Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Tildren 500 mg Lyophilisate for Solution for Infusion for Horses

Date Created: February 2016

PuAR correct as of 08/04/2019 when RMS was transferred to AT.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0560/001/DC
Name, strength and pharmaceutical form	Tildren 500 mg Lyophilisate for Solution for Infusion for Horses
Applicant	AUDEVARD 42-46 rue Médéric 92110 Clichy France
Active substance(s)	Tiludronic acid (as disodium salt)
ATC Vetcode	QM05BA05
Target species	Horses over 3 years of age
Indication for use	As an aid in the treatment of clinical signs of lameness associated with bone spavin in combination with a controlled exercise regime.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	17 December 2015
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria

I. SCIENTIFIC OVERVIEW

Tildren 500 mg lyophilistate for solution has been developed as a generic of Tildren 5 mg/ml powder and solvent for solution for injection, authorised by Ceva Sante Animale in France since 2002. In addition, Equidronate 500 mg lyophilistate for solution for infusion is cited as a European reference product, which has been authorised by Ceva Animal Health Ltd in the UK since July 2011. Exemption from bioequivalence studies has been permitted in accordance with section 7.1.d) of the Guideline on the Conduct of Bioequivalence Studies for Veterinary Medicinal Products (EMA/CVMP/016/00-Rev2) and on the basis that the product is an autogeneric.

The product is indicated for the treatment of clinical signs of lameness relating to bone spavin and administered via intravenous infusion following reconstitution and dilution. The product is administered at a dose rate of 1 mg tiludronic acid per kg of bodyweight, corresponding to 5 ml of reconstituted solution per 100kg. Tildren is contraindicated in horses less than 3 years old, and in those with impaired renal function. The product should not be administered in cases of known hypersensitivity to bisphosphonates or to any of the excipients.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC.[1] 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 efficacy [2] of the product was demonstrated according to the claims made in

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains tiludronic acid (as disodium salt) as the active substance and the excipient mannitol (E421). The container/closure system consists of a clear glass (Type II) vial with a chlorobutyl rubber closure secured with an aluminium overseal and plastic flip-off cap. Single vials are packaged in a cardboard carton. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation is justified. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of mixing the active and excipient until dissolved before sterilisation. The solution is then filled in vials before freeze drying, final stoppering and packaging. Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substance is tiludronic acid (as disodium tiludronate) an established active substance not described in a Pharmacopoeia. Data on the active substance have been supplied in the form of an Active Substance Master File (ASMF). 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.

The excipient, mannitol, is a well-established excipient in medicinal product and complies with the relevant European Pharmacopoeia (Ph. Eur.) monograph. A certificate of analysis has been provided.

II.C.4. Substances of Biological Origin

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.E. Control Tests on the Finished Product

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. Control tests on the finished product include those for identification and assay of the active substance and degradation products, appearance of powder and reconstituted solution, pH, sterility 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.

II.F. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. A retest period of 3 years has been determined.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions. Data were provided for batches of the finished product stored at 25°C/60% RH for 36 months and at 40°C/75% RH for 6 months. Photostability studies were also performed, which indicated there was a small increase in degradation if the product was stored out of the packaging in intense light.

Additionally, in-use stability studies were provided. Data were provided for batches following reconstitution with saline or 5% glucose and stored under ambient or refrigerated conditions.

G. Other Information

Shelf life of the finished product as packaged for sale is 3 years.
After reconstitution and dilution according to directions, the product may be stored at 2 to 8°C for no longer than 24 hours.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

As this is a generic application according to Article 13 (1) according to Directive 2001/82/EC as amended, and bioequivalence with a reference product has been demonstrated, the results of pharmacological studies are not required.

Toxicological Studies

As this is a generic application according to Article 13 (1) according to Directive 2001/82/EC as amended, and bioequivalence with a reference product has been demonstrated, the results of toxicological studies are not required.

User Safety

A full user risk assessment was not provided in compliance with the relevant guideline as the product is qualitatively and quantitatively identical to the reference product. The risk to the user is therefore the same. The same warnings and precautions as for the reference product are listed on the product literature. The warnings are adequate to ensure safety to users of the product.

- 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 impervious gloves when preparing the solution for injection
- Wash hands after use.

Environmental Safety

An Environmental Risk Assessment (ERA) was submitted in support of the application. The ERA was performed in accordance with VICH and CVMP guidelines.

Phase I:

The environmental exposure to this product will be from the spreading of manure from treated horses on land or direct excretion onto pasture. However, the product will be used to treat horses on an individual animal basis thus limiting the risk of exposure to the environment.

The initial predicted environmental concentration (PEC) in soil was calculated for a stabled horse, and for a pasture reared horse and pony. All the calculated PECs were below the 100 µg/kg trigger value. Therefore, environmental exposure will be low and a Phase II ERA was not required.

III.B.2 Residues documentation

Residue Studies

As this is a generic application according to Article 13 (1) according to Directive 2001/82/EC as amended, and bioequivalence with a reference product has been demonstrated, the results of residue depletion studies are not required.

MRLs

Tiludronic acid (as disodium tiludronate) and the excipient mannitol are listed in Table 1 of Regulation 37/2010. No MRL is required for tiludronic acid (as disodium salt) when given intravenously to equidae. No MRL is required for mannitol in all food producing species.

Withdrawal Periods

As the product is identical to the reference product the same withdrawal period has been applied.
Meat and offal: zero days.
Not permitted for use in animals producing milk for human consumption.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

This is a generic application according to Article 13 (1) and the product is qualitatively and quantitatively identical to the reference product, thus fulfilling the criteria for a waiver from bioequivalence studies in accordance with section 7.1.d) of EMA/CVMP/016/00-Rev2. Therefore the product is exempt from bioequivalence studies and no data are required for pre-clinical and clinical studies.

Tolerance in the Target Species

Data were provided on the common adverse events reported for the reference product. The most common adverse events are characterised by abdominal discomfort or changes in renal parameters, but most adverse events are transient and easy to manage or treat. The risk from the product is the same as the reference product, as the products are identical. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

IV.II. Clinical Documentation

This is a generic application according to Article 13 (1) and the product is qualitatively and quantitatively identical to the reference product, thus fulfilling the criteria for a waiver from bioequivalence studies in accordance with section 7.1.d) of EMA/CVMP/016/00-Rev2. Therefore the product is exempt from

bioequivalence studies and no data are required for pre-clinical and clinical studies.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

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 of the product(s) is favourable

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MODULE 4

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.

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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.

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