**SCIENTIFIC DISCUSSION**

| Name(s) of the veterinary medicinal product:               | Quadrisol 5 mg/ml oral gel for dogs  
<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>Quadrisol 1 mg/ml oral gel for dogs</td>
</tr>
<tr>
<td>Marketing Authorisation holder:</td>
<td>Intervet International B.V.</td>
</tr>
<tr>
<td></td>
<td>Wim de Körverstraat 35</td>
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<tr>
<td></td>
<td>P.O. Box 31</td>
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<tr>
<td></td>
<td>NL – 5830 AA Boxmeer</td>
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<tr>
<td></td>
<td>The Netherlands</td>
</tr>
<tr>
<td>Active substances:</td>
<td>Vedaprofen hydrochloride</td>
</tr>
<tr>
<td>International non-proprietary name:</td>
<td>Vedaprofen</td>
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<tr>
<td>Pharmacotherapeutic group (ATCvet code):</td>
<td>Anti-inflammatory and anti-rheumatic products, non-steroids (QM01AE90)</td>
</tr>
<tr>
<td>Therapeutic indication(s):</td>
<td>Reduction of inflammation and relief of pain associated with musculo-skeletal disorders and trauma.</td>
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<tr>
<td>Withdrawal period:</td>
<td>N / a</td>
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CVMP/030/99-Rev.2  1/15  ©EMEA 2002
1. INTRODUCTION

Quadrisol 5 mg/ml is an extension to the existing marketing authorisation for Quadrisol 100 mg/ml oral gel for horses. Therefore, cross-reference in several sections of the dossier has been made to the original application.

Quadrisol is a non-steroidal anti-inflammatory drug (NSAID) developed for veterinary use containing vedaprofen as the active ingredient. Vedaprofen is a substance having anti-inflammatory, anti-pyretic and analgesic effects. Like other aryl-propionic acid derivatives, vedaprofen contains an asymmetric carbon atom. The product contains a racemic mixture of the (+) enantiomer and the (-) enantiomer of vedaprofen. Most of the pharmacological, and all of the toxicological and clinical studies, have been performed with the racemic mixture.

Quadrisol 5 mg/ml oral gel for dogs is indicated for the reduction of inflammation and relief of pain associated with musculo-skeletal disorders and trauma. Since Quadrisol 5 mg/ml is contraindicated for the use in dogs with a bodyweight of less than 10 kg, the Marketing Authorisation Holder submitted in May 2001 an application for an extension for a further strength containing 1 mg vedaprofen per ml oral gel. This extension was granted on 10 July 2002.

2. OVERVIEW OF PART II OF THE DOSSIER: ANALYTICAL ASPECTS

2.A QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

The product contains per ml:

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Quadrisol 5 mg/ml</th>
<th>Quadrisol 1 mg/ml</th>
<th>Quality standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vedaprofen</td>
<td>5.0 mg</td>
<td>1.0 mg</td>
<td>in house monograph</td>
</tr>
</tbody>
</table>

Excipients:

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Quadrisol 5 mg/ml</th>
<th>Quadrisol 1 mg/ml</th>
<th>Quality standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propylene glycol</td>
<td>130.00 mg</td>
<td>130.00 mg</td>
<td>Ph.Eur.</td>
</tr>
</tbody>
</table>

Container:

The packaging materials used for the 15 ml (used for Quadrisol 1 & 5 mg/ml) and 30 ml (used for Quadrisol 5 mg/ml) presentations are the same as used for Quadrisol 100 mg/ml oral gel for horses (EU/2/97/005/001). The container of the oral gel is a 15 ml or 30 ml graduated multidose oral syringe consisting of high density polyethylene. The oral syringes are closed with a cap and seal made of low density polyethylene. The colour of the cap differs in the different strengths, i.e. blue (Quadrisol 1 mg/ml), red (Quadrisol 5 mg/ml) and white (Quadrisol 100 mg/ml), respectively. The oral syringes are graduated in 0.5 ml and 1 ml increments respectively and packed either in individual cartons (single presentation) or in multipacks of 5 oral syringes, each containing 15 ml or 30 ml gel.

Product Development Studies:

Vedaprofen is formulated as a gel, because pharmacodynamic studies have shown that the tolerance of vedaprofen in the target species is better when it is given as a solution (gel), as compared to a suspension.

The gel is intended to be administered orally to dogs. To increase palatability of the gel, chocolate flavour has been added. However, for stability reasons this excipients had been deleted in March 2000, following a Type I No 6 variation. Propylene glycol is added, which has a preservative action.
For stability reasons the pH has to be above 8.0 since the potassium vedaprofen salt is at risk of precipitation when the pH falls below 8.0. However, for palatability reasons the pH has to be less than 9.5.

No incompatibilities between the gel and the container have been encountered under recommended storage conditions. Studies were carried out in which the level of propylene glycol was not monitored. However, it is evident that the propylene glycol acts as a satisfactory preservative for this preparation.

Dose uniformity of expelled weights was established for the 15 ml and 30 ml presentation:

(a) 15 ml presentation:
The consistency of the dosing device was proven in five injectors each containing 15 ml, which were emptied at a rate of 0.5 ml and 1 ml per dose on two different occasions. The dosing accuracy meets the Ph.Eur. requirements for single dose preparations. The uniformity of fill was studied in 24 oral syringes. The syringes were weighed empty, after filling and expression. The results show that the amount filled into the syringes is sufficient to express 30 and 15 doses of 0.5 and 1 ml respectively.

Further to the original studies for Quadrisol 5 mg/ml, another study was carried out confirming compliance with the Ph. Eur. requirements for single-dose preparations and that the fill volume is adequate to allow satisfactory withdrawal of 15 doses. However, the Committee expressed concern that preservative efficacy had neither been examined during the stability studies nor during the in-use study and required preservative efficacy studies initially and at the final time-point in the formal stability studies on the first production batches. The Applicant committed to provide such stability studies on the first two production batches, including preservative efficacy, on the fresh batches and at the end-of shelf-life (Commitment 1). The joint CPMP/CVMP guideline on process validation should be considered regarding what level of detail should be provided.

(b) 30 ml presentation:
The 30 ml oral syringe is identical to that for Quadrisol 100 mg/ml oral gel for horses (EU/2/97/005/001). While dose accuracy had been shown for that preparation with 1 ml dosages, dose accuracy with this presentation has also been performed for Quadrisol 5 mg/ml. These results also confirm satisfactory dose accuracy.

The discrepancy between a recommended dosage of 1 ml per 10 kg body weight, the lowest dosing capacity, its limited dosing accuracy and dosing of animals of intermediate weights was resolved in the SPC and product literature of the 5 mg/ml presentation by contraindicating the use of Quadrisol 5 mg/ml in dogs of less than 10 kg body weight.

2.B METHOD OF PREPARATION

The manufacturing formula is calculated for 100 litre (=102.3 kg) batches. The product meets the release specifications set and the scale up from 100 to 250 litres is satisfactory.

The maximum batch size during the trials for the 1 mg/ml presentation was 25 l; however, the proposed batch quantities for the production batches range from 100 to 1000 l. The Applicant therefore, committed to provide data for the validation of the first two production batches with a batch size of 300 l of the first batch. When the process validation of this batch is complete, the following batch will be manufactured and validated and the size of this batch will be 300 liters or multiples thereof (Commitment 2).

The manufacturing method consists of dissolving vedaprofen in a solution followed by the addition of propylene glycol. After necessary pH adjustments the homogenous gel is filled into polyethylene oral syringes. In March 2001, the Applicant submitted a type I No 15 variation, changing the pH adjustment in order to facilitate the procedure being performed on a liquid intermediate rather than a gel form. The remaining water will be added before the gel is allowed to cool down in order to achieve quicker homogenisation due to a lower viscosity.
In-process control is standard.

Process validation is undertaken on the basis of information supplied on one production batch of 250 litre. Samples were taken at regular intervals during the filling procedure, which were assessed for various parameters including content of each ingredient, pH, appearance, colour, syringeability, homogeneity, expressed weight. Given the similarity between Quadrisol 5 mg/ml and the previously authorised Quadrisol 100 mg/ml oral gel for horses (EU/2/97/005/001), the limited data on process validation were considered to be acceptable. Furthermore, the Applicant submitted further process validation studies for Quadrisol 100 mg/ml oral gel for horses as part of post-authorisation commitments, which have been found acceptable by CVMP. Furthermore, validation studies for the first two production batches are to be submitted as post-authorisation commitments for Quadrisol 1 mg/ml.

2.C CONTROL OF STARTING MATERIALS

Since the active ingredient vedaprofen is not described in a pharmacopoeia, a monograph has been supplied.

Specifications of all materials used in the synthetic process have been provided. The specifications in general are satisfactory. The majority of analytical methods are based on pharmacopoeial methods. Of the in-house methods used the details are somewhat brief for the HPLC method, for the starting material and the GLC method for methanol. However, the Applicant has confirmed that all excipients are tested in accordance with the requirements of their respective Ph.Eur. monographs.

The Applicant provided confirmation that none of the excipients come from human, bovine, ovine or caprine source material (TSE Compliance).

The in-process control procedure performed during the synthetic process is conducted at three stages but few details are given on the criteria applied. However, the process is reasonably well controlled although some of the specifications of materials used were considered insufficient and an identity test was requested and later supplied by the Applicant.

The information on chemical development consists of elementary analysis, infrared spectra, 1H nuclear resonance spectra, UV spectrum and optical rotation. The physico-chemical properties, solubility, particle size, pH and pKa value and polymorphism which is not relevant considering that the product is present in a solution, have been investigated. Details on light or moisture sensitivity are not considered relevant for this product.

With regard to impurities, apart from the solvents, only the dimethylester and the t-butyl ester of vedaprofen have been detected. The analytical method to determine the two impurities is HPLC, for which the analytical conditions are similar to those used in the assay of the active ingredient itself. The HPLC tracing shows good separation of vedaprofen its two by-products, and linearity is shown for the two impurities. Additional validation data used in the determination of solvents have been submitted by the Applicant in July 1998 and December 1999 as a follow-up commitment and have been found acceptable by the CVMP.

The limits set for specified and non-specified individual and total related compounds in the drug specification were considered too generous in the light of batch data reported, but could have been considered acceptable provided the clinical trial batches could be shown to be based on drug containing the proposed levels of by-products as that intended to be commercialised. The CVMP agreed that individual unknown impurities be limited to ensure that they were below levels at which identification became necessary. The Applicant has subsequently tightened the limits as now declared because data on batches used in clinical trials were not available.

Details for the analytical method and its validation used in the determination of solvents are based on the standards current at the time of application. More detailed specifications on the reference substances used have been submitted by the Applicant post-authorisation as a follow-up measure for
the oral gel for horses. Limits for the drug substance have been tightened considerably. Individual identifiable impurities are proposed at 0.4%, somewhat wider than levels observed, but controlled by a total limit of 0.5%. Individual unknowns are limited to 0.2% with a total of 0.4%. Given more data such limits could be subject to revision in due course.

2.D  CONTROL AT INTERMEDIATE STAGES OF THE MANUFACTURING PROCESS

There are no intermediate products and therefore no testing occurs at this stage.

2.E  CONTROL OF THE FINISHED PRODUCT

After production and filling, the final product is checked for the vedaprofen content, pH, filling weight, individual and total related known and unknown compounds and propylene glycol content. Further appearance, identity of vedaprofen and propylene glycol and syringeability are checked. Identity and content of vedaprofen and propylene glycol are checked by an adequate, validated HPLC method. The pH is checked by the Ph.Eur. method V.6.3.1 (potentiometric). The filling weight is determined by weighing.

The stability data indicate that the pH during two years drops by 1 unit. At the lower release limit of 8.5, the value after two years could be as low as 7.5, which would be below the present shelf life specification of pH 8. Thus, the Applicant agreed to raise the lower pH release limit from 8.5 to 9. The CVMP considered this as an acceptable solution, as it would allow the anticipated drop during shelf life to be accommodated thus ensuring that pH check limits could be met.

The preparation is said to be sensitive to pH with the precipitation of vedaprofen below a pH of 8. It would therefore be prudent to obtain some evidence showing that a lower pH limit of 8 would not induce precipitation. However, the Applicant has supplied several sets of data close to the lower pH limit or, for instance, at around 8.05 or indeed at pH below 8, which was achieved at temperatures of 37°C. No precipitation of vedaprofen was observed under these conditions.

The HPLC assay of the active substance has been validated over the concentration range of the 10% product and of the 0.5% product, which represents a twenty fold difference. The Applicant revisited the question of the stability indicating nature of the assay and has exposed the product to 60°C over a nine-day period and has not found any changes.

The Applicant has submitted batch results for three development batches and three recent production batches. The results are consistent with the present specification. The low impurity levels are noteworthy. The results of the development batches are only of limited value as they were tested to reduced specifications operative at the time.

Additionally, data of three batches (2.5 kg, 25 kg and 25 kg) were submitted for Quadrisol 1 mg/ml.

2.F  STABILITY

2.F.1 Stability tests on the active substance

Stability data of the active ingredient of three batches show that the compound is stable when stored at room temperature for 24, 36 and 50 months. The compound is also stable after exposure to various stress conditions (temperature, relative humidity, exposure to air and alkaline solution) for a longer period of time (up to 4 years).
2.F.2 Stability tests on the finished product

The stability studies conducted in the dark were based on the present market formulation and container. The product is marketed in an opaque container within a cardboard box. In addition, the Applicant has conducted a broaching test under light conditions. No adverse light effects have been found. The proposed shelf life by the Applicant was two years. The analytical methods used are those utilised in finished product testing.

In the course of the development of Quadrisol, the release specifications and the specifications at the end of the shelf life have been amended because propylene glycol was initially not included in the stability programme. The identity and the content of propylene glycol have been added later to the list of requirements. However, in the stability data provided the propylene glycol content of 2 batches had been determined after storage for 36 months at 8, 25 and 37°C. The data demonstrate that the propylene glycol content does not decrease during 3 years of storage at all the temperatures studied.

Three 20 litre batches were subjected to storage temperatures of 8°C, 25°C and 37°C for 24 months. The parameters monitored consisted of assay of active and related compounds, pH, polarity and colour. The assay results reported show ranges of 92.7%, 95% and 99% of initial values at 24 months and ranges of 95.2%, 98.0% and 98.4% at 19 to 21 months. At 8°C, these figures range from 95.2% to 96.7% and 100%. Because of the non-specific nature of reporting of related compounds at the time, these are indicated to be below 0.5% at all temperatures and time intervals. However, the Applicant wishes to retain the shelf life assay limits of 90-105% because of some decreases in assay values during the shelf life period. While the assay method for vedaprofen has been investigated for its stability indicating properties, some stability results show considerable mass balance discrepancies. During 24 months storage at 25°C, the pH appears to drop in all three batches by one unit. The clarity and colour of the product shows no impact.

Furthermore, the Applicant has added a ratio for control of enantiomers, which is acceptable. Three batches based on the market formulation/container were used in the stability studies (2.5 kg, 25 kg, 25 kg). One batch was stored for two years at 4°C, 25°C and 37°C and ambient humidity and, for a third year, under ICH conditions. Two further batches were stored for one and two years respectively at ICH conditions of 25°C/60%RH and 40°C/70% RH. All parameters were tested. In addition, product homogeneity was also addressed as well as a potential by/degradation product. Furthermore, 5 syringes were also exposed to a freeze/thaw cycle at 7 days interval (-31/-24°C to ambient temperature) during two complete cycles.

Shelf-life of the finished product

Based on the above stability tests on the finished product, the shelf life was limited to 12 months with assay limits remaining between 95 – 105%. However, in March 2000, the Applicant submitted a Type I No 6 variation deleting chocolate flavour as excipient. Further stability studies provided indicated that parameters including pH remain stable within the end of shelf life specifications for at least 3 years. Therefore, the shelf life was increased from one to three years. Given the similarity in formulation of Quadrisol 1 mg/ml and Quadrisol 5 mg/ml and the proven stability of the latter, a proposed shelf life of 3 years was also endorsed by the Committee for the Quadrisol 1 mg/ml presentation.

2.F.2.3 In use stability tests

In-use stability tests were performed on two batches (one freshly prepared batch and one batch which has been stored at 25°C for 40 months) demonstrating that after first use the product is stable for at least 8 weeks at room temperature.
The results of these tests show very little change in terms of vedaprofen content and pH values at T₀, 2 weeks, 4 weeks and 8 weeks. A broached vial test of Quadrisol 5 mg/ml oral gel for dogs conducted after storage at 25°C for 28 months has also been reported. During the study, 8 syringes were stored at room temperature. Samples of 0.5 g were expelled from each syringe weekly. Samples taken at 1, 2, 3, 5, 6 and 7 weeks were discarded. Samples taken at the start of the experiment and after 4 and 8 weeks were evaluated for content of vedaprofen and related substances as well as propylene glycol, pH and appearance. The analytical methods used are those used in finished and shelf life product testing.

Fifteen syringes from one batch at the beginning of the shelf life (3 months) were stored at ambient temperature (19.1 to 24.2°C, average 22°C) for 8 weeks exposed to a light (16 hours) and dark (8 hours) cycle. Relative humidity varied from 21 to 60.5% RH with an average of 35.5% RH. 0.5 ml samples were removed and discarded after weeks 1, 3, 5, 6 and 7. Samples of 1.0 ml were taken at week 0, 2, 4 and 8, pooled and analysed. The parameters monitored consisted of content of active and related compounds, pH, appearance, colour and total viable aerobic count. Analytical methods were those of finished product analysis.

Furthermore, the Applicant committed to provide data on the stability testing of the first two production batches (see Commitment 1 in section IIA5.1).

**In-use shelf life**

The results of the in-use stability tests confirmed that broached Quadrisol 5 mg/ml oral gel for dogs is stable for at least 8 weeks. Given the similarity with of Quadrisol 1 mg / ml and 5 mg/ml, an eight week in-use shelf life was also accepted for the Quadrisol 1 mg / ml presentation.
3. OVERVIEW OF PART III OF THE DOSSIER: SAFETY AND RESIDUES

3.A Safety testing:

3.A.2 Pharmacology: see Part IV

3.A.3 Toxicology:

The majority of the toxicology studies were carried out in the late 1970’s or early 1980’s. These studies are not stated to be in compliance with GLP and do not include quality assurance statements. However, the information required has been provided and the studies are considered to be reasonably comprehensive and to have broadly followed the principles of GLP.

Toxicological studies on vedaprofen, including some studies on the gel formulation, have shown the anticipated gastrointestinal toxicity (e.g. gastric ulceration and peritonitis) due to the pharmacodynamic action of the product, inhibition of cyclooxygenase and consequently inhibition of prostaglandin (PG) synthesis.

Repeated dose toxicity studies and tolerance studies reveal that, just like other non-steroidal anti-inflammatory drugs (NSAIDs), the main toxic effects of vedaprofen are gastro-intestinal (ulcers in stomach and digestive tract/peritonitis). Other toxic effects reported include a decrease in body weight and food intake, regenerative hypochromic anaemia and leucocytosis, biochemical disorders, effects on spleen, thymus, liver and kidney. All effects can probably be attributed to the major pharmacodynamic activity of vedaprofen, namely prostaglandin synthesis inhibition. An oral No Observed Effect Level (NOEL) can be established from the 13 week dog study.

Several studies were performed to study the effects of vedaprofen on fertility, reproduction, embryotoxicity, foetotoxicity and teratogenicity (rat/rabbit/dog/horse). In these studies only maternal toxicity was observed (decrease in bodyweight, food intake and faecal output, splenomegaly, mesenteric lymph node hypertrophy), with a NOEL of 5 mg/kg bw/day. No 2-generation reproduction study was performed. Since, in the studies performed, vedaprofen showed no effect on fertility, was not embryotoxic or teratogenic and was used only for non-regular treatment of individual animals, a 2-generation reproduction study was not deemed necessary. Chemically related NSAIDs have no effect on reproduction. Vedaprofen treatment should be discontinued just before the time of parturition, because vedaprofen inhibits the activity and synthesis of PG F2α, which plays an important role during pregnancy.

There was no evidence of a teratogenic effect, although an increase in foetal abdominal abnormalities in rats was noted and no effect on fertility was apparent in a preliminary single-generation reproduction study in rats.

Mutagenicity tests were negative, apart from a non-statistically significant increase in chromosome aberrations in an in-vivo cyto genetic test at the highest dose level (333 µg/ml). The quality of the in-vivo micronucleus test in rats is considered to be inadequate and an absence of mutagenicity in-vivo cannot therefore be confirmed.

Chronic toxicity/carcinogenicity studies have not been performed with vedaprofen. These are not deemed necessary because vedaprofen does not belong to a class of drugs which is known to be carcinogenic, and because mutagenicity and toxicity studies have not revealed any suspect signs.

3.A.4 User safety of the gel formulation:

There was no evidence of an allergic response following intradermal or topical administration of vedaprofen. Topical application produced a very weak response, which could not be interpreted definitively as being allergic in nature.

Vedaprofen was initially developed for human use. Pharmacokinetic and tolerance studies have been performed in healthy volunteers. Maximal plasma levels are reached within 2 hours after
administration and elimination from plasma is rapid, with a half-life of 2-3 hours. No accumulation in plasma occurs after repeated oral administration of 100 and 200 mg vedaprofen, and general tolerance is good apart from upper abdominal discomfort (particularly at the high dose).

The formulation characteristics of Quadrisol and the proposed method of dosing indicate little potential for exposure of personnel to the product formulation. Given the formulation characteristics, the inhalation risk is minimal and accidental ingestion of sufficient quantities of Quadrisol to cause toxicity is unlikely. Any other accidental exposure of humans to Quadrisol whilst treating dogs is likely to be very low and good basic hygiene procedures will sufficiently take care of skin spillage etc.

Special immunotoxicity and neurotoxicity studies have not been carried out, as immunotoxicity and neurotoxicity are not known as classic effects of NSAIDs.

3.A.5 Ecotoxicity:

The potential for environmental exposure to Quadrisol is limited. The structure of vedaprofen and its metabolites does not result in immediate concern for environmental effects. Direct exposure of the environment is possible as a consequence of spillage of Quadrisol so that it is recommended in the product literature that unused product is disposed of by appropriate means.

3.B Residues:

Not applicable
4. OVERVIEW OF PART IV OF THE DOSSIER: 
PRE-CLINICAL AND CLINICAL STUDIES

4.1 Pre-clinical studies:

4.1.A Pharmacology

4.1.A.1 Pharmacodynamics:

Most of the in vitro, in vivo and pre-clinical target animal studies were performed between 1977 and 1991. Hence, the current standards of GLP and GCP were not applied. In some cases the animal numbers used were low.

The studies performed adequately demonstrate the anti-inflammatory, anti-pyretic and analgesic properties of vedaprofen. Like other NSAIDs, vedaprofen induces a reversible inhibition of the platelet synthesis of TXB₂ in serum and inflammatory exudate, and of PGE₂ synthesis in exudate. Leukocyte migration into exudate was reduced and the anti-oedematous effect of vedaprofen was evident. Whilst most studies concentrate on the anti-inflammatory effects, the smaller numbers of anti-pyretic and analgesic studies are further supported by data presented in clinical studies. As expected, the major side-effects include gastro-intestinal ulceration, which is to be expected with this type of compound, and studies show ulcerogenic activity of vedaprofen to be comparable to other NSAIDs. Vedaprofen was best tolerated in laboratory animal studies as the gel formulation.

In vitro cyclo-oxygenase inhibition studies show the S (+) enantiomer to be approximately 70 times more potent than the R (-) enantiomer, however further studies showed that both enantiomers contribute to the pharmacological activity and therapeutic action. The mode of action is probably not fully understood.

The COX-1 and COX-2 inhibiting potency of vedaprofen was investigated showing that vedaprofen racemate is 8.75 fold selective towards COX-2, activity being attributable to the (+) enantiomer. This higher selectivity of vedaprofen towards COX-2 is an important beneficial attribute for the safety of this compound.

Three studies were performed with the target species dog. A suitable model for acute arthritis was developed by means of intra-articular injection of endotoxin (lipo poly saccharid/LPS) into the knee joint. A dose of LPS of 50 ng/kg was needed to induce lameness that lasted for 6-8 hours. The treatments were given 1 hour after injection of LPS.

In a dose titration study performed with the arthritis model, the doses of vedaprofen in a gel formulation were 0, 0.125, 0.25, 0.5, 0.75 and 1.0 mg/kg (n=28). General behaviour, lameness score and appearance of the affected knee joint at regular intervals up to 24 hours after treatment were recorded. Despite a wide variation in response to the LPS injection a dose-response effect was obtained. The onset of activity of vedaprofen was rapid and the effects lasted for 2-3 hours. The threshold dose for a significant effect was 0.25 mg/kg. The lameness scores differed significantly from the no-effect dose of 0.125 mg/kg for all other groups at 2 hours after treatment. Only the 0.75 mg/kg dose differed significantly from 0.125 mg/kg at 3 hours. The total score including presence of palpable synovia, pain on superficial and deep palpation, local warmth, pain on flexion/extension and lameness score was significantly lower in the 0.75 mg/kg and the 1.0 mg/kg group at 2 and 3 hours and in the 0.5 mg/kg group at 3 hours compared to the LPS control group.

A comparative study with flunixin meglumine (1.0 mg/kg) using the acute arthritis model showed that 1.0 mg/kg of vedaprofen was more effective than 0.5 mg/kg. The lameness score for flunixin was significantly better than vedaprofen treatment after 3 hours but not at any other time points (2, 4, 6, 8 and 10 hours). Vedaprofen given directly after LPS injection shows that the lameness scores are not or only increased to a limited extent as compared to untreated animals. In the dog, which was given vedaprofen at 2 hours after LPS injection, a clear reduction in lameness score was observed after vedaprofen administration.
A 28 days study investigating the **effect of the way of administration** of vedaprofen in relation to the time of feeding (either before or with feeding) on the inhibition of cyclo-oxygenase activity *in vitro* was submitted to support a possible change in the dosage schedule. The study showed that both routes of administration give comparable efficacy with a similar duration of action and are well tolerated, particularly at the gastrointestinal level, by dogs.

4.1.A.2 Pharmacokinetics:

**Absorption:**

The influence of the time of dosing with regard to the time of feeding on the kinetics of vedaprofen was studied. The study showed that when the product is given with the food the bioavailability is about 80% as compared to administration before feeding. The bioavailability of vedaprofen given 15 minutes after feeding was 57% as compared to administration before feeding. It is likely that the tolerance of the product is better when administered at feeding as compared to administration before feeding. The CVMP considered that it would be inadvisable to administer the compound after feeding as bioavailability is reduced. Although efficacy has been demonstrated under all conditions, it is recommended that the product is given shortly before feeding. This was taken into account under section “Advice on correct administration” of the product information.

**Distribution:**

The total volume of distribution is inversely related to the terminal rate constant, which in turn depends on to which time point the product can still be measured in plasma. The analytical method used in the 1 and 2.5 mg/kg intravenous study had a detection limit of 50 ng/ml. In the 0.5 mg/kg intravenous study, which was conducted later in the development, the analytical method used had a detection limit of 28 ng/ml. This explains to a large extent the longer terminal half-life and larger volume of distribution found in the 0.5 mg/kg intravenous study as compared with the 1.0 and 2.5 mg/kg intravenous study. Moreover, secondary peaks were observed between about 8 and 24 h after intravenous treatment at a dosage of 0.5 mg/kg, suggesting enterohepatic recirculation. This contributed to the terminal half-life of 16 h observed in this specific study.

**Metabolism and elimination**

The metabolic fate of vedaprofen has been addressed in *in vitro* studies in rat and dog hepatic microsomes. The compound undergoes extensive biotransformation to a range of mono- and dihydroxylated metabolites. Hydroxylation appears to occur in the cyclohexyl ring with the second hydroxyl group being inserted into the isopropyl side-chain in the di-substituted metabolites. Hydroxylation does not occur in the naphthalene moiety. In blood plasma 7 major peaks have been identified and characterised. The most abundant metabolite in 0 - 24 hour pooled urine is a monohydroxylated derivate (metabolite VII or D) which accounts for 9 - 13% of the administered dose. This metabolite undergoes further biotransformation to an ether and an ester glucuronide, accounting for a further 6 - 9% of the dose. Urinary excretion accounted of 71 - 73% of the total dose and faecal excretion for 10 - 14%. All metabolites were 2.5 - 20 times less active than vedaprofen as judged by thromboxane B2 formation inhibition. The most abundant metabolite (VII or D) was more than 20 times less active than vedaprofen. The principal component found in plasma is the parent compound followed by metabolite VII or D. In urine the parent compound is virtually absent whilst metabolite VII or D is the most abundant metabolite.

**Bioequivalence of Quadrisol 1 mg/ml and Quadrisol 5 mg/ml oral gel**

A new GLP compliant pharmacokinetic study was provided using the Quadrisol 1 mg/ml oral gel formulation demonstrating bioequivalence to the 5 mg/ml oral gel formulation. Despite the upper confidence interval for T_max being outside the normally accepted range, the Committee accepted that bioequivalence between the two formulations was adequately demonstrated.
Conclusion

Vedaprofen was rapidly absorbed with a bioavailability of 86 – 100 %. Peak plasma levels were reached at 1 hour after administration (2.7 ± 0.7µg/ml) and terminal half-life was calculated to around 13 hours. Multiple dose pharmacokinetics for 14 days with the recommended dose of 0.5 mg/kg daily showed that vedaprofen does not accumulate after repeated administration. The oral bioavailability of vedaprofen is reduced when administered at or close after feeding. The metabolism of vedaprofen is extensive in the dog and the main metabolites have been characterised and found to be significantly less active compared to the parent compound. The plasma protein binding of vedaprofen is very high in the dog (in vitro binding >99.9%).

4.1.B Tolerance in the target species:

Some, but not all, laboratories that performed tolerance studies were GLP certified. However, the trials were well set up with protocols. Enough time was allowed to assess any side effects of treatment and whether such effects were reversible.

In a full 90-day safety study in the dog using the gel formulation, the NOEL was determined to 0.125 mg/kg and at the next dose of 0.5 mg/kg typical adverse reactions in the form of gastrointestinal lesions were seen. The effects were reversible. The CVMP concluded that this study and the safety data collected in the clinical trial show that vedaprofen causes a similar pattern of adverse reaction as other inhibitors of cyclo-oxygenase. Vedaprofen was well tolerated at the dose range of 0.5-1.0 mg/kg and the effects are reversible. The recommended therapeutic dose was not associated with any significant pathology of the oral cavity. Whilst higher dosage levels were associated with pallor of the mucous membranes, there was still no evidence of erosions or ulcers in these studies. This product does not seem to be different in its safety profile from other NSAIDs approved for dogs. The nature and frequency of adverse reactions noted in the clinical trial support this statement. In addition it is stated in the product literature that the medication of the product should be ceased if adverse reactions such as gastric-intestinal bleeding would occur.

As with other NSAIDs the therapeutic safety margin is narrow with vedaprofen. The side effects observed are the expected ones with this type of compound. However, the CVMP requested that the tolerance of the compound in the target species, particularly with regard to the alimentary tract should be further addressed. A detailed analysis of the overall incidence and severity of such cases, particularly with regard to the need to cease medication temporarily or permanently, was requested. In consequence the Applicant discussed in detail the analysis on the tolerance of the product. In this discussion a separation is made between mild and transient side effects and side effects leading to interruption of treatment. The mild and transient side effects were vomiting, diarrhoea and anorexia. The effects were seen only once or for a very short period of time and were mild. Side-effects that led to the interruption of treatment were basically the same in nature but more severe or persistent as the side effects that did not lead to interruption of treatment: vomiting, diarrhoea, anorexia or a combination of these. After discontinuation of treatment, the side effects disappeared within a few days. Out of 390 treatments with the product, treatment was interrupted because of these side effects in 11 cases (2.8 %).

The occurrence of side effects was taken into account under “Undesirable effects” in the product literature.

Quadrisol is used for treatment of dogs suffering from musculo-skeletal disorders. In practice most dogs, which need NSAID treatment, are older dogs. The dogs included in the field trials demonstrate this. No dogs with an age below 6-12 weeks were included in the trials. Therefore, the product will be contraindicated for use in dogs less than 12 weeks of age. The SPC and labeling has been adjusted accordingly.

Studies on the safety of vedaprofen in pregnant bitches were submitted. The animals were treated with vedaprofen in a gel formulation with a dose of 1.0 mg/kg or placebo between either day 26-40 or
day 38-52 of pregnancy. No abnormalities were noted in the clinical examination of the bitches or in the new-born pups. However, vedaprofen should not be used at the time of parturition, because of its effects on the inhibition of the PGF$_{2\alpha}$ production.

No specific information on the use the product is available in lactating bitches. The safety profile of the product does not give concern over the use of the product in lactating bitches itself. However, a safety concern could potentially arise for puppies in the case when vedaprofen is excreted into the milk. Although excretion studies indicate that vedaprofen in dogs is not or only to a minimal extent excreted into the milk, specific safety data in lactating bitches are not available. Therefore, a contraindication has been included in the product literature that the product should not be used in lactating bitches since the effects during lactation have not been studied.

No tolerance data were provided for the new 1 mg/ml formulation in the dog. However, the Committee considered that the tolerance profile of vedaprofen in the target species has been established in the previous applications for Quadrisol. Furthermore, Quadrisol 5 mg/ml oral gel for dogs has been on the European market for several years and no cases of severe adverse reactions have been reported. Although the volume of vehicle is obviously increased which could theoretically contribute to intolerance in the target species, the Committee agreed that the absence of tolerance data for the new lower strength formulation was considered acceptable.

The product is filled into oral syringes with indication marks on the syringe for dosing of 0.5 and 1.0 ml. Dose accuracy data for Quadrisol 5 mg/ml on the 1.0 ml dose unit were presented in the original dossier (Quadrisol 100 mg/ml) and further dose accuracy studies on the 0.5 ml dose unit were provided by the Applicant for Quadrisol 5 mg/ml. However, the dose accuracy is open to variation in between the multiples of 5 kg bodyweight. The problem is particularly significant in animals between 6 and 9 kg bodyweight. Below 10 kg bodyweight, some animals receive a dose significantly above or below the recommended therapeutic dose. Based on the provided information the CVMP concluded that Quadrisol 5 mg/ml should be limited to animals weighing 10 kg or more. At bodyweights above 10 kg, although variations occur in the actual dose delivered, the CVMP considered that the values are acceptable and are similar to the problems faced by other NSAIDs.

Consequently, the Marketing Authorisation Holder submitted in May 2001 an application for a further strength containing 1 mg vedaprofen per ml oral gel thus allowing the treatment of smaller dogs with a bodyweight of less than 10 kg.

4.II Clinical data:

4.II.1.1 Dosage

The effect of the product at a dose of 0.5 mg/kg daily was investigated in four controlled trials of sufficient size including acute, recurrent and chronic cases of musculo-skeletal disorders such as arthritis, arthroses, hip dysplasia and lumbar pain. The reference substances used were flunixin and meloxicam at the recommended dosages. The choice of the dose is a compromise between the desired effect and the tolerance in the target animal. Tolerance studies have shown that 0.5 mg/kg given daily for up to 90 days is well tolerated. The model studies have shown that 0.5 mg/kg is the lowest effective dose under severe challenge conditions. Increasing this dose would lead to an increasing risk of possible adverse effects. A reduction of this dose would lead to a reduction in the effectiveness. In clinical trials, the selected dose of 0.5 mg/kg has been proven to be at least equally effective and safe as positive control products. The recommended therapeutic dose of 0.5 mg/kg bodyweight led to improvements in various parameters. The Applicant explained that the experimental model of arthritis used was more severe than that normally seen in veterinary practice and that a recommended therapeutic dose of 0.5 mg/kg bodyweight was chosen to minimise the side-effects and improve the overall tolerance of the formulation. Therefore, the CVMP agreed to accept that the lowest proven clinically effective dose should be used for a compound of this class.
4.II.1.2 Duration of treatment

The inclusion and exclusion criteria for the target animals to the clinical trials are considered suitable. The number of animals used was sufficient. Two additional uncontrolled studies with vedaprofen lysinate were provided in the application, but the results of these studies can only be regarded as supportive. The treatment periods varied from 7 to 28 days, but an average treatment period of 14 days with vedaprofen was used. In cases where there was a need for a longer duration of treatment, animals were treated continuously with the product. From the 390 treatments that were given, 59 cases were treated for more than 28 days. The maximal treatment duration was 69 days. In the tolerance study performed it was shown that the product could be given safely for a period of 90 days. However, the Applicant has proposed that after a treatment period of maximally one month, the condition of the dog should be re-evaluated by the veterinarian in order to establish the need for continuation of treatment. The clinical trials have demonstrated that ongoing treatment after one month is safe and effective. The CVMP considered that many animals with chronic arthritis would require repeat courses of treatment or continual medication on humane grounds. Furthermore, repeat or prolonged treatment should only be undertaken on the recommendation of the veterinarian based on a risk benefit analysis for that individual case.

4.II.2 Field trials

In general, the effect of vedaprofen was scored using subjective parameters and a visual analogue scale which is the state of the art for evaluation of similar veterinary medicines. The investigators scored the symptoms, i.e. pain, limitation of movements and lameness using a visual analogue score ranging from 100 (maximum severity) to 0 (free of symptoms) and gave an overall score for the severity of condition on a graded verbal scale (cured, improved etc). The Applicant also provided the measures adopted to avoid a large degree of subjective variation between different investigators.

4.II.2.1 Control of inflammation and the relief of pain and inflammation associated in musculo-skeletal disorders and trauma

The investigators selected dogs suffering from chronic lameness. In a large number of cases the investigators diagnosed an arthrosis of the hip joints, or arthrosis of the stifle or knee. In a limited number of cases the clinical and orthopaedic examination did not reveal an exact location of chronic lameness. In the case of spondylosis, the diagnosis was made by a distinct stiff gait in combination with a reduced flexion of the lumbar vertebral column after exclusion of abnormalities at the hip, stifle or knee. The CVMP considered that spondylosis is a distinct clinical syndrome, the diagnosis of which is confirmed radiologically. However, the CVMP understands this deficiency in trial design as such cases are routinely seen in clinical practice and may not always be confirmed radiologically. Whilst most of the data relates to chronic musculoskeletal disorders, a reasonable amount of data has also been presented for acute cases. Furthermore, the inhibition of prostaglandin synthesis is the same proposed anti-inflammatory mechanism of action of this compound, irrespective of whether the inflammation is acute or chronic. As vedaprofen is indicated for the treatment of inflammation, and not the specific disease entity, then consideration of the acute or chronic nature of the complaint was not considered important. As vedaprofen works well in chronic cases, the CVMP considers it will work equally as well for more acute cases.

The safety and clinical efficacy of Quadrisol 5 mg/ml in the dog for the control of inflammation and the relief of pain and inflammation associated in musculo-skeletal disorders and trauma has been studied in several clinical trials. From these clinical trials, it was concluded that vedaprofen at the recommended dose rate (i.e. 0.5 mg/kg bodyweight) was safe and effective. As bioequivalence of Quadrisol 1 mg/ml oral gel and Quadrisol 5 mg/ml oral gel has been shown, the indication was accepted for Quadrisol 1 mg/ml oral gel, too.
4. II2.2 Treatment of post-surgical pain and inflammation

A new placebo controlled study in dogs after surgery of the elbow joint was presented investigating the use of Quadrisol 5 mg/ml for an additional indication, the treatment of post-surgical pain and inflammation. As bioequivalence of Quadrisol 1 mg/ml oral gel and Quadrisol 5 mg/ml oral gel has been shown, the indication for post-surgical pain was applied for Quadrisol 1 mg/ml oral gel, too. However, in the absence of sufficient data to support this new claim, the Committee agreed that the study presented does not allow for a definitive conclusion on the positive effects of vedaprofen for the treatment of post-surgical pain and inflammation. Further data should be submitted before permitting such an indication.

5. RISK-BENEFIT ASSESSMENT AND CONCLUSION

The quality points, such as the limited dosing accuracy, process validation on a 250 litre batch, the possible decrease in pH during shelf life and the assay method for the stability indicating properties of vedaprofen, raised in the initial quality assessment of Quadrisol 5 mg/ml oral gel for dogs have been resolved. For the new 1 mg/ml strength, the Applicant has committed to perform stability and preservative efficacy studies on the first two production batches, and to conduct process validation studies on these initial two batches.

The Applicant has satisfactorily dealt with outstanding safety issues, such as treatment in the acute arthritis model, the possible occurrence of oral lesions and user safety. The use of the product in the treatment of lactating bitches has been contraindicated, as there are no data establishing levels of vedaprofen in their milk.

Furthermore, the Applicant has resolved issues on pharmacokinetics such as the volume of distribution and high protein binding of vedaprofen, and issues on tolerance in the target species such as the possibility of gastrointestinal side effects.

The therapeutic dose has been adequately justified. Quadrisol 5 mg/ml is contraindicated for dogs under 10 kg body weight as those animals cannot be accurately dosed. Therefore, the Marketing Authorisation Holder submitted in May 2001 an application for a further strength containing 1 mg vedaprofen per ml oral gel thus allowing the treatment of smaller dogs with a bodyweight of less than 10 kg, which was accepted by the CVMP in March 2002.

As feeding reduces oral bioavailability, it is recommended that the administration of the product take place shortly before feeding. In addition the Applicant has adequately justified the indications agreed. A new study investigating the effect of the time of administration of vedaprofen (either before or with feeding) on the inhibition of cyclo-oxygenase activity \textit{in vitro} was submitted together with the application for the 1 mg/ml strength in order to support a possible change in the dosage schedule. However, it was considered that any change in the time of dosing should be addressed in terms of a variation application for both strengths of formulation for the dog.

Based on the original and complementary data presented in support of the use of Quadrisol 5 mg/ml in dogs, the Committee for Veterinary Medicinal Products concluded that the quality, the safety and the efficacy of the product were considered to be in accordance with the requirements of Council Directive 81/852/EEC and supported the claims now proposed by the Applicant.

Consequently, the Committee recommended on 14 October 1998 that the product could be recommended for the granting of a Community marketing authorisation.