I. INTRODUCTION

Equidronate 500 mg lyophilisate for solution for infusion contains the active substance tiludronic acid (as disodium salt) 500 mg. This product is authorised to be used in horses over 3 years of age in the treatment of clinical signs of lameness associated with bone spavin in combination with a controlled exercise regime. The product is to be given by intravenous route, by infusion and the amount to be administered is 1 mg of tiludronic acid per kg of body weight.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. The formulation uses well-established excipients in a simple formulation that is manufactured by a standard mixing process. It has been shown that the product can be safely used in the target species. The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

Product Development and Composition

The product contains the active substance tiludronic acid (as disodium salt) and excipient mannitol (E421).
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The product is presented in clear glass (type II) vial with chlorobutyl rubber closure secured by aluminium overseal with plastic flip-off cap within a cardboard carton. The choice of the formulation is justified.

Active Substance

The active substance is tiludronic acid (as disodium salt). The active substance is manufactured in accordance with the principles of good manufacturing practice.
The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided

Other Substances

The excipient used in the formulation is stated to comply with the latest version of the Ph. Eur. and specifications have been provided confirming this.

Packaging Materials

The product is packed in clear glass (type II) vial with chlorobutyl rubber closure secured by aluminium overseal with plastic flip-off cap within cardboard carton**.** A certificate of analysis has been supplied for each packaging component. The specifications are considered adequate and appropriate

Manufacture of the Finished Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.
Process validation data on the product have been presented in accordance with the relevant European guidelines.
There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

Finished Product Quality Control

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. The tests include appearance, residual moisture, uniformity of dosage units, reconstitution time, appearance of solution, pH, identity and assay of tiludronic acid, sterility tests and endotoxins. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

Stability of the Product

Active substance

Data generated by the active substance manufacturer have been provided. These data demonstrated satisfactory stability for the duration of the test, and justified the retest interval of three years.

Finished Product

Stability data on the finished product were provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.
A shelf life of 3 years was considered justified when stored in the outer carton in order to protect from light.

In-Use

A shelf-life of 24 hours after reconstitution according to directions is justified when stored at 2 to 8ºC.

Other Information

Shelf-life of the veterinary medicinal product as packaged for sale: 3 years.
After reconstitution, the product may be stored at 2 to 8°C for no longer than 24 hours.

Special precautions for storage

Keep the vial in the outer carton in order to protect from light.

CONCLUSIONS ON QUALITY

The product is satisfactorily formulated and controlled. A shelf-life of 3 years in an unopened pack and in-use shelf life of 24 hours is justified when reconstituted solution is stored at 2 to 8ºC.

III. SAFETY ASPECTS

Pharmacology

The applicant has provided extensive peer-reviewed references relating to the pharmacodynamics and pharmacokinetics of tiludronic acid in various species.

Pharmacodynamic

The pharmacodynamic effects of tiludronic acid have been investigated in routine laboratory species.

The following results were obtained in the series of pharmacodynamic studies on tiludronate:

- Tiludronate was a powerful inhibitor of bone resorption when used concomitantly to an evolving osteolytic process.
- Tiludronate inhibited bone resorption without altering renal function.
- Tiludronate appeared to have a significant potential to increase bone mass, as a result of the inhibition of bone resorption without impairing bone formation.
- At a dose level that totally inhibited mineral resorption tiludronate had no effects on the crystal deposition phase (mineralisation).
- At a dose of 100mg/kg/day per os, 6 days/week for 3 weeks tiludronate reduced the intensity of arthritis in rats.
- Tiludronate reduced the intensity of the inflammation-induced osteopenia in male rats and was not associated with an undesirable effect on mineralisation.
- The oral administration of tiludronate at a dose of 100mg/kg 3 days out of 7 for 4 weeks inhibited the development of osteopenia in rats.

Pharmacokinetic

Oral bioavailability of tiludronic acid has been demonstrated to be low in rabbits, rats, dogs, monkeys and mice. The primary route of excretion was shown to be via the urine with only a small amount excreted in the faeces. Tiludronic acid was excreted primarily as the unchanged acid (no biotransformation). Accumulation of radioactive tiludronic acid was shown to be in the bones.

Toxicology

Single Dose Toxicity

References were provided to studies conducted orally in rats, and orally and intravenously inmice. Multiples of the recommended dose of tiludronic acid were administered. Signs of toxicity included decrease in body weight gain. Macroscopic examination of animals revealed pale renal cortex and renal medulla congestion, and slightly congested lungs. At the end-of–study post-mortem, pale renal cortex increased kidney size and irregular kidney surface were observed.

Repeated Dose Toxicity

Subacute and subchronic toxicity:

References were provided to studies conducted orally and intravenously in rats and baboons, orally in mice and intravenously in dogs. Multiples of the recommended dose of tiludronic acid were administered over varying time periods. Typical observations at dose levels up to 200 mg/kg include dose related decreases in food intake, pale kidneys, changes in haematology, changes in thymus and kidney weights and decreased urinalysis.

Chronic Toxicity
References were provided to studies conducted orally in rats and baboons. Multiples of the recommended dose of tiludronic acid were administered over varying time periods. Dose rates of 12.5 mg/kg gave rise to decreased food consumption (males only) and decreased albumin (females only). At 50 mg/kg: additionally transient haematology changes and clinical chemistry changes were observed. At 200 mg/kg: additionally, decreased body weight gain, ECG changes, clinical chemistry greater changes and urinalysis. Animals in 200 mg/kg group showed restlessness, increased reaction to external stimuli, poor health condition, loss of teeth and white teeth. There was also evidence of decreased liver, thymus and adrenal weight and changes to the kidney.

Embryotoxicity/fetotoxicity, including teratogenicity
References were provided to studies conducted orally in rats, mice and rabbits. Slightly reduced foetal weight at 400 mg/kg/day in mice was observed. In rats the administration of tiludronic acid as the disodium salt by at 600 mg/kg/day gave rise to slight maternal toxicity (reduced body weight gain) and slight embryotoxicity (reduced foetal weight). At dose levels of 75, 150 and 300 mg/kg/day no adverse effects were observed. In rabbits treatment with tiludronic acid gave rise to severe maternal toxicity at 600 mg/kg/day. This was observed in non-mated females treated at doses of 450 and 500 mg/kg/day. A dose of 450 mg/kg/day was selected as a suitable high dose for a teratology study. Maternal toxicity at 240 mg/kg/day gave rise to slightly reduced body weight gain. No effects on post-implantation losses. At doses of 15 and 60 mg/kg/day, no maternal toxicity, embryotoxicity or teratogenicity were revealed.

Mutagenicity
References were made to mutagenicity studies. In all studies, tiludronic acid showed negative mutagenicity.

Carcinogenicity:
Reference was made to a carcinogenicity study from which tiludronic acid was not considered to possess carcinogenic potential.

Studies in Humans
Reference was made to information on adverse effects in humans treated with tiludronic acid at daily doses of 100 to 1600 mg/person/day for 7 days to 6 months, 70% of subjects being treated with 400 mg/day, the recommended dose. The mean length of treatment was 3 months. The main adverse effects reported were gastrointestinal disturbances, which consisted of abdominal pain, nausea and diarrhoea. They were of low intensity and the increase of the incidence was dose-dependent.

User Safety
The applicant has provided a satisfactory user risk assessment, identifying the users of the product and the potential routes of exposure for the operator. The risks have been identified and appropriate warnings included in the SPC and product literature. These are:
Avoid contact with skin and eyes.
Avoid accidental self-injection: it is recommended to insert the intravenous infusion needle into the vein before the reservoir containing the product is connected.
In the case of self injection, seek medical advice immediately and show the package leaflet or the label to the physician.
Wear suitable gloves when preparing the solution for injection
Wash hands after use.

Residues

The applicant has provided reference to a residue depletion study in which it was concluded that following intravenous administration of [^{14}C] tiludronate, kidneys contained the highest mean concentration of radioactivity in the retained tissues followed by liver, composite fat and gluteal muscle.

MRL

The CVMP considered the following:

- Tiludronic acid as the disodium salt is used in a small number of individual animals
- Tiludronic acid as the disodium salt is intended for infrequent or non-regular treatments

And in addition that:

- An ADI of 21 µg/kg (i.e. 1260 µg/person/day) was established
- The oral bioavailability of tiludronic acid in humans is low (approximately 6%)
- Residue depletion data were only provided for intravenous use
- At 12 hours after intravenous treatment the amount of residues likely to be ingested by consumers is far below the ADI and represents only a low fraction, approximately 15% of the ADI; 97% of this fraction of the residues being found in kidney and liver, the two equine tissues which are not considered as a food commodity in the EU.

The CVMP concluded that there was no need to establish an MRL for tiludronic acid it is included in Annex II of Council Regulation No 2377/90.

Withdrawal Periods

Tiludronic acid is included in Annex II of Council Regulation No 2377/90 and a zero day withdrawal period is considered acceptable since:

- Tiludronic acid is used in a small number of animals
- Tiludronic acid is intended for infrequent or non-regular treatment
- Tiludronate has a low oral bioavailability in humans
- The main fraction of residues are found in kidney and liver, tissues which are not considered as food commodities in the EU.
- The amount of drug derived residues in the muscle is far below the ADI for Tiludronic acid.

Therefore, a zero day withdrawal period for meat and offal is considered appropriate.

Environmental Safety

The product is indicated for treatment of locomotory problems and will by given to horses on an individual animal basis. The PEC_{soil} calculation for horses both in housing and at pasture demonstrated that the PEC_{soil} was below the 100 µg/kg value at which further action is required. Environmental exposure is not considered to be extensive and the assessment can end at Phase I.

CONCLUSIONS ON SAFETY AND RESIDUES

Conclusions on User Safety
Equidronate is not expected to present an undue hazard to the user under normal conditions of use.

Conclusions on Consumer Safety
Consumer safety is considered acceptable under normal conditions of use.

Conclusions on Environmental Safety
The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV. CLINICAL ASPECTS

Clinical Pharmacology
The applicant has provided both published references and some data obtained with different models (*ex-vivo*, *in-vivo*) about the pharmacodynamics related to the therapeutic effects including:

- cellular effects
- pharmacodynamic action on bone
- pharmacodynamic effects on calcium metabolism
- pharmacodynamic effect on inflammation and anti-arthritic effects

and the general pharmacodynamics:

- central nervous system
- cardiovascular and respiratory systems
- gastrointestinal system
- urinary system

Tiludronate has been demonstrated to reduce osteoclast activity *in-vitro* and inhibit bone resorption induced *in-vivo.* Therefore tiludronate inhibits bone resorption dose-dependently without reducing bone mineralisation. The mode of action is via incorporation of the drug into the bone matrix from where it is taken up by active osteoclasts. Therefore, by inhibiting bone resorption this secondarily leads to a slow down in bone formation and a slow down of bone remodelling. Bisphosphonates act as regulators of bone metabolism in every situation where there is excessive bone resorption (or bone lysis) such as early cases of bone spavin in the horse. The general pharmacodynamic investigations showed that tiludronate had no or minimal effects on the different systems investigated.

A study showed that the total exposure of a horse to the drug was considered the same whether the tiludronate was injected by 10 x 0.1 mg/kg injections or 1 mg/kg infusion on one day, therefore the studies submitted using 10 x 0.1 mg/kg injections were supportive of this application. C_{max} increases in proportion with an increase in administered dose. The total exposure of the horse to the drug (AUC) also increases as the dose increases, however clearance was the same irrespective of dose rate. There was no accumulation of tiludronic acid in plasma over the repeated dose rate tested indicating that the capacity of the bone to bind the drug was not saturated over the dose range tested.

Tolerance in the Target Species

The applicant conducted target animal tolerance studies using multiples of the recommended dose in the target species. The studies demonstrated that at the recommended dose rate and infusion rate, signs of colic can appear up to approximately 1 hour after the infusion. The signs were mild and transient and did not require treatment. Signs appeared to be limited to gastrointestinal signs, however when the infusion rate was doubled at 5x recommended dose rate, there were more severe signs of abdominal discomfort with moderate biochemical signs of renal dysfunction which appeared to last for 12 days. However creatinine is a relatively insensitive indicator of kidney function and only significant changes in values would reflect significant renal dysfunction. The studies illustrated that infusion of 1 mg/kg tiludronate over 30 minutes has a wide safety margin. The applicant's summary of all adverse reactions noted in all the submitted studies in horses, states that reactions such as signs of abdominal discomfort, restlessness, occasional recumbency, colic, tremor, sweating and increased frequency of urination, will be mild and transient, occurring in less than 11 % of treated horses. It appears that increasing the rate of infusion may cause an increase in abdominal pain in some horses and a suitable warning is included in the SPC. It is also stated that, as tiludronate chelates calcium, as do some antimicrobials such as tetracyclines and the adverse effects of some antimicrobials such as the neuromuscular blocking effect of aminoglycosides, an appropriate warning is included in the SPC to warn against intravenous injections of these products shortly after or before an infusion of tiludronate.

There is no model in horses for use in dose determination or dose confirmation studies to study inhibition of bone resorption by osteoclasts. Therefore, for dose determination, the applicant has taken all the information from the pharmacodynamics and pharmacokinetics sections and combined this with extrapolating the effective dose used in *in-vivo* non-target species models. The clinical expert explained that this may be considered satisfactory with products that are not extensively metabolised prior to excretion from the body. Passive processes such as glomerular filtration (related to clearance) appear to be related to the size of the animal allowing an allometric scaling approach to be used.

Clinical Efficacy

Two clinical trials were carried out by the applicant to assess the efficacy and the tolerance of tiludronate. The studies were conducted in accordance with GCP. At the dose rate of 0.1 mg/kg injected intravenously for 10 days, the product was well tolerated. Some general signs such as colic and tremor were reported but these were transient and resolved without treatment. Local reactions were moderate and resolved after a few days. There was no significance between the treated or placebo groups indicating that the local reaction was more due to the actual physical injection rather than the product itself. As there are no data relating to the adverse effects of tiludronate on the skeleton of young animals, a suitable warning is included in the SPC:

In the absence of any data relating to the adverse effects of tiludronic acid on the skeleton of young animals, do not administer to a horse less than 3 years old.
Do not administer to a horse with known impaired renal function.
Do not use in case of known hypersensitivity to biphosphonates or to any of the excipients.

In the pivotal clinical study a suitable number of horses were recruited to demonstrate efficacy of the product. As there is no recognised 'treatment' for bone spavin, comparison with the placebo of conservative treatment was appropriate.

Lameness was compared between the groups before and after treatment which showed no difference between the groups at the start of the study, but by day 60, the difference in degree

of lameness almost reached significance (p=0.064). This was significant when corrected for exercise effects (p=0.022). For a given level of improvement in lameness, there were always more improved horses in the treated group than in the placebo group.

The total population administered treatment was studied for the safety analysis. Local signs were similar between groups and were likely to be due to placement of a catheter. General signs such as muscle tremors, sweating, abdominal pain, diarrhoea and recumbency were seen. Some of these signs may have been due to the effects of sedation, however there was a higher incidence of colic pain, diarrhoea and recumbency in the test product treated group. Signs were transient and mild and if required mediation they resolved with an injection of a NSAID. The incidence of adverse effects was more than that seen in the tolerance studies; this may be due to the fact that the horses were treated away from home and the infusion rate may have been faster than advised. Horses were allowed to use NSAIDs to encourage exercise during this study and no adverse reactions were reported.

The dose rate used was 1 mg/kg by infusion. The vial contains 500 mg of product which is enough to treat a 500 kg horse. For horses weighing more than 500 kg, two vials would be used, with amounts taken from the reconstituted second vial according to the weight of the horse.

Overall at day 60, treated horses receiving Equidronate 500 mg were less lame than the placebo horses. All were undertaking at least two more levels of exercise. Compared to the results of the placebo group, addition of tiludronic acid administration to a controlled exercise regimen improved lameness and increased the ability to do more exercise. The study showed a small but significant sustained improvement in lameness and exercise levels. A beneficial effect has been shown when using tiludronic acid as part of the treatment regimen for bone spavin in horses and the product has been shown to be well tolerated.

PART V. OVERALL CONCLUSION ON THE PRODUCT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit-risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)