Annex I

List of the name, pharmaceutical form, strength of the veterinary medicinal product, animal species, route(s) of administration, marketing authorisation holder in the member states

Member State	Applicant or Marketing Authorisation Holder	Product invented name	Pharmaceutical form	Strength	Animal species	Frequency and route of administration	Recommended dose	Withdrawal period
United Kingdom	CEVA Animal Health Limited	Tildren 500 mg lyophilisate for solution for infusion	Lyophilisate for solution for infusion	500 mg	Horses	Once (the treatment may be repeated on the advice of the veterinary surgeon) Intravenous use	1 mg/kg body weight (5 ml reconstituted solution per 100 kg)	Zero days Not permitted for use in lactating animals producing milk for human consumption
Germany	CEVA Animal Health Limited	Tildren 500 mg lyophilisate for solution for infusion	Lyophilisate for solution for infusion	500 mg	Horses	Once (the treatment may be repeated on the advice of the veterinary surgeon) Intravenous use	1 mg/kg body weight (5 ml reconstituted solution per 100 kg)	Zero days Not permitted for use in lactating animals producing milk for human consumption

Annex II

Scientific conclusions and grounds for suspension or refusal of the granting of the marketing authorisation

Overall summary of the scientific evaluation of TILDREN 500 mg lyophilisate for solution for infusion

1. Introduction

TILDREN 500 mg, lyophilisate for solution for infusion (Tiludronic acid) is a product indicated as an aid in the treatment of clinical signs of lameness associated with bone spavin in combination with a controlled exercise regime in horses over 3 years of age.

A disagreement between the Member States on the efficacy of the product was not solved. In the view of Belgium and Sweden the clinical trial performed according to the recommended dosage failed to show a statistical significant effect of the product. Therefore Belgium and Sweden considered that the benefit/risk balance was negative for Tildren, as the efficacy of the product had not been sufficiently demonstrated.

The CVMP was asked to assess if the efficacy of Tildren had been demonstrated and to conclude on the benefit/risk balance.

2. Assessment of the efficacy of Tildren

Bone spavin is a degenerative joint disease, characterized by bone modelling changes, articular cartilage destruction, and marginal osteophyte formation. Such lesions in the hock joint are responsible for varying degrees of lameness, often with an insidious onset, and leading to a complete ankylosis of the affected joints in the later stages of the disease. It is common for horses affected by this disease to have reduced performance.

Tiludronate belongs to the biphosphonates family. Its main cellular target is the mature osteoclast, the cell responsible for bone resorption. Tiludronate is incorporated into the bone matrix and the osteoclasts where it affects ATP-dependent intracellular enzymes leading to apoptosis. The resulting effect of osteoclast inhibition is inhibition of bone resorption. As bone resorption and bone formation are two coupled processes responsible for the integrity of bone mechanical properties, the inhibition of resorption secondarily leads to a slow-down in bone formation and, consequently, to a slow down in remodelling. By inhibiting bone resorption, tiludronate acts as a regulator of bone metabolism in situation where there is extensive bone resorption. Tiludronate is considered to reduce pain as bone disorders with increased osteoclastic bone resorption are frequently associated with pain. Further tiludronate inhibits the enzyme secretion by chondrocytes or synovial cells. These enzymes are responsible for the degradation of the joint cartilage matrix. Tiludronate has anti-inflammatory and anti-arthritic properties by acting on macrophages.

Two clinical trials were carried out under field conditions. The first clinical study was carried out in accordance with GCP to assess the efficacy and tolerance of tiludronic acid in the treatment of 3 clinical conditions including bone spavin and to compare two dosage regimes with treatment administering a placebo (vehicle only). However, in the assessment for this opinion only those horses suffering from bone spavin and treated with 0.1 mg/kg/day for 10 days are included.

The second clinical study was performed in accordance with GCP to assess the efficacy and the safety of tiludronic acid administered as a single infusion at the dose of 1 mg/kg bw in the treatment of bone spavin in horses.

In the first study a number of criteria were chosen to evaluate efficacy, including lameness score, response to treatment, effect of pain on palpation or mobilisation of the limb, response to flexion

test and level of activity. Further, a complementary analysis assessed the percentage of horses with no or minimal lameness and the percentage of horses with normal level of activity.

In both the treated and the placebo group lameness improved but there was no statistically significant difference between groups.

In the second study, efficacy was judged on the criteria of lameness score, level of exercise, assessed according to the type of animals and the combination of changes in lameness score and exercise level. The data demonstrate a treatment effect on lameness whereas the role of exercise in connection with treatment was considered unresolved. The marked improvement in the placebo group was unexpected and may have been influenced by concomitant treatment with NSAIDs and the specific exercise program.

On the other hand treatment with Tildren has been associated with abdominal disorders. Nevertheless the analysis of the Periodic Safety Update Report demonstrated that the number of serious adverse reactions was small and the CVMP concluded that there are no major concerns regarding the safety of the product.

A number of further questions were addressed to the Marketing Authorisation Holder (MAH) relating to the dosage, clarification of the statistical analyses, the concomitant NSAID treatment and the influence of exercise.

With regard to dosage the MAH responded that there is no existing model in the horse to mimic bone spavin and the dose was extrapolated from a model of bone resorption in rats using an allometric extrapolation. They considered that the selected dose was shown to produce concentrations in bone that are in the range of concentrations shown to inhibit bone resorption in vitro systems and that PK/PD modelling used was adequate to derive a pharmacologically active dose using a marker of bone resorption. The dose of 1 mg/kg was selected as the dose producing approximately 75 % inhibition of bone resorption.

With regard to the concomitant NSAID treatment, the MAH concluded there were no statistical differences between the treated and placebo groups having received NSAID treatment and therefore had not included this treatment in the statistical analysis.

With regard to the influence of exercise, the MAH concluded that the variation in exercise had been controlled to avoid any influence on the objective evaluation of the effect of the Tildren treatment.

The CVMP, however, concluded that the arguments presented by the MAH were not adequate to demonstrate efficacy given the data presented and concerns remained with regard to the influence of the variable exercise programmes and the concomitant use of NSAIDs.

Grounds for refusal of the granting of the marketing authorisation

There are considered to be significant deficiencies in the data provided by the Marketing Authorisation Holder in support of the efficacy of product.

Consequently, in the absence of any demonstrated benefit of this component the risk-benefit analysis for the product is negative, therefore presenting an unacceptable serious risk to human or animal health or to the environment.

Condition for the lifting of the suspension

The efficacy of Tildren for the treatment of bone spavin in horses should be demonstrated through the provision of appropriate field data clearly demonstrating that the administration of the product at an adequate dose shows a specific benefit unrelated to the concomitant use of NSAIDs or horse specific exercise programs.