SCIENTIFIC DISCUSSION

This module reflects the scientific discussion for the approval of Quadrisol (as published in January 2009). For information on changes after this date please refer to module 8 (Steps taken after authorisation).

INTRODUCTION

Quadrisol is a non-steroidal anti-inflammatory drug developed for veterinary use containing vedaprofen as the active substance and expressing anti-inflammatory, anti-pyretic and analgesic activities.

Quadrisol is indicated for the reduction of inflammation and relief of pain associated with musculo-skeletal disorders and soft tissue lesions (traumatic injuries and surgical trauma) in horses. In cases of anticipated surgical trauma, Quadrisol can be given prophylactically at least 3 hours prior to elective surgery.

The product is presented as an oral gel containing vedaprofen hydrochloride in an adjustable pre-filled multidose syringe for use in horses.

Quadrisol contains a racemic mixture of (+) and (-) enantiomers of vedaprofen with a selectively higher inhibitory activity towards COX-2 than COX-1.

The most significant adverse events observed during treatment are those typical for NSAID, such as lesions in the alimentary tract soft faeces, urticaria and lethargy.

The withdrawal period for meat and offal in horses is 12 days. The product is not permitted for use in lactating animals producing milk for human consumption.

Quadrisol was first authorised on 4 December 1997 for oral use in horses. Later approval was given for the oral use in dogs (February 1999) and a solution for injection in horses (November 1999); however, these presentations were withdrawn in 2008 for commercial reasons.

2. QUALITY ASSESSMENT

Composition

Quadrisol oral gel contains per ml 100 mg vedaprofen (as hydrochloride) as the active substance and propylene glycol as excipient.

Container

The container of the oral gel is 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 is white. 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 3.

Clinical trial formulations

The clinical trials for the oral gel presentations were conducted with the final formulation.

Product Development Studies

Vedaprofen is formulated as a gel because studies in the target species (horse) have shown that tolerance of vedaprofen is better when it is given as a solution (gel), as compared to a suspension. Propylene glycol is added, which has a preservative action. For stability reasons the pH has to be above 8.0 since otherwise the potassium vedaprofen salt is at risk of precipitation. 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 30 ml presentations for horses. Dose accuracy has been demonstrated satisfactorily.

Method of preparation

Batch size

The manufacturing formula was calculated for 100 litre batches. The product meets the release specifications set and a scale up from 100 to 250 litres was considered satisfactory.

Manufacturing method

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, a variation was accepted to change 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

Process validation was undertaken on the basis of information supplied on one production batch of 200 litres. 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 and expressed weight. Process validation studies were considered satisfactory.

Control of Starting Materials

Active substance

The active substance vedaprofen is not listed in a pharmacopoeia, but a company monograph has been provided.

A vedaprofen in-house standard was produced with a purity of 99.5%.

Appropriate data on the quality control for vedaprofen in the oral gel formulation have been assessed and accepted. Microbial levels are monitored indirectly by controlling levels of the bulk solution prior to 0.22 μm filtration.

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, the analytical conditions of which are said to be similar to those used in the assay of the active substance itself. The HPLC tracing shows good separation of vedaprofen and 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 wide 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 should be limited to ensure that they were below levels at which identification became necessary. The limits have been subsequently tightened as now declared because data on batches used in clinical trials were not available.

Excipients

Excipients comply with their corresponding European Pharmacopoeia monographs.

Specifications of all materials used in the synthetic process have been provided. The specifications in general are satisfactory. All excipients are tested in accordance with the requirements of their respective Ph.Eur. monographs.

TSE Compliance was shown and none of the excipients come from human, bovine, ovine or caprine source material.

The in-process control procedure performed during the synthetic process is conducted at three stages. The process is reasonably well controlled and an identity is included in the specifications.

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 considered not relevant for this product.

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 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.

Control at intermediate stages of the manufacturing process

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

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 impurities and propylene glycol content. Further tests for appearance, identity of vedaprofen and propylene glycol and syringeability are conducted. 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 (potentiometric). The filling weight is determined by weighing.

The limits for the assay and pH in the shelf-life specification have been tightened and brought in accordance with the limits approved at release. The global by-product limit proposed originally for related substances was not considered acceptable in light of batch results and specification of the drug substance with regard to magnitude and non-specificity. The specifications set for the active substance are also applicable to the finished product at release as well as during shelf life.

The stability data indicate that the pH over 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, it was agreed to raise the lower pH release limit from 8.5 to 9. The CVMP considered that this 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. Data were provided showing that a lower pH limit of 8 would not induce precipitation. No precipitation of vedaprofen was observed at pH around 8.05 or below 8 at temperatures of 37°C.

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 product was exposed to 60°C over a nine-day period indicating stability of the assay.

Batch results for three development batches and three recent production batches were provided and the results are consistent with the specifications set. 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.

Stability tests on the active substance

Stability data for the active substance 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).

Finished Product

The stability studies conducted in the dark were based on the market formulation and container (opaque container within a cardboard box). In addition, a broaching test under light conditions was conducted. No adverse effects under light conditions have been found. The intended shelf life 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. The applicant has committed to incorporate this product specification into on-going stability studies. 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. However, in the data presented over a three-year period evidence is reported with regard to reduction in pH or assay figures.

Three 20 litre batches were stored at 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. The shelf life assay limits of 90-105% were retained 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, a ratio for control of enantiomers was added, 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 VICH conditions. Two further batches were stored for one and two years respectively at VICH conditions of 25°/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 1 year with assay limits remaining between 95 – 105%. 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.

In-use shelf-life

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). The results of these tests show very little change in terms of vedaprofen content and pH values at T_0, 2 weeks, 4 weeks and 8 weeks. It was concluded that after first use Quadrisol 100 mg/ml oral gel for horses is stable for at least 8 weeks at room temperature and an in-use shelf life of 2 months was accepted.

Overall Conclusion on Quality

The product is presented as an oral gel in 30 ml graduated multidose oral syringes containing vedaprofen hydrochloride.

The gel formulation was chosen due to its better tolerance in the target animals as compared to other oral formulations such as a suspension. Propylene glycol is added, which has a preservative action. Dose accuracy has been demonstrated satisfactorily. Process validation studies had been provided

The active substance, vedaprofen, is not listed in a pharmacopoeia, but a company monograph has been provided. Appropriate data on the quality control for vedaprofen in the oral gel formulation have been assessed and accepted. Specifications of all materials used in the synthetic process have been provided.

TSE Compliance was provided and none of the ingredients come from human, bovine, ovine or caprine source material.

The final product is checked for vedaprofen and propylene glycol content and identity, pH, filling weight, individual and total related known and unknown compounds, appearance and syringeability. Limits for assay and pH in the shelf-life specification are in accordance with the limits approved at release.

Stability data of the active substance show that the compound is stable when stored at room temperature for up to 50 months.

The shelf life of the finished product is 3 years and the in-use shelf-life is 2 months.

3. SAFETY AND RESIDUES ASSESSMENT

SAFETY

Pharmacokinetics

Vedaprofen is a racemic mixture of a (+) and a (-) enantiomer. A wide range of studies was performed involving analysis of both racemate and the individual enantiomers. Single and multiple dose kinetic studies with different formulations and by different routes have been carried out.

Absorption

Absorption after oral administration occurs rapidly and is almost complete (80 - 90% in horses). After single (2 mg/kg) and multiple (2 mg/kg, followed by 1 mg/kg every 12 hours for up to 14 days) oral administration of vedaprofen in horses, maximal plasma levels are achieved within 2 hours after administration (approximately 5 μg/ml and 2.5 μg/ml, respectively).

Following multiple dosing by the oral route, steady state is quickly achieved with no significant depletion or accumulation of drug occurring. The kinetics appear to be linear after multiple oral administration of the final formulation.

Absorption and the maximum plasma levels of the product are greatly reduced when the product is administered together with food or shortly after feeding.

In horses, bioavailability of vedaprofen when administered as a top dressing on feed is between 50 - 60% of that achieved when administrated orally two hours before feeding. A recommendation has therefore been included in the SPC and product literature of the oral gel presentation for horses to administer the product before feeding.

Distribution

Like other NSAIDs, vedaprofen is highly bound to plasma proteins (>99%) at plasma concentration ranging from 0.15 to 11 μg/ml.

The less active R (-) enantiomer predominates in plasma and exudate. The S (+) enantiomer resides in plasma for a shorter time than the (-) enantiomer, but both appear to remain in exudate for a similar period. Vedaprofen showed highly enantioselective protein binding (> 99.3 %).

After multiple oral administration maximum, minimum and average plasma concentrations on days 1, 8 and 14 are comparable indicating that steady state is reached quickly after onset of treatment and that no accumulation occurs. Based on a multidose kinetic study in horses, kinetics appear to be linear after oral administration of the gel in the dose range of 1 - 2 mg/kg.

Following oral administration, the terminal $t_{0.5}$ in horses is approximately 6-8. After intravenous administration of 0.5 mg/kg to horses, secondary plasma peaks were observed 8 to 24 h after treatment, suggesting enterohepatic recirculation. This contributed to the terminal half-life of 16 h observed in this specific study.

Kidney and liver appear to be organs in which residues persist for the longest time.

Metabolism

The metabolic fate of vedaprofen has been addressed in *in vitro* studies in rat, dog and horse hepatic microsomes and *in vivo* studies in horses. The compound undergoes extensive biotransformation to a range of mono- and dihydroxylated metabolites. In plasma of the horse 7 radioactivity peaks have been seen. The major peaks have been characterised and identified. In dogs, the main metabolites have been characterised and found to be significantly less active compared to the parent compound.

The most abundant metabolite in both plasma and urine is a monohydroxylated derivative (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%. The metabolites were 2.5 - 20 times less active than vedaprofen.

After oral administration of vedaprofen at the clinical dose for the recommended maximum treatment period for horses, urinary depletion of vedaprofen and its metabolites was determined using a doping control - routine acidic screening method as used by the Horse Forensic Laboratory UK. On days 3 and 5 after first treatment some positive urine samples were observed. Samples were positive for metabolites VII and VIII. On day 7 post treatment all urine samples were negative. By confirmatory GC-MS traces of vedaprofen and its metabolites could still be demonstrated. However, because of the threshold of the routine screening method is higher these samples proved negative in this routine test. Therefore, the advised non-treatment period of 7 days before racing is proposed in the product literature. If, however, more sensitive routine screening methods are going to be used in practice, a revision of the advised non-treatment period before racing might be obligatory.

Excretion

After intravenous administration, vedaprofen is eliminated biphasically with a terminal half-life of 6.39 ± 5.15 h. Elimination was found to be enantioselective, with the S (+) enantiomer being cleared more rapidly. The mean residence time (MRT) of vedaprofen in horses after intravenous injection was 2.49 ± 2.31 h. After administration of the recommended clinical dose, vedaprofen or its phase I metabolites were no longer detectable in urine 72 h after dosing. On average, 95 % of the administered dose is eliminated during the first 10 hours after administration. Plasma pharmacokinetics are linear in the range of 1 to 4 mg/kg.

Whilst the kinetics do appear to be dose-dependent in both horses and ponies, differences were demonstrated in the kinetics between the two in one particular study. The significance of any such differences is unknown.

Toxicological Studies

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 were 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 synthesis.

Repeated dose toxicity studies and tolerance studies in different species reveal that, just like other 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. In a 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.

Reproductive toxicology

Several studies were performed to investigate 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 No Observed Effect Level (NOEL) of 5 mg/kg bodyweight per day.

Since in the studies performed, vedaprofen did not show any 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. Also, chemically related non-steroidal anti-inflammatory drugs (NSAIDs) are known to have no effect on reproduction.

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. 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.

For studies on pregnancy and lactation see section "target animal safety".

Mutagenicity

Mutagenicity tests were negative, apart from a non-statistically significant increase in chromosome aberrations in an *in vivo* cytogenetic 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.

Carcinogenicity

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.

Studies of other effects

Because vedaprofen belongs to a class of drugs, which does not have an effect on the immune system, and because no immunotoxicity signs were observed in the toxicity tests, special immunotoxicity studies are not requested. Special neurotoxicity studies have not been carried out, as neurotoxicity is not known as classic effects of NSAIDs. Vedaprofen belongs to a class of drugs without antimicrobial activity, therefore, microbiological studies were deemed not necessary.

User safety

There was no evidence of an allergic response following intradermal or topical administration of vedaprofen. The potential allergenic properties of vedaprofen were tested in Dunkin-Hartley guinea pigs. Vedaprofen was found not to be allergenic.

In humans, vedaprofen by oral administration is rapidly absorbed with maximal plasma levels within 2 hours after administration and rapidly eliminated from plasma 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). An oral dose of 50 mg per person (single administration) did not lead to an adverse effect.

Given the formulation characteristics (oral gel), the inhalation risk is minimal. Skin exposure of Quadrisol is unlikely to cause toxicity in humans and good basic hygiene should sufficiently take care of skin spillage. Accidental ingestion of sufficient quantities of Quadrisol is unlikely to cause toxicity.

The CVMP concluded that the formulation characteristics of Quadrisol and the proposed method of administration would have little potential for exposure of personnel to the product formulation.

Environmental safety

No special studies on ecotoxicity were submitted. However, the potential for environmental exposure to Quadrisol was considered limited. The structure of vedaprofen and its metabolites do not give rise to immediate concern for environmental effects. Direct exposure of the environment is possible as a consequence of spillage of the product so that it is recommended in the product literature that unused product is disposed of by appropriate means.

As the product is intended for individual treatment and the metabolism in the target species is extensive, direct exposure of the environment will be very limited and the evaluation is concluded at Phase I.

RESIDUES

Depletion of residues

Residue depletion studies for the oral gel presentation have been assessed previously for the MRL application. After oral administration of vedaprofen gel (final formulation) to horses at the intended clinical dosage regimen, vedaprofen could be detected in liver (mean concentrations of 112, 44 and 24 µg/kg after withdrawal times of 4, 8 and 12 days, respectively) and kidney (1918, 488 and 265 µg/kg at 4, 8 and 12 days, respectively), but not in muscle (LOQ: 50 µg/kg) and fat (LOQ: 20 µg/kg). Metabolites of vedaprofen were only observed in liver and kidney at 4 days withdrawal in very small amounts.

Routine analytical method for the detection of residues

The proposed HPLC/fluorescence method for the determination of vedaprofen in horse tissues (with LOQs of 50 µg/kg in muscle, liver and kidney and 20 µg/kg in fat) can be used in tissue residue studies. The method is described in conformity with ISO 78/2, and is fully validated.

Maximum residue levels (MRL)

Vedaprofen, the active substance, has been included in Annex I of Council Regulation (EEC) No. 2377/90 as follows:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Vedaprofen	Vedaprofen	Equine	1000 µg/kg 100 µg/kg 50 µg/kg 20 µg/kg	Kidney Liver Muscle Fat	

Excipients are included in Annex II of Council Regulation (EEC) No. 2377/90 in accordance with the following table:

Pharmacologically active substance	Animal Species	Other provisions
Hydrochloric acid	All food producing species	
Potassium hydroxide (E525) [1]		
Propylene glycol[2]		

Hydroxyethylcellulose and chocolate flavour are not within the scope of Council Regulation 2377/90.

Withdrawal period

Since no MRLs have been set for milk, vedaprofen is not permitted for use in lactating animals producing milk for human consumption. Initial tissue studies have shown that kidney and liver are the two tissues in which residues of vedaprofen persist the longest following treatment.

After oral administration of vedaprofen gel (final formulation) to horses at the intended clinical dosage regimen, vedaprofen could be detected in liver and kidney, but not in muscle and fat. Depletion was observed in time. Metabolites of vedaprofen were observed in liver and kidney at 4 days withdrawal in small amounts. However, with regard to the MRL values for vedaprofen, it is considered that the data support a 12-day withdrawal period. On the data provided, the CVMP agreed on a withdrawal period for meat and offal of 12 days following oral use of vedaprofen in horses.

Overall Conclusion on Safety and Residues

In horses, Vedaprofen is rapidly absorbed after oral administration with a bioavailability of 80 – 100%. Peak plasma levels were reached at 1 – 2 hours after administration. Following oral administration, the terminal half-life in horses is approximately 6-8 hours. Vedaprofen does not accumulate after repeated administration. Absorption and the maximum plasma levels of the product are greatly reduced when the product is administered together with food or shortly after feeding and recommendations on the correct administration have been included in the product literature of the oral gel presentations. Vedaprofen is highly bound to plasma proteins (>99%). The metabolism of vedaprofen is extensive and the main metabolites have been characterised and found to be significantly less active compared to the parent compound.

Toxicity and tolerance studies demonstrated that the main toxic effects of vedaprofen are gastro-intestinal (ulcers in stomach and digestive tract/peritonitis) which are typical for this group (NSAIDs).

Vedaprofen was considered not embryotoxic or teratogenic and did not show any effect on fertility. In laboratory animals, maternal toxicity was observed, in doses above 5 mg/kg bodyweight per day.

[1] OJ No. L 272 of 25.10.96
[2] OJ No. L 045 of 15.02.97

No carcinogenicity studies have been performed with vedaprofen; this was justified by the absence of any suspect signs from mutagenicity and toxicity studies and vedaprofen belonging to a class of drugs, which is known to be carcinogenic. Likewise, NSAIDs are not known to cause immunotoxic or neurotoxic signs and special studies on this were therefore not requested.

Taking into account the formulation characteristics (oral gel) and the methods of administration, vedaprofen was considered safe for the user.

The potential for environmental exposure to Quadrisol was considered limited since the product is intended for individual treatment and the metabolism in the target species is extensive.

MRLs for vedaprofen for equine muscle, fat, liver and kidney have been included in Annex I of Council Regulation (EEC) No. 2377/90. The Applicant provided approved analytical methods.

Based on the data provided and taking into account a sufficient safety span, a withdrawal period for meat and offal of 12 days was considered acceptable. Since no MRLs have been set for milk, vedaprofen is not permitted for use in lactating mares producing milk for human consumption.

4. EFFICAY ASSESSMENT

Pharmacodynamics

Various studies have been performed to investigate the pharmacodynamic properties of vedaprofen. The compound is a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, antipyretic and analgesic activity. Most i*n vitro* and *in vivo* tests in laboratory animals, dogs and horses were performed between 1977 and 1991. Although the current standards of GLP and GCP were not applied and animal numbers in some trials were low, the studies were well planned and seem to have been completed to a high standard.

The studies performed demonstrate the anti-inflammatory, anti-pyretic and analgesic properties of vedaprofen. Whilst most studies concentrate on the anti-inflammatory effects, the smaller number of anti-pyretic and analgesic studies are further backed up by the 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 the ulcerogenic activity of vedaprofen to be comparable to other NSAIDs. Vedaprofen was best tolerated in laboratory animal studies as the gel formulation.

In vitro cyclooxygenase 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 S(+) enantiomer. This higher selectivity of vedaprofen towards COX -2 is an important beneficial attribute for the safety of this compound.

The anti-inflammatory effect of vedaprofen was clearly demonstrated in an established equine experimental acute non-immune inflammation model. A reduction in swelling by 50% clearly demonstrated an anti-inflammatory effect. Like other NSAIDs, vedaprofen induces a reversible inhibition of the platelet synthesis of thromboxane B_2 in serum and inflammatory exudate, and of $PGE_{2\alpha}$ synthesis in exudate. Leukocyte migration into exudate was reduced and the anti-oedematous effect of vedaprofen was evident.

Anti-inflammatory and analgesic effects were demonstrated in lipopolysaccharide (LPS) induced acute arthritis models in dogs and horses. Vedaprofen, which was given intravenously (horses) or orally (dogs) was effective in improving the lameness scores caused by arthritis and the general clinical parameters.

The analgesic effects were further demonstrated in three studies performed in the horse; one pilot investigation in a caecal balloon model in ponies, one comparative study of vedaprofen in an endotoxin (LPS)-induced ileus model in horses and one pilot study in horses on the passage of vedaprofen across the blood-brain barrier. The caecal balloon model was not considered suitable to evaluate analgesic effects of NSAIDs, but the results of the other studies point to a moderate analgesic effect of vedaprofen. Although the pivotal pharmacodynamic study using the model with endotoxin (LPS)- induced ileus employed doses of 1 mg/kg and 3 mg/kg, a dose of 2 mg/kg was considered as a compromise between safety and efficacy.

Tolerance in the target species

Several single and repeated dose studies were performed to investigate the tolerance in horses. Tolerance studies in horses demonstrated that the therapeutic margin is narrow. Vedaprofen causes similar adverse reactions to most known NSAIDs after intravenous as well as after oral administration.

In horses, five tolerance studies were presented; some involved specific tolerance trials in the target species, whereas others draw tolerance data from related studies in the application (e.g. fertility studies). However, the trials were well set up with meaningful protocols. Enough time was allowed to assess any side effects of treatment and whether such effects were reversible.

In the clinical trials, common side effects in horses treated with the oral gel at the recommended maximum dose included lethargy, subcutaneous swellings i.e. urticaria and superficial mucosal lesions in the alimentary tract.

In most studies using 1x or 2x the recommended treatment dosage of 2 mg/kg (initially) followed by 1 mg/kg twice daily (maintenance) was generally well tolerated. However, 3 and 5 times the recommended treatment dosage were detrimental to overall health e.g. depression and anorexia. High doses e.g. 5 times the recommended treatment dosage were associated with serious mortality due to septicaemia/toxaemia.

Side effects observed are the expected ones with this type of compound. Erosions and ulcers in the mouth and gastrointestinal tract were the most common features. Although the incidence and severity of such alimentary tract lesions were dose dependent to some extent, such lesions did also occur with the recommended treatment dosage. Effects on blood protein levels were also demonstrated. The trial data show most such effects to be reversible when the product is withdrawn. Appropriate warnings have been included in the product literature.

High foal mortality in the pregnant mare study submitted in the original dossier, albeit not apparently product-related (mortality was observed in both treatment and control group), raised concern regarding safety in the pregnant mare. Therefore, the Committee initially concluded that the safety for use in pregnant and lactating animals had not been established and agreed that Quadrisol must not be given during gestation or to foals under the age of 6 months as stated in the SPC and label. However, the company provided in July 2001 a new GLP compliant safety study of vedaprofen (oral gel) in pregnant mares. Safety was investigated during early (2-3 months), mid (4-6 months) and late (9-11 months) pregnancy. A total of 4 mares per time point were employed, with a similar number of placebo-treated controls. The vedaprofen-treated animals received twice the recommended therapeutic dose, and were treated for the maximum treatment period of 14 days. The results demonstrated the safe use of the product in pregnant mares and consequentially, the Committee agreed to allow the use of the oral gel in mares during gestation. However, the contraindication for lactating horses remains.

Dose selection

Preclinical studies demonstrated that vedaprofen at a dosage level of 3 mg/kg bodyweight by the intravenous route was more potent as an anti-inflammatory agent than the proposed treatment dosage of 2 mg/kg bodyweight followed by a maintenance dosage of 2 x 1 mg/kg bodyweight per day.

However, due to the narrow safety margin of vedaprofen, particularly with regard to erosions/ulcers in the oral cavity and gastrointestinal tract in horses, and the observed anti-inflammatory, antipyretic and analgesic effects at lower dose levels, the applicant proposed a dose that provided a balance between clinical efficacy on the one hand and tolerance on the other. Efficacy of the proposed dose was supported by the results of the clinical trials.

Therefore, the CVMP agreed to accept that the lowest proven clinically effective dose should be used for a compound of this class.

Clinical studies

Five multicentre clinical trials were performed between 1990 and 1995 with a large number of animals included. These studies were completed before the implementation of GCP guidelines. Protocols were well thought out and executed. The owner compliance and acceptance of the dosage formulation with vedaprofen gel was assessed and deemed satisfactory. One study was an open clinical trial, whilst the other 4 involved the incorporation of positive controls. Randomisation was performed by means of the closed envelope technique. It was not possible to follow a blind study design, because of differences in the formulation and dosage regimes.

Animals were included if they satisfied the intended indications for the final product i.e. musculo-skeletal disorders and soft tissue lesions. All animals were under the care of the participating veterinarian and the animals satisfied the clinical criteria established for each trial, which included prophylaxis of soft tissue injury following surgery, lameness and signs of pain/discomfort. Animals that had been treated with any NSAID or short acting corticosteroid within 7 days prior to the admission to the trials were excluded from the trials (in the case of longer acting corticosteroid treatment, the interval between such treatment and inclusion in any study had to exceed the claimed duration of action of the steroid preparation). Also excluded were animals showing signs of chronic symptoms, impaired cardiac, hepatic or renal function, and animals, which were suspected of having signs of a bone fracture or tendon/ligament rupture. Exclusion during the treatment period occurred if animals developed a significant health problem occurring after the start of the study, but not related to the original disorder for which they were admitted to the trials. Cases where a significant deviation from the intended dose occurred for any reason were also excluded.

Medicinal products used as positive controls included flunixine meglumine and phenylbutazone. Flunixine meglumine was chosen as it was considered a modern and potent anti-inflammatory and analgesic agent. Phenylbutazone was chosen for inclusion as it can also be given for a 14-day period, the same as vedaprofen gel. Efficacy was assessed using a clinical score system of 0-5 for lameness and 0-3 for soft tissue injuries. Three clinical assessments were made per animal - at the start of the study, 5-7 days later and 7 days following cessation of treatment.

Efficacy for vedaprofen in the horse was proven both by significant reductions in clinical scores between the start and end of treatment and by the percentage of test animals judged cured or as having shown an overall improvement at study termination. Such reductions in clinical scores for lameness and soft tissue injuries were statistically significant for the vedaprofen treated animals. Furthermore, when compared with the results obtained for the reference compounds i.e. flunixin meglumine and phenylbutazone, there was no statistically significant difference between the results for the three different compounds.

The tolerance of the product in general was good. Some side effects were those routinely associated with the use of NSAIDs and appeared to be reversible after discontinuation of treatment. In the clinical trials conducted to evaluate efficacy in cases of lameness, a wide range of conditions including arthritis, bursitis, laminitis, osteo-chondro dystrophy, tendonitis etc. were included which are considered to be addressed by the proposed indication "*Reduction of inflammation and relief of pain associated with musculo-skeletal disorders".* The Committee agreed that it would not be meaningful to narrow the clinical indications down to specific categories of conditions, e.g. tendonitis, laminitis etc. as vedaprofen is not for treatment of the specific condition, but is intended to alleviate the inflammation and pain associated with that condition.

No specific duration of treatment could be recommended for individual conditions, as this needs to be a clinical decision made by the veterinarian for each individual animal under his/her care at field level.

In the case of prophylactic treatment, the Applicant states that such treatment should commence as soon as is practical e.g. prior to surgery, or as soon as soft tissue injuries are incurred, rather than after the onset of clinical signs.

The Committee considered the data sufficient to support the proposed indications for the "*Reduction of inflammation and relief of pain associated with musculo-skeletal disorders and soft tissue lesions (traumatic injuries and surgical trauma). In cases of anticipated surgical trauma, Quadrisol can be given prophylactically at least 3 hours prior to elective surgery.*"

Overall Conclusion on Efficacy

Vedaprofen is a non-steroidal anti-inflammatory drug (NSAID). Various *in vitro* and *in vivo* studies investigating the pharmacodynamic properties of vedaprofen have been performed in different animal species including dogs and horses confirming anti-inflammatory, anti-pyretic and analgesic properties of vedaprofen.

The COX-1 and COX-2 inhibiting potency of vedaprofen was investigated, showing that vedaprofen is a racemate with 8.75 fold selectivity towards COX-2. This higher selectivity of vedaprofen towards COX -2 has been attributed to the S(+) enantiomer.

Tolerance studies in horses demonstrated that the therapeutic margin is narrow. Vedaprofen causes similar adverse reactions as other NSAIDs, i.e. erosions and ulcers in the mouth and gastrointestinal tract. Quadrisol oral gels can be used during pregnancy

Since no foals were included in the clinical trials, the product is contraindicated for use in foals under the age of 6 months.

The therapeutic dose has been adequately justified taking into account the effective dose versus a sufficient safety margin.

The clinical efficacy was demonstrated in five multicentre clinical trials including a large number of animals with musculo-skeletal disorders and soft tissue lesions. Efficacy for vedaprofen in the horse was demonstrated by significant improvement in clinical scores for lameness and soft tissue injuries. Furthermore, there was no statistically significant difference between the results from vedaprofen-treated animals and horses that had been treated with a positive control. The Committee considered the data sufficient to support the proposed indications for the "Reduction of inflammation and relief of pain associated with musculo-skeletal disorders and soft tissue lesions (traumatic injuries and surgical trauma). In cases of anticipated surgical trauma, Quadrisol can be given prophylactically at least 3 hours prior to elective surgery."

5. RISK-BENEFIT ASSESSMENT

Quadrisol is a non-steroidal anti-inflammatory drug developed for veterinary use containing vedaprofen as the active substance. The product is presented as an oral gel in 30 ml (horses) graduated multidose oral syringes containing vedaprofen hydrochloride. The gel formulation was chosen due to its better tolerance in the target animals as compared to other oral formulations such as a suspension.

Confirmation has been provided that none of the ingredients in the product are derived from human, bovine, ovine or caprine source material (TSE compliance).

The shelf life of the finished product is 3 years and the in use shelf-life is 2 months.

After oral administration, vedaprofen is rapidly absorbed and peak plasma levels are reached at 1 – 2 hours after administration. However, absorption and maximum plasma levels of the product are greatly reduced when the product is administered together with food or shortly after feeding. Therefore, recommendations to administer the product shortly before feeding have been included in the product literature.

Vedaprofen is highly bound to plasma proteins (>99%). A warning has therefore been included in the product literature not to use the product together with other substances with high protein binding, which might compete for binding and consequentially increase toxic effects.

Toxicity and tolerance studies demonstrated that the main toxic effects of vedaprofen are gastro-intestinal (ulcers in stomach and digestive tract/peritonitis) which are typical for this group (NSAIDs).

Vedaprofen was considered not embryotoxic or teratogenic and did not show any effect on fertility. NSAIDs are not known to be carcinogenic, immunotoxic or neurotoxic and special studies on this were therefore not requested.

Taking into account the formulation characteristics (oral gel) and the method of administration, vedaprofen was considered safe for the user.

The potential for environmental exposure to Quadrisol was considered minimal since the product is intended for individual treatment and the metabolism in the target species is extensive.

MRLs for vedaprofen for equine muscle, fat, liver and kidney have been included in Annex I of Council Regulation (EEC) No. 2377/90 and a withdrawal period for meat and offal of 12 days was accepted. Since no MRLs have been set for milk, vedaprofen is not permitted for use in lactating animals producing milk for human consumption.

Various *in vitro* and *in vivo* studies investigating the pharmacodynamic properties of vedaprofen have been performed in different animal species including horses confirming anti-inflammatory, anti-pyretic and analgesic properties of vedaprofen.

Quadrisol contains a racemic mixture of (+) and (-) enantiomers of vedaprofen with a selectively higher inhibitory activity towards COX-2 than COX-1.

Tolerance studies in horses demonstrated that the therapeutic margin is narrow.

Vedaprofen causes similar adverse reactions as other NSAIDs after oral administration, i.e. erosions and ulcers in the mouth and gastrointestinal tract. Quadrisol oral gels can be used during pregnancy

Since no foals were included in the clinical trials, the product is contraindicated for use in foals under the age of 6 months.

In horses, the clinical efficacy was demonstrated in five multicentre clinical trials including a large number of animals with musculo-skeletal disorders and soft tissue lesions. Efficacy for vedaprofen in the horse was demonstrated by significant improvement in clinical scores for lameness and soft tissue injuries. Furthermore, there was no statistically significant difference between the results from vedaprofen-treated animals and horses that had been treated with a positive control. The Committee considered the data sufficient to support the proposed indications for the “Reduction of inflammation and relief of pain associated with musculo-skeletal disorders and soft tissue lesions (traumatic injuries and surgical trauma). In cases of anticipated surgical trauma, Quadrisol can be given prophylactically at least 3 hours prior to elective surgery.”

Based on the original and complementary data presented, 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, as amended and supported the claims proposed by the Applicant.