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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

EUROPEAN PUBLIC MRL ASSESSMENT REPORT (EPMAR)

TILUDRONIC ACID
Extension to poultry species

INTRODUCTION

On 9 June 2009 the European Commission adopted a Regulation[1] establishing maximum residue limits for tiludronic acid (in the form of disodium salt) in poultry, valid throughout the European Union. These maximum residue limits were based on the favourable opinion and the assessment report adopted by the Committee for Medicinal Products for Veterinary Use.

Tiludronic acid is intended for use in poultry for the improvement of the egg shell quality by sub-cutaneous injection.

Tiludronic acid had maximum residue limits already established for *equidae*.

Ceva Santé Animale submitted the application for the extension of maximum residue limits to the European Medicines Agency (EMEA), on 4 January 2008.

Based on the original and complementary data in the dossier, the Committee for Medicinal Products for Veterinary Use concluded that it was not necessary for the protection of public health to establish maximum residue limits in poultry for the substance when used subcutaneously and therefore tiludronic acid should be included in Annex II of Council Regulation (EEC) 2377/90, in accordance with Article 3. This recommendation was confirmed on 15 May 2009 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 9 June 2009.

EXPLANATORY NOTE

The European Public MRL Assessment Report is a public document giving the overview of the assessment carried out by the Committee for Medicinal Products for Veterinary Use (CVMP) of an application submitted for the establishment of maximum residue limits (MRLs). The document is based on the CVMP assessment report of the application from which confidential information has been deleted.

KEY WORDS: tiludronic acid (in the form of disodium salt, poultry, *equidae*

[1] Commission Regulation (EC) No 485/2009, O.J. L 145, of 10.06.2009

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SUMMARY OF THE SCIENTIFIC DISCUSSION FOR THE ESTABLISHMENT OF MRLs

Substance name:	**Tiludronic acid, disodium salt**
Procedure number:	**EU/08/162/CEV**
Applicant:	**CEVA Santé Animale**
Target species:	**Laying and breeder hens**
Intended therapeutic indication:	**Improvement of the egg shell quality**
Route of administration:	**Single subcutaneous injection of 10 mg/kg b.w. in the back of the neck**

1. Introduction

Tiludronic acid as the disodium salt (disodium tiludronate), is a synthetic derivative of pyrophosphate belonging to the class of biphosphonates. In veterinary medicine, this 4-chlorophenyl-thiomethylene biphosphonate is intended for use as an intravenous solution in horses to treat navicular disease, bone spavin and fetlock suspensory ligament enthesopathies. The recommended dose is 0.1 mg/kg bw per day for 10 days. It is also used in human medicine, in Paget's disease at a recommended therapeutic dose of 400 mg per person per day (6.6 mg/kg bw) for 3 months.

Currently, tiludronic acid is included in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Tiludronic acid, disodium salt	*Equidae*	For intravenous use only

An application has now been submitted for the extension of the entry in Annex II of Council Regulation (EEC) No 2377/90 for tiludronic acid to laying and breeder hens. The proposed indication for laying and breeder hens is improvement of the egg shell quality. The proposed recommended dose is a single subcutaneous injection of 10 mg/kg bw in the back of the neck. The birds are around 18 weeks of age, before the onset of laying.

2. Safety assessment

Tiludronic acid was previously assessed by the CVMP and a pharmacological-toxicological ADI of 21 µg/kg (i.e. 1260 µg/person) was established based on the LOEL of 4.2 mg/kg bw from a 13-week toxicity study in rats for effects on plasma phosphorus levels and from a long term/carcinogenicity study in rats for effects on bone trabeculae, applying a safety factor of 200.

2.1 *Overview of evaluation by other international committees*

No MRLs for tiludronic acid have been established by JECFA/Codex Alimentarius.

3. Residues assessment

3.1 *Pharmacokinetics in target species*

After subcutaneous injection of ^{14}C-tiludronic acid at a dose of approximately 11 mg/kg bw to layer hens a maximum concentration in plasma of 5.03 mg equivalents/kg (C_{max}) was reached at 0.5 hours (T_{max}). Plasma half-life of elimination was 58.5 hours. The highest concentration of radioactivity was recovered in the bones of the carcass with 22.32 mg equivalents/kg accounting for the majority of the administered dose (49.85 %). Edible tissues such as liver, kidney and fat showed intermediate concentrations of 1.34 mg, 0.664 mg and 0.175 mg equivalents/kg while the concentration in muscle was low (0.028 mg equivalents/kg), less than in plasma (0.033 mg equivalents/kg). Overall 17.8 % of the dose was recovered in the excreta pooled over 6 – 144 hours. The overall mean recovery of radioactivity accounted for 79.21% of the dose.

Data clearly demonstrate that bone is the target tissue for the drug. Tiludronic acid shows comparatively low residues in tissues which are used for human consumption. The distribution of tiludronic acid in laying hens is similar to the distribution which is observed in other species including humans, where tiludronic acid is known to have a high affinity to bone tissues.

Specific studies on the metabolism of tiludronic acid in poultry have not been provided. However, there is evidence from extensive metabolism studies in laboratory animals such as rat, mice, rabbit, dog, baboon and in the horse that tiludronic acid undergoes little if any metabolism after parenteral or oral administration of the drug (no metabolites were detected in plasma and urine). Tiludronic acid is also not metabolised in human liver microsomes and hepatocytes. Based on this it seems reasonable to assume that parent tiludronate is the relevant residue in edible tissues.

3.2 *Residue depletion studies*

Residue depletion of ^{14}C-tiludronic acid subcutaneously administered to laying hens was investigated in tissues and eggs. Thirty laying hens treated by a single subcutaneous injection to the back of the neck at a mean overall dose level of 13.4 mg tiludronic acid /kg bw. Six animals per sampling time were slaughtered at 6, 12, 24, 72 and 144 hrs after treatment.

Within 24 hours after treatment the highest ^{14}C-total residues in tissues were detected at the injection site (10.2 mg equivalents/kg) followed by liver (3.3 mg equivalents/kg) and kidney (4.39 mg equivalents/kg). By contrast radioactivity in muscle (0.096 mg equiv./kg) and skin+fat (0.469 mg equivalents/kg) was rather low. Between 24 and 144 hour post application radioactivity declined slowly with time to 1.9, 1.53, 0.035, 0.222 and 1.20 mg equivalents/kg in liver, kidney, muscle, skin+fat and injection site.

A residue study in eggs was performed with radiolabelled ^{14}C-tiludronate sodium in which 15 laying hens were treated with a single subcutaneous injection to the back of the neck at a mean overall dose level of 14.0 mg tiludronic acid/kg bw. Egg production started after 12 — 28 days following the subcutaneous injection and eggs were collected up until 22—38 days after the onset of laying. The total radioactivity was measured in the first 10 eggs laid by each hen from the onset of laying by Liquid Scintillation Counting (LOQ: 5µg/kg).

In eggs residue levels were low (on average 0.211mg equivalents/kg) and were observed in egg 1 (first egg) from the onset of laying. This was followed by a continuous decline of the concentrations up to egg 10 post dosing (0.064 mg equivalents/kg). The results do not indicate an accumulation of tiludronic acid in eggs during egg production.

3.3 *Selection of marker residue and target tissues*

In regard to the data already presented in the MRL safety file, for the establishment of MRLs in horses (tiludronic acid, disodium salt Summary Report EMEA/MRL/774/01-Final), it was concluded that

tiludronate is not metabolised in animals and humans and is the only relevant residue constituent in edible tissues.

3.4 *Elaboration of MRLs*

Exposure assessment based on a worst case scenario taking into account injection site residues and the highest residue values in eggs, showed that intake of tiludronate residues via chicken derived food does not present a consumer concern. Therefore, the determination of MRLs for edible tissues of laying and breeder hens is considered not to be necessary. The extension of the current entry in Annex II of Council Regulation (EEC) No 2377790 is proposed.

Need for restrictions of use

For the establishment of MRLs for poultry the CVMP considered the need for restricting the use of the substance with regard to the route of administration and the target species for the entry in Annex II. The Committee concluded that in view of the fact that residue studies were conducted only after subcutaneous administration, the conclusions on the establishment of maximum residue limits could only be drawn with regard to the parenteral use. Furthermore, taking into account that within 12 to 24 hours after administration residues intake from tissues including injection site would represent 88% of the ADI the Annex II entry should be restricted to the use of the substance in laying and breeder birds only. Therefore the following restrictions on the use of the substance should be applied: “For parenteral use only and for use in laying and breeder birds only”.

Reference to MRLs established by other international committees

N/a

3.5 *Calculation of theoretical daily intake of residues*

The maximum theoretical daily intake of total tiludronic acid equivalents was determined at 6, 12, 24 hours, 3 and 6 days post final dose and compared with the ADI. Exposure was assessed based on a worst case scenario taking into account the standard food basket with 300 g muscle, 100 g liver, 10 g kidney, 90 g injection site instead of skin+fat (as the neck of poultry, corresponding to site of injection, is mainly skin and fat at that site) and the highest residue values in egg (100 g).

According to this exposure scenario residue intake via the standard food basket (injection site residues included) represented a worst case of 103 % of the ADI at 6 hours post dosing (70 % residues were from the injection site) and was reasonably below the ADI within 12 to 24 hours after treatment, representing 88 % of the ADI.

3.6 Analytical method for monitoring of residues

As an Annex II entry is proposed for tiludronic acid (as disodium salt) in laying and breeder hens, it is not necessary to develop an analytical method for the routine detection of residues.

3.7 Considerations on possible extrapolation of MRLs if applicable

The application for the extension of the existing Annex II entry for tiludronic acid (equidae) to laying hens included data for the major species, chicken. For this reason, a recommendation to extend the Annex II entry to poultry species can be made.

4. Conclusions and recommendation

Having considered the criteria laid down by the Committee for Medicinal Products for Veterinary Use for the inclusion of substances in Annex II of Council Regulation (EEC) No 2377/90 and in particular that:

- an ADI of 21 µg/kg (i.e. 1260 µg/person/day) was previously established for tiludronic acid,
- the parent compound is the only residue of relevance,
- following the recommended treatment residues in eggs are low; residue intake via eggs amounts to less than 2 % of the ADI,
- in edible tissues, calculation of the theoretical residue intake amounts to approximately 88% of the ADI (including the injection site residues) within 12 to 24 hours after subcutaneous administration,
- the drug is administered as single injection at the start of the laying period, well in advance of slaughter;

the Committee for Medicinal Products for Veterinary Use concludes that there is no need to establish an MRL for tiludronic acid, as the disodium salt, and recommends the amendment of the current entry in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Tiludronic acid, disodium salt	*Equidae*	For intravenous use only
	Poultry	For parenteral use only and for use in laying and breeder birds only

Glossary

ADI – Acceptable daily intake
LOEL – Lowest observed effect level
MRL – Maximum residue limit

Background information on the procedure

Submission of the dossier:	4 January 2008
Steps taken for assessment of the substance:	
Application validated:	17 January 2008
Clock started:	18 January 2008
CVMP opinion adopted:	16 April 2008