoxins was sufficiently validated. The limit of detection was calculated to be 2.97 EU/ml which is approximately 10% of the specified endotoxin limit. The other test methods are either simple or compendial methods and need no further validation.

Analysis results were provided of the three full scale batches of 300 l of the solution for injection. Each batch was manufactured and released at the proposed production/release site, and packaged in the proposed packaging. Three certificates of analysis are included in the dossier. All samples passed the release criteria.

The batches were tested according to the specification in force at the time of testing in which higher levels of related substances were proposed. In order to evaluate the proposed limits for related substances, batch analysis results of batches tested according to the currently proposed specification were provided. Three certificates of analysis have been issued according to the submitted finished product specifications. All results comply with the submitted as well as with the newly proposed finished product specifications.

STABILITY

Active substance

Three industrial batches were used in stability studies. Two pilot batches and one laboratory batch were used in stress and forced degradation tests and tested for all stability indicating parameters, i.e. appearance, identification by IR and X-ray diffraction pattern (only at 30°C and 40°C), loss on drying, clarity of solution, colour of solution, assay and related substances.

All test results of the stability trials demonstrated stability of the active substance, when stored under ordinary conditions. Furthermore, no interaction with the primary packaging material could be observed, indicating that the primary packaging material is suitable for the active substance. The stability tests with the pilot batch demonstrated that the active substance is stable for 24 months at freezing temperatures -15°C to -25°C and refrigerator temperatures (2°C to 8°C), whereas light stability tests proofed that solutions of the robenacoxib should be protected from light.

Based on the available stability data, the active substance is sufficiently stable in the original non-opened package for at least 48 months. A re-test period shelf life of 4 years without storage recommendations is proposed, provided the product is stored in the original bulk container.

Finished Product

Tablets

Three batches of each tablet strength were used in stability studies. The batches were tested for all stability indicating parameters, i.e. appearance, water content, dissolution, microbial quality, assay and related substances. For all strengths the tablets as packaged for sale (Al/Al blister) it was found that they were chemically and galenically stable and fulfilled the shelf life specifications throughout the reporting period at all the storage conditions tested. The microbial limit tests were performed at onset of stability testing, and met the specifications.

The claimed extrapolated shelf life of 2 years for the 6 mg tablets for cats was supported by the results obtained at 40°C/75%RH and therefore acceptable. Regarding the tablets for dogs since significant changes are seen at 40°C/75% RH extrapolation of the storage time to twice the period covered by the long-term data was not considered acceptable. 24-month stability data for the dog tablets supported a shelf life of 2 years with the storage instruction "Do not store above 25°C" for all tablet strengths for dogs.

The bulk holding time (bulk shelf life) of the dog tablets was considered 6 months. The 9-month data available for the cat tablets support a bulk holding time (bulk shelf life) of 9 months. Tablets stored in bulk remained within the release specification throughout the bulk holding time. Therefore, there is no fundamental quality difference at packaging between tablets packed immediately after manufacture and tablets packed after storage in bulk. For these reasons, real-time stability studies of tablets blistered after having been stored for the maximum time in bulk, were deemed unnecessary.

Two batches of each tablet strength were used in bulk stability studies stored in multi-layer compound bag (two polyethylene layer) in a metal container. The batches were tested for all release parameters. For all tablet strengths the bulk product was found to be chemically stable and fulfilled the release specifications during storage and the current bulk storage container was considered adequate to protect the bulk of the tablets for 6 months.

In addition to these studies, one batch of cat tablets was used in light stress tests. Based on the reported results, no light protection is needed for the cat tablets.

Solution for injection

Three batches of solution for injection were used in stability studies. The batches were tested for all stability indicating parameters, i.e. appearance, pH, sterility, content of sodium metabisulfite, assay and related substances. Besides, antimicrobial preservative efficacy was tested. The product was found to be chemically and galenically stable and fulfilled the specifications throughout the reporting period

at all storage conditions tested. The assay of robenacoxib remained stable. 18-month stability data of the on-going stability studies with 3 batches of solution for injection stored at 5°C, 25°C/60%RH, 30°C/65%RH and 40°C/75%RH (6 months) has been provided.

Based on the reported results, on the basis of extrapolation, a shelf life of 3 years without storage instructions is proposed.

In-use stability tests

Two batches of solution for injection (20 ml amber glass vial closed with a rubber stopper and aluminium cap) were used in stability studies. Two broached vials studies with freshly manufactured batches were performed to simulate the realistic use of the solution for injection. The batches were tested for all stability indicating parameters, i.e. appearance, pH, content of sodium metabisulfite, assay and related substances. Antimicrobial preservative efficacy was also tested.

The product was found to be chemically and galenically stable and fulfilled the specifications throughout the in-use stability test. The assay of robenacoxib remained stable. One degradation product increased slightly at 30°C/65%RH only. No other degradation product was observed at the 0.3% VICH reporting level. The sum of degradation products increased slightly with time and temperature. The sodium metabisulfite content decreased with time and temperature. This decrease is expected in broached vials as sodium metabisulfite is consumed to protect the formulation from oxidation following air ingress as a result of the broaching. pH decreased with time and temperature as a result of the sodium metabisulfite reaction. Appearance of the product remained unchanged. The Antimicrobial Preservative Efficacy Test met the Ph.Eur. Criteria A throughout the in-use stability test.

An in-use shelf-life of 28 days was supported based on the data provided.

Two pilot batches of solution for injection were used in stress tests. The batches were tested for appearance, pH, assay and related substances. The product was found to be chemically and galenically stable under freeze/thaw conditions. No significant change in any parameter tested was induced by freezing and thawing. Based on the results, no precautionary statement against freezing is necessary.

CONCLUSIONS ON QUALITY

Onsior is presented as tablets for dogs and cats and as a solution for injection for both dog and cat containing the active substance robenacoxib. The tablets are immediate release tablets presented in aluminium/aluminium blisters packs. The tablets for dogs are available in four dosage strengths containing 5, 10, 20 or 40 mg of active substance while the tablet for cats contains 6 mg of active substance. The different strengths have been developed in order to permit an oral administration of 1 or 2 tablets per dose. The tablets for dogs and cats differ slightly with regard to different flavour agents included which is intended to improve the palatability specifically for the target species. The solution for injection contains 20 mg of robenacoxib per ml which can be administered to both target species (dog and cat). It is packed in an amber multidose glass vial closed with a rubber stopper.

Robenacoxib is not described in any Pharmacopoeia. Full information is provided in the dossier to justify the quality of batches. Excipients used in the manufacture of the product are considered quite common for use in tablets or injection preparations. The dossier provides a suitable description of the active substance and the chosen formulations, and confirms production of the active substance and the products to a consistent quality. Analytical methods are well described, and data of their validation confirm their suitability.

Manufacturing processes are sufficiently detailed for all preparations and demonstrate that production of the final product leads to a consistent quality. The specifications for the final products contain sufficient acceptance criteria and corresponding tests. Stability studies have been performed according to VICH guidelines. The stability studies on the active substance and the finished products allow a re-test period of 48 months for robenacoxib and justify a shelf-life of 2 years for the tablets for dogs and cats and 3 years for the solution for injection, with a 28 day in-use shelf-life.

SAFETY ASSESSMENT

TOXICOLOGICAL STUDIES

Single dose toxicity

Data were provided from two GLP (Good Laboratory Practice) compliant single dose toxicity studies in rats, one using the oral route and the other using the intraperitoneal route. In the oral dosing study groups of 5 males and 5 females were dosed 500 mg/kg bw robenacoxib, 2000 mg/kg bw robenacoxib or vehicle (carboxymethylcellulose) and observed over a 14 day period. In the intraperitoneal dosing study groups of 5 males and 5 females were dosed with 200 mg/kg bw robenacoxib, 500 mg/kg bw robenacoxib or vehicle (carboxymethylgellulose).

In the oral dosing study mortality was seen at 2000 mg/kg bw group. In the intraperitoneal dosing study mortality was seen in doses of 200 mg/kg bw and more. Clinical signs included subdued behaviour, ataxia, ptosis, tremors, piloerection, ventral decubitus, pallor, staggering gait and irregular or gasping breathing. Body weight loss or very low body weight gain was noted at the higher dose in both studies. At necropsy, liquid in thoracic and abdominal cavities and adherence between organs were noted in one high dose male after oral administration. Dilatation of intestines, thymus reduction/atrophy and/or presence of pinkish liquid in urinary bladder were noted in 2 high dose animals administered robenacoxib intraperitoneally.

It is concluded that, with an oral LD₅₀ between 500 and 2000 mg/kg bw and an intraperitoneal LD₅₀ between 200 and 500 mg/kg bw, the active substance was orally well absorbed. The observed signs were dose-dependent and the necropsy findings indicate stress and gastrointestinal irritation.

Repeat dose toxicity

A GLP compliant 28 day repeat oral dose study was performed in rats with 0, 20, 60 or 200 mg robenacoxib /kg bw. At the highest dose (200 mg/kg), food consumption and body weight gain were slightly reduced, and neutrophil counts, cholesterol levels and liver enzyme activities were increased. Creatinine levels were slightly reduced at 60 and 200 mg/kg bw. Kidney and liver were concluded to be the target organs, presenting slight inflammatory changes. At 20 mg/kg bw the findings appeared to be marginal. Generally, the dose effect response was not pronounced and some control animals were affected as well. A clear No-Observed-Effect-Level (NOEL) was not reached, but 20 mg/kg bw was considered to be a No-Observed-Adverse-Effect-Level (NOAEL). For the subsequent 13-weeks study, 60 mg/kg bw was proposed as the highest dose level.

A 90 day oral study was undertaken in rats with doses of 0, 5, 10, 20 or 60 mg/kg bw robenacoxib, daily. Results revealed no mortality or abnormal clinical signs, and no effect on food consumption or bodyweight. Decreased creatinine levels were observed in all females and in males in the 60 mg/kg bw group. The effect was argued to be a metabolic response to treatment. Males in the 60 mg/kg bw group also had higher kidney weights, with no histopathological changes.

Overall, robenacoxib was well tolerated up to a dose of 60 mg/kg bw/day and consequently the NOAEL was considered of 60 mg/kg bw/day.

Reproductive toxicity, including teratogenicity

No data were provided on the reproductive toxicity of robenacoxib. Consequently, the product should not be used in breeding animals of both target animal species, including pregnant and lactating animals. Furthermore, submitted data contain insufficient information to allow conclusions to be drawn on possible residual effects of treatment on male and female fertility. However, it was noted that cyclo-oxygenase inhibitors may produce adverse effects on the foetus or neonate if administered during gestation.

Mutagenicity

Robenacoxib was tested in vitro for its ability to induce:

- gene mutations in bacteria (Ames test) with and without metabolic activation
- gene mutations in L5178Y mouse lymphoma cells
- chromosome aberrations in cultured human lymphocytes with and without metabolic activation.

Robenacoxib was also tested in vivo in the mammalian erythrocyte micronucleus test in rat bone marrow, at a dose of up to 1000 mg/kg bw.

All of the above studies were GLP compliant. No evidence of mutagenic potential was seen.

Carcinogenicity

No long term carcinogenicity studies were performed with robenacoxib. Given the lack of concern resulting from mutagenicity testing this is considered acceptable.

Special studies (skin irritation/sensitisation)

GLP compliant studies were performed to investigate:

- skin irritation/corrosion in the rabbit using robenacoxib and using the lactam metabolite
- contact hypersensitivity in the albino Guinea pig using robenacoxib and using the lactam metabolite

Following exposure of clipped skin to robenacoxib or its lactam metabolite and application of a semi-occlusive dressing for 4 hours no irritation was seen in rabbits (animals were observed up to 72 h after exposure). No hypersensitivity was seen in the guinea pig when robenacoxib or its lactam metabolite was injected into the skin at a concentration of 1% or applied epidermally at a concentration of 50%, with a subsequent challenge 2 weeks after the initial exposure and using a robenacoxib concentration of 10%. Similar results were observed with a 5% injection fluid and a 20% challenge substance.

These data indicate that robenacoxib and its lactam metabolite did not cause skin irritation or skin sensitisation.

Observations in humans

No data were provided as robenacoxib is not used in human medicine. However, it was noted that robenacoxib is structurally related to diclofenac, which is widely used in human medicine.

Studies on metabolites, impurities, other substances and formulation

The lactam metabolite of robenacoxib, which is also a named impurity in the product specification, was investigated in the following GLP-studies:

- gene mutation study in *Salmonella typhimurium* reverse mutation assay and *Escherichia coli* reverse mutation assay
- chromosome aberration study in Chinese hamster V70 cells
- in silico prediction of potential toxicological properties
- 2 repeat dose toxicity studies in dogs, using pilot formulations spiked with the lactam metabolite.

No evidence of mutagenic potential was seen in the bacterial mutagenicity or chromosome aberration studies and the in silico study predicted that there was a low likelihood of the substance being tumourigenic in rodents following life-long exposure.

The first of the repeat dose studies used an injectable formulation with and without the lactam at 2%, administered by subcutaneous injection over 5 weeks. The 9-injection regimen consisted of three consecutive days of dosing, starting on day 0, with an 11-day interval between dosing cycles, for a total of three dosing cycles. Dosages of 0, 2, 6, 20 and 20 (+2% lactam) mg/kg body weight were administered. In the second repeat dose study oral dosing of a tablet formulation was used. A dose of 10 mg/kg bw with and without ~5% of the lactam was administered daily for 28 days.

In both repeat dose studies there was no difference in any of the evaluated parameters between animals receiving the high dose with or without the lactam impurity.

USER SAFETY

The applicant provided a user safety assessment which in general followed the CVMP guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-FINAL).

Tablets

Repeated dermal and accidental oral exposure

Following repeated dermal administration, no local effects (e.g. skin irritations) are expected based on the negative local studies with robenacoxib and the available information on the excipients.

Systemic effects were assessed taking into account two studies: an oral 28-day study with robenacoxib in rats where an NOAEL of 20 mg/kg bw/day was concluded and a study conducted with the structurally related substance diclofenac (0.1 mg/kg bw) in pregnant rats on day 21 of pregnancy (premature constriction of the ductus arteriosus).

After repeated dermal absorption, followed by accidental oral ingestion no risk for non-pregnant users was expected based on an margin of exposure (MOE) of 32260.

However, taking into account the known effects of cyclo-oxygenase inhibitors on the foetus or neonate if administered during gestation, the risk for pregnant women was also calculated. Taking into account effects observed in animal studies, pharmacodynamic showing effects in the range of 0.5 mg/kg bw (mainly ED₅₀ values), even after single exposures, and assuming that the NOAEL for pharmacodynamic effects is 5 times lower than the ED₅₀; this would result in a NOAEL in the range of 0.1 mg/kg bw and a MOE of 160. Considering possible intra- and inter-species variation and considering that reprotoxicity data are extrapolated from those for diclofenac, reprotoxic effects could not be excluded based on a MOE of 160.

Consequently, relevant warnings have been provided in the SPC and product literature. (*“Wash hands after use of the veterinary medicinal product. For pregnant women, particularly near term pregnant women, prolonged dermal exposure increases the risk for premature closure of the ductus arteriosus in the foetus.”*)

Accidental ingestion of one or more tablets by a child weighing 15 kg

The applicant compared potential exposure to the NOAEL for repeat dose toxicity only, which resulted in a MOE of 7.5 for one 40 mg tablet, and even lower MOEs for more tablets.

However, as accidental ingestion is considered an acute single exposure the applicant considered this to be a worst case approach. It was argued that, typically, the NOAEL from an acute study using comparable endpoints is higher than the NOAEL from a repeat dose study. Therefore, in this case a MOE of less than 100 is acceptable. The applicant considered it unlikely that a 15 kg child would exhibit serious adverse effects after ingesting up to three large tablets (40 mg). However, the CVMP disagreed with this and considered, that comparing potential exposure to the NOAEL from a repeat dose study

does not take sufficient account of adverse pharmacological effects that may arise as a result of user exposure. If, as above, the NOAEL for pharmacodynamic effects is assumed to be 5 times lower than the ED₅₀ this would result in a NOAEL in the range of 0.1 mg/kg bw and a MOE of 0.04.

This indicates that adverse pharmacological effects (analgesia and suppression of inflammation) can be expected after accidental ingestion by children. Consequently a warning to seek medical advice after oral ingestion by children is included in the product literature (*"In small children, accidental ingestion increases the risk for NSAID adverse effects. In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician"*). Oral ingestion by adults including pregnant women is considered unlikely and consequently a recommendation to seek medical advice after ingestion is not required for adults.

Solution for injection

The following three scenarios were considered relevant, all for professional users only:

Accidental injection

The applicant used an estimated exposure level of 0.67 mg/kg based on exposure to 2 ml. This was compared to a NOAEL of 200 mg/kg bw from an acute intraperitoneal injection study and to an LOAEL for the structurally related compound diclofenac of 0.1 mg/kg bw on day 21 of pregnancy in rats (based on premature constriction of the ductus arteriosus). The first comparison results in an MOE of 299. Therefore, the applicant concluded that no general toxicity after accidental injection is expected. The second comparison results in an MOE of 0.15. Therefore, the applicant proposed to include a warning for pregnant women.

The CVMP considered that, as a worst case approach, a NOAEL of 20 mg/kg bw/day from the repeat dose toxicity study could be used for general toxicity. This results in a MOE of approximately 30, which is acceptable because the assumed injection volume of 2 ml is considered to be the very worst case and because the NOAEL from a repeat dose study is used for this acute exposure scenario. The CVMP agreed with the conclusion that effects in pregnant women cannot be excluded.

With regards to pharmacological effects, the available pharmacodynamic data show effects in the range of 0.5 mg/kg bw for single exposure. The NOAEL for pharmacodynamic effects is assumed to be 0.1 mg/kg bw. This results in an MOE of 0.15 or of 1.5 for accidental injection with a more likely exposure volume of 0.2 ml. Effects can therefore not be excluded.

However, as professional users are aware of the pharmacological effects a warning is not considered necessary.

Accidental dermal exposure

The estimated exposure level was 0.67 mg/kg based on exposure to 2 ml. As the dermal bio-availability of robenacoxib is considered to be less than the bioavailability following injection, toxicity following accidental dermal exposure can be expected to be less than that seen after accidental injection. As robenacoxib did not cause skin irritation or sensitisation, no local effects are expected.

CVMP agreed that no warnings are required for general toxicity and pharmacological effects as bio-availability following dermal exposure is expected to be lower than following injection.

No assessment of possible reprotoxic effects for this exposure scenario was provided. As there are no data to estimate the dermal bio-availability and because of possible hand-mouth contact, reprotoxic effects cannot be excluded. Therefore, a warning and advice to wash hands and all exposed skin is required in the product literature.

Accidental eye exposure

No exposure amount was estimated for eye exposure because the risk posed by this scenario was considered qualitative. The risk of eye irritation after accidental eye exposure is considered to be unlikely. The CVMP agreed that the risk of eye irritation is very limited.

To take account of user safety concerns the following text is included in the package leaflet:

*Wash hands and exposed skin immediately after use of the veterinary medicinal product
For pregnant women, particularly near term pregnant women, accidental injection and prolonged dermal exposure might increase the risk to the foetus.
In case of accidental ingestion or self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.
In small children, accidental ingestion increases the risk for NSAID adverse effects.*

ENVIRONMENTAL RISK ASSESSMENT

Phase I Assessment

As this product is only intended for use in companion animals and in accordance with the VICH guideline on environmental impact assessment (EIAS) for veterinary medicinal products – phase I (CVMP/VICH/592/98-FINAL), no further testing is required.

CONCLUSION ON SAFETY.

Although the information is limited, the data submitted indicate the toxicity of robenacoxib to be low. The oral LD₅₀ for the rat was between 500 and 200 mg/kg bw and signs of intoxication did not indicate a specific toxic effect. When administered to rats for 13 weeks at a dose of 60 mg/kg bw/day, a decrease in creatinine levels in female rats was observed.

Reproduction toxicity was not studied. However, it was noted that cyclo-oxygenase inhibitors may produce adverse effects on the foetus or neonate if administered during gestation.

Robenacoxib is not considered to be mutagenic or carcinogenic.

Robenacoxib does not cause dermal irritation or hypersensitivity.

The applicant provided a user safety assessment taking account of different product formulations (tablets and solution for injection) and scenarios. CVMP identified potential risk for users of the tablets as accidental ingestion by children and prolonged dermal contact by pregnant woman and for the solution for injection, accidental self-injection by the veterinarian or accidental dermal exposure by pregnant women. Relevant user warnings were included in the SPC and product literature.

The use of Onsior (tablets or solution for injection) does not pose a risk to the environment.

EFFICACY ASSESSMENT

PHARMACODYNAMICS

The Applicant provided a number of well-designed pharmacodynamic studies in different animal species. In addition, results from some pre-clinical studies (dose determination) were used to confirm the findings from pharmacodynamic studies.

Primary pharmacodynamic effects

A series of *in vitro* and *in vivo* studies confirmed the anti-inflammatory potency of robenacoxib and its specificity as a COX-2 inhibitor in different species. *In vitro* data using ovine COX-1 and recombinant human COX-2 showed a 25-fold greater affinity for COX-2 as compared to COX-1. In cats, an approximately 500-fold COX selectivity for COX-2 as compared to COX-1 was demonstrated using an *in vitro* whole blood assay with IC₅₀ values for robenacoxib of 28.9µM (COX-1) and 0.058µM (COX-2). This was also confirmed by *ex vivo* studies in cats and dogs. In dogs, robenacoxib (solution for injection and tablets) produced significant inhibition of COX-2 but had no effect on serum TxB2 production (an index of COX-1 activity) over the dosage range 0.5 to 4 mg/kg, however, in higher doses (8 mg/kg) robenacoxib significantly inhibited serum TxB2 1 hour after dosing (the T_{max}).

Robenacoxib exhibited analgesic and anti-inflammatory effects in different animal models (rat model of carrageenan-induced oedema, rat air pouch model, dog model of urate crystal-induced stifle synovitis, feline kaolin-induced acute paw inflammation model). The ED₅₀ for robenacoxib in the rat studies was approximately 0.3 to 0.5 mg/kg. In dogs, laboratory studies using the force plate analysis also showed an analgesic effect of robenacoxib. The studies were well designed and the techniques used appropriate for the assessment of NSAID-effects in dogs and cats.

Secondary pharmacodynamic effects

No specific studies have been conducted; however, effects similar to other NSAIDs might be expected (e.g. gastrointestinal, liver and kidney effects). However, robenacoxib is a selective COX-2 inhibitor, likely to produce fewer effects on the gastrointestinal tract.

4.2 PHARMACOKINETICS

A number of pharmacokinetics studies were provided in rats, dogs and cats. Additional pharmacokinetic data were available from other studies (i.e. target animal safety, dose determination). Determination of robenacoxib and metabolites in various body fluids and tissues appeared to be complicated and analytical methods were developed, adapted and improved over time. Analytical methods are described in detail and are considered adequate. Studies were GLP-compliant and well designed.

Absorption

Absorption after oral and subcutaneous administration is rapid with a T_{max} of less than 2 hours.

Cat: After subcutaneous injection of 2 mg robenacoxib /kg bw a T_{max} of 1 h, a C_{max} of 1464 ng/ml and an AUC of 3128 ng.h/ml is obtained. After a subcutaneous administration of 1 mg/kg the systemic bioavailability is 69%. After oral administration of approximately 2 mg/kg T_{max} is 0.5 h. Administration of food has some impact on absorption: C_{max} was 1159 ng/ml and 1201 ng/ml and AUC was 1337 and 1383 ng.h/ml when administered without or with a small amount of food (up to a third of the daily food ration). Lower values were obtained when robenoxib was administered with the daily food ratio (C_{max} of 691 ng/ml and AUC of 1069 ng.h/ml). The average systemic bioavailability of robenacoxib tablets was 49% without food.

Dog: After subcutaneous injection of 2 mg robenacoxib/kg bw, a T_{max} of 1 h, a C_{max} of 615 ng/ml, and an AUC of 2180 ng.h/ml is obtained. After a subcutaneous administration of 1 mg/kg the systemic bioavailability is 88% in dogs. Following oral administration of 1 mg robenacoxib /kg, T_{max} is 0.5 h. Administration of food has some impact on absorption: C_{max} was 1124 ng/ml and AUC was 1249 ng.h/ml when administered without food while slightly lower values were obtained when robenoxib is administered with food (C_{max} of 832 ng/ml and AUC 782 ng.h/ml). The average systemic bioavailability of robenacoxib tablets in dogs was 62% with food and 84% without food. Following long-term treatment (6 months), a relatively high variability in C_{max} and AUC was observed; however, the relevance of this finding for a short term treatment is not known.

Distribution

Robenacoxib has a relatively small volume of distribution (V_{ss} of 190 ml/kg in cats and 240 ml/kg in dogs) and is highly bound to plasma proteins (>99%). Since robenacoxib showed tissue selectivity, efficacy duration might be longer than predicted from plasma level profiles.

Metabolism

In radiolabelled studies, blood, faeces, and urine were sampled at regular intervals and analysed for radioactivity (total residues), by HPLC/MS (parent), and by TLC (metabolites). In both, the dog and the cat, a metabolite was observed with a considerable persistence. Apart from this lactam metabolite (a synthetic precursor of robenacoxib and also a potential by-product and/or degradation product of robenacoxib), the identity of other metabolites is not known in cats or dogs. However, no pharmacological action resulting from metabolites was demonstrated.

Robenacoxib is rapidly metabolised by the liver in cats and dogs. Metabolite(s) persisted much longer in the blood than the parent molecule. At 24 hours after oral dosing, no parent compound but substantial amounts of radioactivity were still detectable in the blood as unidentified hydrophilic breakdown products. No parent compound was detected in the urine. A rather complex pattern of metabolites was present in the faeces, with a more lipophilic fraction and some parent compound detected as well.

Elimination

After intravenous administration, robenacoxib is rapidly cleared from blood (CL of 0.44 L/kg/h in cats and 0.81 L/kg/h in dogs) with an elimination $t_{1/2}$ of 1.1 h in cats and 0.8 h in dogs. After subcutaneous administration, the terminal half-life from blood was 1.1 h in cats and 1.2 h in dogs. After oral administration (tablets), the terminal half-life from blood was 1.7 h in cats and 1.2 h in dogs. Robenacoxib persists longer and at higher concentrations at sites of inflammation than in blood. Persistence of blood levels after a single treatment did not seem to exceed 12 hours post-administration.

Robenacoxib is excreted predominately via the biliary route in cats (~70 %) and dogs (~65 %) and the remainder via the kidneys. Clearance is age and condition dependent (higher in healthy young animals), which might have clinical impact.

In the cat, results were highly variable for both the injection and the tablet. In inhibiting COX-2 activity in the central compartment, robenacoxib appeared to be short acting; 1-2 hours for the tablet and 6 hours for the injection. Inhibition of COX-2 was up to 24 hours at sites of inflammation.

Accumulation

Repeated oral or subcutaneous administration of robenacoxib to dogs at dosages up to 10 and 20 mg/kg, respectively, produced no change in the blood profile, with neither bioaccumulation of robenacoxib nor enzyme induction. Bioaccumulation of metabolites was not tested.

The pharmacokinetics of robenacoxib did not differ between male and female cats and dogs and showed dose-dependant effects (linear over the range 0.5-4 mg/kg).

Bioavailability

Some studies were undertaken using a slightly different formulation to the final one. However, for dog studies the applicant had provided sufficient data to demonstrate bioavailability between formulations used in pivotal studies. For the cat studies, CVMP concluded that differences in the formulation were not of concern. Furthermore, the final formulation was used in the pivotal studies.

In pharmacokinetic studies, presence of food showed reduced bioavailability for robenacoxib and the SPC and product literature, therefore, recommend the oral administration of robenacoxib without food or with small amounts only.

TARGET ANIMAL TOLERANCE

The applicant provided a number of target animal safety studies for both, dogs and cats using both, the tablet and the solution for injection formulation. In addition, relevant data from other studies (pharmacology, dose determination, field studies) were considered.

Cats (tablets)

A number of studies were submitted to support the target animal safety of oral administration of robenacoxib to cats.

The well-designed GLP-compliant, pivotal oral target animal safety study in cats was performed in young cats (aged 7-8 months) for 42 consecutive days with oral doses of 0, 2, 6 or 10 mg for robenacoxib/kg bodyweight (i.e. 1 x, 3 x and 5 x the RTD) administered twice daily (i.e. 2 x the recommended once daily dose). Animals were observed for clinical signs, blood and urine samples were taken for clinical laboratory analysis and at the end of the study a complete necropsy was conducted.

All dose levels were well tolerated and no treatment related clinical signs were noted. No effects on haematology, clinical chemistry (including the protein fractions), coagulation and urinalysis were observed. Post-mortem results did not indicate treatment related effects. It was concluded that robenacoxib was well tolerated systemically in cats at different dose levels up to 10 x the RTD over extended treatment duration of up to six weeks. No evidence was found of any gastrointestinal, kidney or liver toxicity and no effect on bleeding time was observed.

In an additional study, investigating the tolerance in cats in oral doses of 0, 5 or 10 mg robenacoxib/kg bodyweight over 28 days, clinical chemistry revealed some changes (5 mg/kg: Hb decreased; leucocytes, Ht and monocytes increased. 5 and 10 mg/kg: erythrocytes increased). However, these were considered to fall within normal ranges and it was concluded that oral administration of robenacoxib as tablets in doses of up to 10 mg robenacoxib/kg bodyweight for 28 days was well tolerated in cats.

Dogs (tablets)

A number of studies were submitted to support the target animal safety of oral administration robenacoxib to dogs.

A well-designed GLP-compliant, pivotal oral target animal safety study in dogs was performed in young beagle dogs (aged 5-6 months,) receiving daily oral doses of 0, 2, 4, 6 and 10 mg/kg (i.e. 1 x, 2 x, 3 x and 5 x RTD) for 6 consecutive months. Animals were observed twice daily for general health. Detailed clinical observations, as well as body weight and food consumption measurements, were made twice weekly. A complete physical, ophthalmoscopic, electrocardiographic examination and buccal bleeding time test was carried out at the beginning and end of the study. Blood and urine samples were collected before the start of the study and at 1, 2, 4 and 6 months for haematology, clinical chemistry and urinalysis. A full necropsy was carried out at the end of the study.

All dose levels were well tolerated and no treatment related clinical signs or effects on ophthalmoscopic, electrocardiographic examination and buccal bleeding time, as well as on haematology, clinical chemistry and urinalysis were noted. It was concluded that the oral administration of robenacoxib tablets was well tolerated in dogs in doses up to 10 mg robenacoxib/kg bodyweight (i.e. 5 x RTD) when administered over an extended period (6 months).

In another study, repeated oral administration of 20 mg robenacoxib/kg bw for 4 weeks resulted in significant increases in creatinine kinase and aspartate aminotransferase activity. The cause may be metabolic, with the liver as the target organ, which is in line with findings in the field trials. Appropriate warnings are addressed in the SPC.

Cats (solution for injection)

The applicant provided several studies investigating the local tolerance in dogs and cats of robenacoxib containing solutions for injection using slightly different formulations (preservatives). Based on the results of these studies, it was concluded that pain reactions were more likely in relation to excipients than to the active substance itself. A number of studies were submitted to support the target animal safety of subcutaneous robenacoxib administration to cats.

The acute injection site tolerance in cats was investigated in two tolerance studies. One study was performed with 2 mg and 10 mg robenacoxib/kg bodyweight (i.e. 1 x and 5 x the RTD) administered subcutaneously once a day over three consecutive days; the second study, over two consecutive days, with doses of 2 and 4 mg robenacoxib/kg bodyweight (i.e. 1 x and 2 x the RTD). Treatment tolerance was evaluated on the basis of clinical observations and physical examinations, clinical pathology parameters and injection site observations (macro and microscopic evaluation).

Injection site reactions were seen in all dose groups, consisting of pain at injection and transient swelling which disappeared within 24 hours. Histopathological analysis of skin biopsies noted minimal inflammation at the injection site of several animals up to 7 days post dose, this minimal inflammation was reversible 14 days post dose. Creatinine kinase was higher in treated cats than in controls. The increased creatinine kinase levels were attributed to muscle necrosis caused by the injections.

Dogs (solution for injection)

A number of studies were submitted to support the target animal safety of subcutaneous administration of robenacoxib to dogs.

The pivotal target animal safety study in dogs using the solution for injection was performed in young dogs (aged 6 months) with doses of 2, 6, and 20 mg robenacoxib/kg bodyweight (i.e. 1x, 3x, 10x RTD). The treatment regimen consisted of three cycles of three consecutive once daily injections (i.e. 9 administrations over a 5 week period). The highest dose was tested in two different formulations, with and without lactam. A saline treated, negative control group was included. Each injection was given at one of the nine predetermined injection sites per dog. Animals were observed for clinical signs (general and local tolerance) and haematology, coagulation testing (including buccal mucosal bleeding time), clinical chemistry and urinalysis were performed. All animals were subjected to a complete gross necropsy examination at days 33 / 34.

In general, robenacoxib was well-tolerated systemically in dogs at all dose levels. Locally, apart from pain on injection (particularly in the higher dose groups), there were no post-dosing findings of pain, abnormal temperature, erythema, oedema, or necrosis at injection sites during the course of the study. Reversible inflammation at the injection site was noted in all groups (including controls) but was more severe in the higher dosage levels of 6 and 20 mg/kg (3 x and 10 x dose multiples, respectively). Robenacoxib produced local effects manifested by subcutaneous inflammation (mild to moderate) of the injection site. The injection site lesion changes resolved with time as evidenced by the lack of significant microscopic lesions at the week 0 injection sites by the end of the study. No other clinical signs were noted.

Higher haemoglobin values and a higher mean buccal mucosa bleeding time were noted in treated animal as compared to controls. However, no dose-related trends were apparent and both statistically

higher values were well within the normal range, indicating that these differences are of no toxicological significance. No toxicological effects on ECG recordings, no statistically significant or toxicologically meaningful differences in mean indirect blood pressure measurements and no treatment-related ocular findings were observed.

Similar findings on local tolerance were also described in other studies. Pain reactions of different intensities during the injection were described in a supportive tolerance study. This is reflected in the SPC. Another study indicated slight acute muscle necrosis following subcutaneously administration of three consecutive doses of 2 mg or 4 mg robenacoxib/kg bodyweight / day (i.e. at 1 x and 2 x the RTD).

DOSE DETERMINATION

Cats (tablets) - acute musculoskeletal disorders

The recommended dose for this indication is 1 mg/kg bodyweight (range 1-2.4 mg/kg).

No dose titration studies on tablets for cats were conducted. A dose of 1-2 mg robenacoxib/kg bodyweight was chosen based on the results from the subcutaneous dose determination study in cats using the kaolin-induced paw inflammation model. Since PK and PD parameters were approximately similar in cats and dogs, a species-extrapolation was undertaken and then used as supportive data for dose establishment for subsequent clinical evaluation.

The CVMP raised some concerns about this approach in view of the absence of a clear relationship between a pharmacodynamic effect (i.e. analgesia) and blood levels (i.e. higher concentrations in exudates than plasma) and the impact of age and condition on robenacoxib pharmacokinetics (higher clearance in young, healthy animals). However, the efficacy of the proposed dose was later confirmed by clinical studies and therefore accepted.

Dogs (tablets) - chronic osteoarthritis

The recommended dose for this indication is 1 mg/kg bodyweight (range 1-2 mg/kg). The applicant provided a number of dose determination studies using the acute stifle joint arthritis model in dogs and also a dose determination study under clinical field conditions using three different doses.

Two multicentre, randomised, blinded dose determination studies were performed under field conditions in dogs with osteoarthritis. In the first trial, three different single doses of robenacoxib (0.5-1 mg/kg/d; 1-2 mg/kg/d; 2-4 mg/kg/d) or a positive control (meloxicam) for 28 days were administered once daily. The study included dogs of various age groups, breeds and gender with radiographically confirmed osteoarthritis and clinical signs for at least 3 weeks. Since analysis of efficacy showed no clear relationship between the efficacy and dosage, another study was performed using the same study design and the same daily doses as in the first study, but split into twice daily administrations (i.e. 0.25-0.5, 0.5-1 mg/kg or 1-2 mg/kg b.i.d.). Since results again did not show significant differences between treatment groups, the CVMP considered both field studies of limited value due to lack of a clear dose-effect relationship and the possible lack of (statistical) power.

The pivotal pre-clinical study was well-conducted GCP-compliant and blinded, using the urate crystal induced stifle synovitis model in five different doses (0.5, 1, 2, 4 and 8 robenacoxib) as compared to a negative (placebo) and positive (meloxicam) group. The urate crystal synovitis model is an established model which has been used to evaluate other NSAIDs, i.e. urate crystals are administered into predetermined stifle joints inducing moderate to severe lameness associated with joint inflammation/pain. Lameness (force plate and subjective assessment) and blood parameters were evaluated up to 6 hours post-administration.

Analgesic effects were seen in all groups with peak responses at 3 to 5 hours following oral administration. Maximum analgesic efficacy was achieved with 2 mg/kg, with an ED₅₀ of approximately 0.6-0.8 mg/kg. The lowest effective dose for analgesia was 1 mg/kg. All doses of robenacoxib had a faster

onset of action and a faster time to peak efficacy than meloxicam. To maximise the safety index, the applicant selected the (minimal) oral dose of 1 – 2 mg/kg for the clinical trials.

There was no clear dose-response-relation for inhibition of swelling over the range 0.5 – 8 mg/kg; and the CVMP considered the relevance of measuring the inhibition of COX-2 activity in blood as low. However, considering the model used, the CVMP agreed that the 2 mg/kg dose did produce a maximum inhibition of COX-2 activity and that the data would support the proposed dose of 1 (-2) mg/kg bodyweight. Due to the study design non-responders to treatment could not be assessed, but a number of non-responders would be expected to appear in the field trials. Furthermore, duration of efficacy was not assessable in this short-acting model.

Cats (solution for injection) – post-operative use

Dose determination was based on a laboratory study using a kaolin-induced paw inflammation model in the cat. Ten healthy young (1-2 years) cats of both sexes received a single subcutaneous dose of 2 mg robenacoxib/kg bodyweight 47 hours after kaolin injection. A dose of 2 mg robenacoxib/kg bodyweight was chosen based on extrapolations from the results in the dog studies. (In this model, kaolin is injected subcutaneously into the paw of cats inducing a well defined and reproducible inflammatory response, which results in increases in body temperature, skin temperature and paw volume and moderate to severe lameness. The inflammatory response (untreated) lasts 4 to 5 days with body temperature, gait and behaviour patterns being normal again after one week.).

Animals were checked for clinical responses (body/skin temperature, locomotion) and blood samples were collected. Blood samples were analysed by a GLP validated analytical method using HPLC-UV and LC-MS with a limit of quantification of 3 ng/ml. The study was followed by a PK/PD analysis.

Results indicated that a subcutaneous dose of 2 mg robenacoxib/kg produced some analgesic and anti-inflammatory effects in the cat (impact on body temperature, skin temperature, locomotion and paw withdrawal time), with peak responses for all endpoints between 2.6 and 3.5 hours post administration. ED₅₀ for the lameness and locomotion scores were determined as 1.5 and 3 mg robenacoxib/kg, respectively. Inter-individual variability was high, but this is not uncommon for the cat and might also be based on large pain threshold differences from one cat to another.

Most effects had returned to pre-treatment levels by 6-8 hours and the CVMP expressed concern about the proposed dosage regimen of once daily (as compared to twice daily). The applicant justified the once daily dosing proposal with the results from a clinical study where non-inferiority between once and twice daily doses of 1-2 mg/kg robenacoxib was shown. Preliminary results from a new pilot study in cats showed reduction in pain after soft tissue surgery following treatment with both injectable and tablets in the proposed (once daily) dose regime. Although the results were not finalised and some shortcomings in the study were noted, the CVMP agreed that the new study supported the proposed once daily dosing regime.

Dogs (solution for injection) - post-operative use after orthopaedic or soft tissue surgery

Two dose determination studies were performed, one (pivotal) in a model (urate synovitis) and another one in a field trial (orthopaedic surgery).

A GCP-compliant, dose determination (field) study was submitted investigating three different single doses of subcutaneously administered robenacoxib (0.5, 1 or 2 mg/kg) or a positive control (meloxicam) in 80 dogs after orthopaedic surgery. Robenacoxib was administered before surgery, at the time of induction of anaesthesia and pain was assessed. Additional parameters included investigation of blood samples (haematology, clinical chemistry), buccal mucosal bleeding and local tolerance. Results did not show statistically significant differences between the treatment groups, and a clear dose-response relationship could not be made. In view of a considerable degree of variation in efficacy parameters and the inconclusive results from this study, the CVMP did consider this study of limited value.

The study using a model of urate crystal induced stifle synovitis (was well-conducted, GCP-compliant and was performed in eight beagle dogs with doses of 0.25, 0.5, 1, 2, or 4 mg robenacoxib / kg body-weight. Lameness (force plate and subjective assessment) and blood parameters were evaluated up to 12 hours post-administration.

The results showed a rapid onset of analgesic action of about 1 hour (0.5-2 h) for the two highest dose groups (2 and 4 mg/kg). Spontaneous recovery from the induced synovitis (not attributed to treatment) was rather high during the assessment period, so no clear conclusions on the duration of efficacy could be made.

The CVMP noted that only the higher dose of 4 mg/kg resulted in significant superiority over meloxicam and questioned the applicant's choice of the lower dose of 2 mg/kg as RTD. The applicant explained that effects at 2 mg/kg were non-inferior to those achieved with the positive control (containing meloxicam) and were superior to the placebo. In addition the results show a plateau for effect indicating that a maximum in COX2 inhibition has been achieved for robenacoxib. To maximise the safety index, the lower dose of 2 mg was chosen as RTD. The CVMP accepted this justification.

CONCLUSION ON THE PRECLINICAL PART

Robenacoxib is a selective inhibitor of COX-2. *In vitro* data in cats indicate an approximately 500-fold COX selectivity for COX-2 as compared to COX-1. In dogs, robenacoxib was approximately 140 fold selective for COX-2. Analgesic and anti-inflammatory effects were confirmed in different animal models. In dogs, a maximum inhibition in COX-2 activity was achieved following a single intramuscular dose of 2 mg/kg bw. In the models used, a dose-response relationship in dogs was noted.

Following oral or subcutaneous administration, absorption is rapid with a T_{max} of less than 2 hours. Presence of food reduced bioavailability for robenacoxib and it is recommended to administer the product without food or with small amounts only. Robenacoxib has a relatively small volume of distribution and is highly bound to plasma proteins (>99%). Since robenacoxib showed some tissue selectivity at sites of inflammation, efficacy duration might be longer than predicted from plasma level profiles. Apart from one lactam metabolite, the identity of other metabolites is not known in cats or dogs, but no pharmacological action was demonstrated for any known metabolite. Robenacoxib is rapidly metabolised by the liver. Following subcutaneous or oral administration, the terminal half-life from blood was less than 2 hours in both, cats and dogs. Robenacoxib is excreted predominately via the biliary route in cats (~70 %) and dogs (~65 %) and the remainder via the kidneys. Clearance is age- and condition dependent (higher in healthy young animals), which might have clinical impact. Accumulation was not observed.

In general, tolerance in dogs and cats was considered good. Target animals safety studies with the oral formulation showed good tolerance for both, dogs and cats receiving daily doses of up to 5 x the recommended daily dose over 1 month (cats) or 6 months (dogs). Since robenacoxib is a selective COX-2 inhibitor, effects on the gastrointestinal tract are expected to be less severe than generally for NSAIDs. This was also confirmed in laboratory studies where robenacoxib was well-tolerated gastro-intestinally in rats.

The subcutaneous injection can cause local reactions, being somewhat more severe in the cat than in the dog. Pain at injection can be observed; injection site reactions disappear within a few days. Pain at injection site has been addressed in the SPC. Increased creatinine blood levels were considered as a result of muscle necrosis following subcutaneous injection. However, it should be noted that tolerance studies were carried out in young healthy dogs. Since clearance is much higher in young animals, the validity of the result from the tolerance studies is limited with respect to the safety of robenacoxib in animal patients. Complications concerning cardiovascular disorders (as found in humans for COX-2 inhibitors), have not been observed in animals.

In cats, no dose titration study was performed but PK/PD modelling was conducted from results with 2 mg/kg by subcutaneous injection in the kaolin model and since PK and PD parameters were approximately similar in cats and dogs, a species-extrapolation was undertaken and an oral dose of 1-2 mg

robenacoxib/kg bodyweight was chosen. For the subcutaneous solution, a single laboratory study was provided using an injectable dose of 2 mg/kg in a kaolin-induced paw inflammation model. The study was followed by a PK/PD analysis. Overall, sufficient efficacy was shown for the tested dose of 2 mg/kg although a considerable degree of variability in pain scores was present. A new pilot study in cats was submitted as a response to questions, supporting the clinical efficacy in cats and the once-daily dosing regime.

Dose determination in the dog was mainly based on the urate synovitis model. No marked gain in efficacy was seen when the dose was raised above 2 mg/kg although considerable variability in efficacy responses was seen. The applicant's intention was to select the lowest effective dose, to maximise the safety index. Therefore, the applicant selected a minimal oral dose of 1 mg/kg and an injectable dose of 2 mg/kg for the clinical trials. Non-responders were seen in the urate arthritis model but the extent was not directly assessable and therefore the field trials are pivotal in the assessment of effect. Considering the model used, it is concluded that the 2 mg/kg dose did produce a maximum inhibition of COX-2 activity.

CLINICAL STUDIES

Cats (tablets) – acute musculo-skeletal disorders

The efficacy of robenacoxib tablets was tested in a multi-centre, parallel-group designed, randomised and blinded European field study in cats with acute musculoskeletal disorders. Cats received either robenacoxib (1-2 mg/kg), administered either once daily or twice daily or a positive control containing ketoprofen over 5-6 days.

The study included cats of different age groups (from 6 weeks), gender and breeds (2.5 – 12 kg) with signs of acute musculo-skeletal pain and inflammation such as musculoskeletal injuries due to sprain or strain, subluxation or acute worsening of osteoarthritis or other trauma, abscesses, bites and scratches. Exclusion criteria included cats with acute pain and inflammation due to other underlying diseases, cats that were pregnant, lactating or intended for breeding and cats with severe concomitant disorders or animals that received concomitant treatment with other analgesic substances.

Efficacy was assessed using numerical rating scales based on pain at palpation/mobilisation, inflammation and mobility scores and overall response to treatment. The efficacy results scores were similar (non-inferior) in all treatment groups; however, the frequency of diarrhoea was significantly higher in the robenacoxib group treated twice daily as compared to the once daily or ketoprofen group and the applicant therefore considered once daily treatment more appropriate.

The CVMP expressed some concern about the inclusion criteria of cats, in particular the high number of cats with bites and scratches or abscesses, which would not necessarily be considered as musculo-skeletal disorder. However, the applicant provided an analysis comparing the efficacy of treatment in the different sub-groups confirming non-inferiority to control group with regard to all primary and secondary endpoints. The applicant also confirmed that the case recruitment was made by the investigators involved in the clinical study and reflected the understanding of a veterinary practitioner on "cats presented with signs of acute musculo-skeletal disorder".

The CVMP accepted this justification and agreed with the conclusion of the applicant, i.e. that treatment with robenacoxib was non-inferior to treatment with a positive control.

CATS - SOLUTION FOR INJECTION (& TABLETS) – POST-OPERATIVE USE AFTER SOFT TISSUE SURGERY

The applicant provided a multicentre, European field study investigating the efficacy of robenacoxib in solution for injection and tablets for peri-operative pain and inflammation after soft tissue surgery in cats.

Prior to surgery, cats received a single injection of 2 mg robenacoxib/kg bw or a positive control (meloxicam) subcutaneously between the shoulder blades. Treatment was followed by once daily oral administration of either 1-2 mg/kg robenacoxib or a placebo for up to 11 days. The study included cats of different age groups (from 6 weeks), gender and breeds (2.5 – 12 kg) that received soft tissue surgery (e.g. ovariectomy, gastro-intestinal surgery, genito-urinary surgery). Animals were examined at the initial visit, at 3, 8 and 22 hours after extubation, at 4 hours after first oral dosing and at the end of the study, approximately 10 days after surgery. Efficacy parameters were based on the animal's posture and behaviour of the animal as well as pain on palpation/manipulation.

Tablets:

For the oral treatment, the results were inconclusive and the study design was not acceptable. The applicant, therefore, withdraw this indication (post-operative use after soft tissue surgery in cats).

Solution for injection:

For the solution for injection, however, results showed equivalent (non-inferior) efficacy to the approved comparator product (meloxicam) up to 22 hours after extubation. Pain control appeared to be sufficient as rescue therapy was only needed in 1 cat in each group.

Further support for the efficacy of a single subcutaneous dose in the reduction in pain was provided by the applicant with a preliminary study, in which a placebo treated group was included. Results indicate that robenacoxib can be effective when used peri-operatively.

Based on the data presented the CVMP agreed that a single subcutaneous dose of 2 mg robenacoxib per kg bodyweight would provide a satisfactory analgesic effect in cats for up to 24 hours.

DOGS (TABLETS) - CHRONIC OSTEOARTHRITIS

Two GCP-compliant confirmatory field trials were provided in dogs with chronic osteoarthritis. Both studies were blinded, positively controlled and included randomised parallel-group comparisons of robenacoxib to a positive control, carprofen or meloxicam.

The pivotal field study was a multicentre European study and included dogs with osteoarthritis present for at least 3 weeks. Dogs received for 12 weeks robenacoxib at a daily dose of 1-2 mg/kg bodyweight, administered by the animal owners.

Concomitant treatments were administered to 63% of the dogs. Any medication that was likely to affect the assessment of the main efficacy parameters was prohibited during the study, in particular: other analgesic substances (including opioids), NSAIDs, corticosteroids, pentosan polysulphide sodium, PSGAG, chondroitin sulphate or glucosamine. Assessments were made by the clinician and the owner using Numerical Rating Scales (NRS). The primary endpoint parameter "Global Functional Disability" was calculated from the sum of posture, lameness at walk and trot, willingness to raise the contralateral limb and pain at palpation Numerical Rating Scales (NRS) scores. Secondary endpoints were clinician and owner criteria. Animals were checked at days D0, D7, D14, D28, D56 and D84.

Results showed in both treatment groups a rapid and significant control of signs of osteoarthritis being evident for all parameters; statistically significant improvement as compared to baseline values was recorded from the first time point of day 7 for all efficacy endpoints. The results show that robenacoxib had statistically non-inferior efficacy to carprofen for the primary endpoint, the Global Functional Disability using non-inferiority analysis and the delta of 0.75 pre-defined in the protocol. In addition to the secondary endpoints, non-inferior efficacy was shown for all but one of the parameters (pain at palpation/mobilisation).

A second European field study was conducted in dogs suffering from osteoarthritis (OA). The design of the studies was the same. Dogs were treated for up to one year using tablets at dose levels ranging from 0.5 to 2 mg robenacoxib /kg bw/day or with a positive control containing meloxicam. Meloxicam was administered at the same time as feeding (in line with the SPC) while robenacoxib was given with or without food. Clinical examinations and owner's assessment were used to evaluate the efficacy.

This field study showed that robenacoxib tablets at a dosage of 0.5-2 mg/kg were equivalent to the reference product (meloxicam). Robenacoxib showed better gastrointestinal tolerability. However, elevations of ALT were more frequently noted than meloxicam, although there was no evidence for increased risk of liver adverse events. The CVMP noted that the interpretation of results was difficult since the dosing recommendations varied during the study.

Based on the results of these two studies, the CVMP agreed that the efficacy of robenacoxib was non-inferior to treatment with positive controls, which are authorised in Europe.

The applicant was requested to justify the duration of treatment with robenacoxib in dogs with osteoarthritis since some dogs may benefit from intermittent treatment. The applicant explained that the duration of treatment should be based on the decision of the attending veterinarian and the duration of treatment was therefore specified in the SPC and package leaflet to “*as long as required (as directed by the veterinarian)*”. Furthermore, it was reflected in the SPC that for longer term treatment the dose of Onsiar can be adjusted to the lowest effective individual dose and that regular monitoring should be undertaken by the veterinarian.

Dogs – solution for injection (& tablets) - orthopaedic or soft tissue surgery

Two pivotal field studies were submitted for use of robenacoxib in dogs after orthopaedic and soft tissue surgery. One single injection of either 2 mg/kg (1 ml/10 kg) robenacoxib or a positive control containing meloxicam was given prior to surgery and was followed by an oral treatment (1-2 mg/kg) administered once daily for up to 12 (\pm 2 days). The studies were performed as GCP-compliant, multi-centre European, parallel-group designs, and were randomised and blinded. Pain was assessed by the clinician 1, 2, 4, 8, 24 hours after treatment (before administration of the tablets) and at the end of the study (D12). For the oral treatment, the animal owner noted the pain scores daily.

Parameters selected for the study were in agreement with the Guideline for the Conduct of Efficacy Studies for Non-Steroidal Anti-Inflammatory Drugs (EMEA/CVMP/237/01). Both VAS and NRS (Glasgow pain scale score) were used for the assessment of efficacy. The concomitant treatments administered can be regarded as standard in the course of soft tissue surgery e.g. diazepam for muscle relaxation, fluids, antibiotics (injection, then oral in most cases). Antibiotics used belonged to several classes: β -lactams, fluoroquinolones, aminoglycosides, imidazols, macrolides, sulfamides, pyrimidines, tetracyclins and lincosamides. No interaction with the test product was evidenced.

Solution for injection

Pain scores gradually decreased over 24 hours following injection. However, the efficacy of robenacoxib was found being non-inferior to meloxicam including the 24 hours observation time point. In view of the gap in assessment between 8 hours and 24 hours, the decrease of pain noted at 24 hours might be due to the recovery of animals from surgery rather than due to treatment. Taking into account the results obtained from pre-clinical studies, the CVMP therefore concluded that sufficient efficacy of robenacoxib for analgesia was only demonstrated up to 8-10 hours after extubation.

Tablets

For the oral post-operative treatment, the study design was considered inadequate to confirm the efficacy of robenacoxib at the proposed dose and duration of treatment. The choice of animal owner's demeanour scores were not considered suitable and the selected positive control is not authorised in Europe for this indication. The CVMP therefore did not accept this proposed indication.

Tolerance in field studies

At the recommended dosages, the general level of adverse effects after administration of robenacoxib (oral or injection) was low and constituted mainly non-serious gastrointestinal events (vomiting, diarrhoe, soft faeces). Most dogs recovered without treatment. In general, robenacoxib showed better gastrointestinal tolerability than positive controls used in the trials. This corresponded to the pharmacological properties of robenacoxib (selective COX-2 inhibition).

In general, the solution for injection was locally well tolerated; pain at injection was only reported in individual animals (some might be most susceptible to pain).

Cases of serious liver function impairment were observed in some dogs in the clinical trials. These were only seen in animals with evidence of pre-existing liver pathology. The SPC adequately reflects the risk for dogs with potential liver problems.

In some dogs with long-term oral treatment with robenacoxib, increased liver enzymes (ALT) were seen more frequently as compared to dogs treated with a positive control (containing ketoprofen or meloxicam); however, the increases remained in the normal range and no clinical evidence was noted for increased risk of liver adverse events. The SPC includes appropriate warnings and recommendations for such events.

Changes in plasma biochemistry and blood haematology values were noted but mainly attributed to the recovery from surgery. Robenacoxib did not show any significant changes in bleeding time (as described for other, non-COX-2 selective NSAIDs). No evidence of impaired wound healing was observed.

Palatability

The palatability of the final tablets for dogs (containing yeast and artificial beef flavour as palatability enhancers) was tested in a palatability trial. Approximately 80% of large dogs and 60% of small dogs took the tablets from the hand of the investigator when offered. 10% (large) and 20% (small) dogs refused to take tablets voluntarily. In field trials, tablets were in general well accepted. The palatability of the final tablets (containing yeast as only palatability enhancer) for cats was tested in the pivotal field trial. It was concluded that the tablets were well accepted by most cats since 66% either took the tablets voluntarily or swallowed it easily when placed on the tongue.

CONCLUSION ON THE CLINICAL PART

Onsior is available in different tablet strengths and as solution for injection for different indications in the two target species, cats and dogs. In support of the individual indications, the applicant provided GCP compliant clinical studies for each indication and target species.

For cats, the CVMP accepted the following indication and dose: Treatment of acute pain and inflammation associated with musculo-skeletal disorders at a once daily dose of 1 mg/kg body weight up to six days. For dogs, the CVMP accepted the following indication and dose: Treatment of pain and inflammation associated with chronic osteoarthritis at a once daily dose of 1 mg/kg body weight as long as required (as directed by the veterinarian).

The solution for injection is intended for use in dogs and cats for a single subcutaneous dose of 1 ml per 10 kg of body weight (2 mg/kg). For cats, the CVMP accepted the following indication: Treatment of pain and inflammation associated with soft tissue surgery. For dogs, the CVMP accepted the following indication: Treatment of pain and inflammation associated with orthopaedic or soft tissue surgery in dogs.

In the field studies the level of poor responders was equal to that of other NSAIDs when used for the same indications, being within the range of 10-15% among the osteoarthritis canine patients and few in the other patients groups for both dogs and cats. This has been reflected in the SPC.

Both tablets and solution for injection were in general well tolerated. Most common adverse effects were non-serious gastrointestinal reactions (vomiting, diarrhoe, soft faeces), which did not require further treatment.

Cases of serious liver function impairment were observed in the clinical trials in a few dogs with pre-existing liver pathology. In some dogs with long-term oral treatment, increased liver enzymes (ALT) were seen. Although these increases remained in the normal range and did not result in clinical signs, the SPC includes appropriate warnings and recommendations for long term oral treatment. Pain at injection was only reported in individual animals.

Tablets were in general well accepted by both cats and dogs.

BENEFIT - RISK BALANCE

BENEFIT ASSESSMENT

DIRECT BENEFITS

Tablets

In cats sufficient reduction of acute pain and inflammation associated with musculo-skeletal disorders has been demonstrated to accept as an indication.

In dogs sufficient pain reduction has also been presented to accept as an indication for the treatment of chronic osteoarthritis. The indications for relief of pain and inflammation after surgery for the tablets were insufficiently substantiated for both dogs and cats and, therefore, these indications do not contribute to the benefits of the product.

Solution for injection

Sufficient clinical efficacy has been presented for the peri-operative use in both cats and dogs treated with the injectable formulation at the recommended dose. For cats this concerned the use after soft tissue surgery only, where as in dogs, this concerned the use after orthopaedic as well as soft tissue surgery.

Additional benefits

The risk for gastro-intestinal bleeding after robenacoxib treatment is considered lower as compared to non-selective COX-inhibitors.

RISK ASSESSMENT

At the recommended dose range, the level of adverse effects after administration of robenacoxib is low. Clinical signs are similar to those of other NSAIDs and within acceptable limits. Robenacoxib may have an effect on liver enzymes in dogs. However, liver toxicity was reversible after stopping the treatment. It appears mainly to pose a risk in dogs with evidence of pre-existing liver pathology and sufficient SPC warnings have been included.

EVALUATION OF THE BENEFIT RISK BALANCE

Discussion

Efficacy has been demonstrated for peri-operative use in cats and dogs for the injection formulation. In addition, efficacy of tablets has also been demonstrated for reduction of pain associated with osteoarthritis in dogs, and reduction of acute pain and inflammation associated with musculo-skeletal disorders in cats. The benefits of these effective treatments outweigh the risks which were low at the recommended dose. Risks for cats and dogs suffering from gastro-intestinal bleeding, and risks for dogs with a hepatic disease could be mitigated by contra-indicating the use of the product in these animals.

For the use of the tablets in dogs and cats for relief of pain and inflammation following surgery, no direct benefits were identified, and consequently the benefit-risk balance is not favourable for this proposed indication.

CONCLUSIONS

Based on the original and complementary data presented, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the quality, safety and efficacy of Onsior were considered to be in accordance with the requirements of Council Directive 2001/82/EC, as amended, and that the benefit-risk balance was favourable for the following indications and posology:

Tablets

Cats: Treatment of acute pain and inflammation associated with musculo-skeletal disorders at a once daily dose of 1 mg/kg body weight up to six days.

Dogs: Treatment of pain and inflammation associated with chronic osteoarthritis at a once daily dose of 1 mg/kg body weight as long as required (as directed by the veterinarian).

Solution for injection:

Cats: Treatment of pain and inflammation associated with soft tissue surgery at a single dose of 2 mg/kg body weight given by subcutaneous injection before the start of surgery.

Dogs: Treatment of pain and inflammation associated with orthopaedic or soft tissue surgery in dogs at a single dose of 2 mg/kg body weight given by subcutaneous injection before the start of surgery.