



ADVICE SUMMARY

APPLICATION FOR REGISTRATION OF A CHEMICAL PRODUCT

Product name: TILDREN 500MG LYOPHILISATE FOR SOLUTION FOR INFUSION
Applicant: CEVA SANTE ANIMALE S.A.
Product number: 63793
Application number: 46517

Purpose of Application and Description of Use: Registration of a 500mg tiludronic acid as disodium tiludronate freeze dried powder product for the treatment of lameness associated with bone and cartilage changes such as those observed in navicular disease and bone spavin in horses.

Active Constituent(s): TILUDRONIC ACID AS DISODIUM TILUDRONATE

Regulatory Decision:

To grant the application subject to the following conditions:

Standard Conditions of Registration/Approval

For full conditions, refer to http://www.apvma.gov.au/advice_summaries/adv_summaries.shtml.

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External Efficacy Reviewer

An external reviewer evaluated data presented by the applicant to support safety and efficacy of the proposed product ***Tildren 500mg Lyophilisate for Solution for Infusion (APVMA Approval No: 63793)***. The applicant provided published data on tolerance and effects of tilduronate on bone metabolism in horses (26976), plus safety studies, efficacy studies and pharmacokinetic/pharmacodynamic studies to support the application.

Reference is made to the related product ***Tildren Injection (APVMA Approval No: 58057)***. The proposed product is intended for single administration by slow IV infusion as opposed to daily IV injections for Tildren Injection.

Tiludronic acid is a synthetic derivative of pyrophosphate belonging to the class of biphosphonates, which are used as inhibitors of bone resorption in human osteoporotic disease. The target tissue is bone and to a lesser extent, cartilage.

The published data (26967) supports the effect of tiludronic acid on bone desorption when given at the proposed dose rate of 1mg/kg.

Study (26977) compared the bioavailability of tiludronic acid when administered once daily as an intravenous bolus of 0.1 mg/kg bodyweight for ten consecutive days (the dose regime for ***Tildren Injection (APVMA Approval No: 58057)***) vs a single slow infusion of 1mg/kg in 12 healthy adult horses. The intravenous administration of a single dose of 1mg/kg tiludronic acid by infusion is bioequivalent to daily administration of bolus doses of 0.1mg/kg tiludronic acid daily for 10 consecutive days in horses.

Target animal safety studies (26971), (26973), (26974) and (26969) support safety in the horse. The safety studies included margin of safety in terms of dose but also a rate of infusion study. There was evidence of discomfort during infusion at the proposed dose rate, principally characterized by pawing and kicking but it was concluded that at the dose regime of 1mg/kg of tiludronic acid by infusion over a 30 minute it is considered to be safe in the horse. The product can be administered at 5 fold the recommended dose and a rate of infusion of 2mg/kg/hour without any serious side effects. It has not been tested on young horses and label recommendations attest to this. Conclusions were that clinical tolerance of bisphosphonates is known to be directly related to the dose and rate of administration.

Efficacy studies include (26968) which evaluated the pharmacological effect of the biphosphonate tiludronate in the horse at exercise after a long-term immobilization period. The subsequent observations were consistent with the pharmacological action of tiludronic acid in so much as inhibition of bone resorption occurred (long-term immobilisation results in bone resorption) and tiludronic acid prevented the long-term loss of bone density. Study (26966) was a dose determination study supporting the 1mk/kg dose rate.

Confirmatory field study (26969) was a controlled double-blinded multi-centre clinical trial. The conclusion by the investigator was that efficacy in improving lameness has been demonstrated and this is considered clinically relevant. There was a mild incidence of colic but it was considered that the drug was safe and an aid in the management of bone spavin in horses.

The information provided supports the registration of *Tildren 500mg Lyophilisate for Solution for Injection* with the product to be administered at a dose rate of 1mg of tiludronic acid per kg bodyweight corresponding to 5 mls of reconstituted solution per 100kg by intravenous infusion, to be delivered over a 30minute period.

Based on the advice of the external reviewer and the relied on data the APVMA determines that use of the product in accordance with label instructions would not be likely to have a significant harmful effect in target animals and that use of the product in accordance with the recommendations for its use that the APVMA approves would be effective.

Data relied on to provide the advice

| Data No | Data Source* | Author(s) | Title | Date | Data Type | Data Sub-type | Authorising Party | Inherited Application No. |
|---------|--------------|---|---|--------------|---------------------|---------------|-------------------|---------------------------|
| 26969 | S | Gough M | Study Report No: CLI/145R1/0309: Efficacy and safety of 145R1 in the treatment of bone spavin by the intravenous route at the total dose level of 1mg tiludronic acid/kg in the horse | April 2007 | Efficacy and Safety | Efficacy | Applicant | |
| 26967 | S | Varella A, Lepage OM, Doucet M, Marcoux M and Garnero P | Tiludronate in horses: Tolerance and short-term effects on bone metabolism | 2002 | Efficacy and Safety | Efficacy | Public | |
| 26968 | S | Lepage OM | Study Report No: REC/145R1/0301: Evaluation of the pharmacological effect of the bisphosphonate tiludronate in the horse at exercise after a long term immobilisation period | Sept 2005 | Efficacy and Safety | Efficacy | Applicant | |
| 26966 | S | Guyonnet J | Study Report No: MPK/145R1/0517: Pharmacokinetic report of the study | Feb 2007 | Efficacy and Safety | Efficacy | Applicant | |
| 26970 | S | Anon | 1451 Lyophilisate for solution for infusion. Part IV. Synthesis Forward volume to the pre-clinical documentation. Volume 1/1. File No.: C518.4.01.E1 | October 2008 | Efficacy and Safety | Efficacy | Applicant | |
| 26977 | S | Doucet M | Study Report No: MPK/145R1/0504: | March | Efficacy and Safety | Efficacy | Applicant | |

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|-------|---|-------------|--|--------------|---------------------|------------------------------|-----------|--|
| | | | Comparative bioavailability of two intravenous dosage rates of tiludronic acid in healthy horses | 2007 | | | | |
| 26975 | S | Ovaert P | Study No: 8384. PV.PSU.09.RM.3: Periodic Safety Update Report: Tildren | Sept 2006 | Efficacy and Safety | Target Animal Safety Studies | Applicant | |
| 26973 | S | White G | Study Report No: ST-MPK/148R1/0340: Pilot study to determine the feasibility of administering 145R1 (tiludronic acid) at five times (5x) the therapeutic dose in the horse | April 2006 | Efficacy and Safety | Target Animal Safety Studies | Applicant | |
| 26974 | S | Szkuta O | Study Report No: ST-MPK/145R1/0512: Tolerance of 145R1 and pharmacokinetics study of tiludronic acid in plasma following intravenous administration as a 30 minute infusion at increasing doses in the horse | March 2007 | Efficacy and Safety | Target Animal Safety Studies | Applicant | |
| 26972 | S | White G | Study Report No: ST-MPK/148R1/0407: The effect of therate of infusion on the tolerance to code 145R1 (tiludronic acid) in the horse | July 2006 | Efficacy and Safety | Target Animal Safety Studies | Applicant | |
| 26976 | S | Anon | 145R1 Lyophilisate for solution for infusion. Part III-A:Synthesis of the Safety Documentation. Volume 1/1.File No.: C518.3S.00.E.1 | October 2008 | Efficacy and Safety | Target Animal Safety Studies | Applicant | |
| 26971 | S | Papelard AL | Study Report No: ARI/145R1/0616: Side Effects of the 145R1 in the Horse | Feb 2007 | Efficacy and Safety | Target Animal Safety Studies | Applicant | |

* S = Data submitted with the application

I = Data inherited (that is, referenced) from another application