Bundesamt für Verbraucherschutz und Lebensmittelsicherheit

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)
Federal Office of Consumer Protection and Food Safety
Mauerstraße 39-42
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(Germany)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Ursoferran 200mg/ml

Date: 20.06.2013

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0149/001/MR
Name, strength and pharmaceutical form	Ursoferran 200mg/ml
Applicant	Serumwerk Bemburg AG Hallesehe Landstr. 105 b; 06406 Bernburg Germany
Active substance(s)	Gleptoferron (Iron(III) dextran heptonic acid complex)
ATC Vetcode	QB03AC91
Target species	Pig (piglet)
Indication for use	For prophylaxis and treatment of iron deficiency anaemia in piglets.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicinal Agencies website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 13a of Directive 2001/82/EC as amended.
Date of completion of the original Mutual recognition procedure	25.07.2012
Date product first authorised in the Reference Member State (MRP only)	19.08.2005
Concerned Member States for original procedure	AT, BE, CZ, DK, ES, FI, FR, HU, IT, LU, NL, PL, PT, RO, SE, SK, UK

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.
It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC.
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 of the product was demonstrated according to the claims made in the SPC.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains 200 mg/ml iron(III)-ions as Gleptoferron (532.6 mg/ml), phenol (preservative) and water for injections.

The product is filled in vials made of either clear glass or LDPE, closed with chlorobutyl rubber stoppers. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the presence of preservative are justified.

The product is an established pharmaceutical form and its development is adequately described.

B. Method of Preparation of the Product

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

The active substance is an established active substance, and it 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.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

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

E. Control on intermediate products

There are no intermediate products.

F. 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.

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.

G. Stability

Stability data on the active substance have been provided, demonstrating the stability of the active substance when stored under the approved conditions.

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 (“Do not freeze”).

An in-use shelf-life of 28 days has been supported by appropriate data.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

None.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data on the general knowledge on the physiological/ pathophysiological function of iron as an essential micronutrient.
After intramuscular injection, the iron complex is absorbed into the lymphatic tissue within 3 days. Here, the complex is split to release Fe3+ which is stored as ferritin in the main storage organs (e.g. liver, spleen and the reticuloendothelial system). In the blood, free Fe3+ binds to transferrin (transport form) and is mainly used for the synthesis of haemoglobin.
These results were plausibly extrapolated to the active substance gleptoferron (iron dextran glucoheptonic acid) of the product.

Toxicological Studies

The applicant has provided bibliographical data which show that iron compounds have shown a low potential of acute toxicity except for iron sulphate which can be considered moderately acute toxic after oral administration. Acute toxicity studies with the product showed, that it was well tolerated in mice after intravenous administration.

No data on repeated dose toxicity, reproductive toxicity and mutagenicity were submitted by the applicant, which was acceptably justified.
One published reference on carcinogenicity in laboratory animals (IARC, 1972) has shown, that repeated i.m. or s.c. administration of iron dextran induced sarcomas in mouse, rat, rabbit and hamster at the injection site. Tests of relatively short duration in squirrel monkeys gave negative results. No conclusive evidence of tumour formation at sites distant from the injection site has been obtained in animals. The carcinogenic activity seems to be a property of the complex itself, since neither iron nor the carbohydrate component alone induces sarcomas.

Observations in Humans

The applicant has provided bibliographical data which show that adverse side reactions like anaphylactoid reactions and discoloration of injection sites have led to a massively reduced usage of Fe-dextrans although in the USA such a product for use in humans is still registered and on the market. Parenteral iron products, however, have nevertheless not been banned for use in humans since there are therapeutic situations where a rapid replenishment of iron is mandatory, i.e. the benefit outweighs the inherent risk.

User Safety

The applicant has provided a user safety assessment which shows that the main routes of exposure are from accidental skin contact or by accidental self-injection. The product is only used by professionals in the stable. Accidental exposure to children is therefore not expected. Both exposure scenarios do not pose a relevant risk for the user beside the risk of anaphylaxis. In that case, an iron chelator should be administered.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. No warnings are required.

III.B Residues documentation

Residue Studies

No residue depletion data were provided.

MRLs

Iron glucoheptonate as well as iron dextrane are listed in Table 1 of Commission Regulation (EU) No 37/2010 for all food producing species with no MRL required. As well for other iron compounds listed in CR (EU) No 37/2010 no MRLs are required. Therefore, this is also considered applicable for Iron-(ill)-hydroxyd-Dextran-Glucoheptonacid-Complex used as active ingredient in Ursoferran 200 mg/ml pro inj.

Pharmacologically active substance	Marker residue	Species	MRLs	Target tissue
Iron glucoheptonate	Not applicable	All food producing species	No MRL required	Not applicable
Iron dextran	Not applicable	All food producing species	No MRL required	Not applicable

Withdrawal Periods

After treatment of piglets with Ursoferran 200 mg/ml pro inj. using the recommended dosage, no critical residue concentrations in edible tissues derived from piglets are expected. Based on considerations on low toxicity of iron, no withdrawal period has to be set to ensure consumer safety.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographical data which reflect the well known role of iron as an essential trace element for the formation of haemoglobin, myoglobin and iron-dependent enzymes. The therapeutic effect of iron dextran compounds on iron deficiency anaemia in piglets is well established. Gleptoferron, which is the active ingredient in Ursoferran 200 mg/ml pro inj., has been shown to possess the same properties. The pharmacokinetic properties of Ursoferran 200 mg/ml pro inj. are well in line with the information from textbooks and published references on iron dextran compounds. In sum, the pharmacological data base was considered adequate for such a “well established use” product.

Tolerance in the Target Species of Animals

Tolerance studies which have been conducted according to the standards as outlined in the Target Animal Safety Guideline were not provided. This is considered acceptable since the veterinary medicinal product was first authorised long time before this guideline was developed in the EU.

Tolerance of Ursoferran 200 mg/ml pro inj. has been investigated in efficacy studies under normal use conditions. In 3 efficacy studies the injections sites were examined clinically and also histopathologically. The predominant findings were brownish discolorations at the injection site, which were found to be transient. With regard to post marketing information covering the period from 2005 to 2009, no new safety concerns were identified. Based on the data provided it was concluded that the local and systemic tolerance of Ursoferran 200 mg/ml pro inj. is acceptable.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

IV.B Clinical Studies (pharmaceuticals and immunologicals)

Laboratory Trials

Laboratory studies were not available.

Field Trials

In support of this “well established use” application (Art. 13 a of Directive 2001/82/EC as amended) the applicant has provided the data of 4 clinical studies and bibliographical references. In the following the clinical studies, which form the pivotal data base for the demonstration of clinical efficacy of Ursoferran 200 mg/ml pro inj., are summarized:

Within an old study (Gürtler, 1996) two experiments were performed each with 3 treatment groups: 1) the test group treated with Ursoferran 200 mg/ml pro inj. containing iron(III)-hydroxide-dextran- glucoheptonic acid-complex, 2) a positive control group treated with a veterinary medicinal product containing iron(III)-hydroxide-dextran-complex and 3) a negative control group treated with physiological saline. Both veterinary medicinal products were administered intramuscularly once at a dose of 200 mg iron per animal. Both experiments were performed with 3-day old piglets. The criteria chosen for evaluation of efficacy and tolerance were appropriate (in both experiments clinical parameters, haematological and clinical chemistry parameters and in experiment 2 also histopathological criteria). Based on the reported results, i.e. especially increase of erythrocyte values, haemoglobin, haematocrit and plasma iron, it was agreed that Ursoferran 200 mg/ml pro inj. was effective in preventing anaemia. Treatment scheme and outcome was in accordance with published data including textbooks. It was also agreed that Ursoferran 200 mg/ml pro inj. shows a good local and systemic tolerance under the claimed conditions for use.

In another study (Zepperitz et al., 2000) 5 treatment groups were included which all use Ursoferran 200 mg/ml pro inj. in different treatment schemes. The claimed treatment scheme, i.e. intramuscular injection of 200 mg Ursoferran 200 mg/ml pro inj. once between the 1st and 3rd day of life, was also covered with this study. The relevant parameter which allowed a direct conclusion on antianaemic effect in this study was the haemoglobin (Hb) concentration in blood. It could be shown that the

haemoglobin levels increased during the course of the study and reached more than 5.0 mmol/l (corresponding to 80g Hb/l) which was taken as a critical threshold in this study (i.e. the critical haemoglobin level that is considered not to compromise the growth in piglets). At day 10 the mean values of the groups were around 100 g Hb/l which increased to more than 120 g Hb/l at day 21. Performance parameter like body weight and litter data were in an acceptable range. The results of this study support the efficacy of Ursoferran 200 mg/ml pro inj. at the claimed treatment scheme.

A further field study (Ritzmann, 2010) focused on the comparative efficacy of Ursoferran 200 mg/ml pro inj. and an authorised veterinary medicinal product as a positive control in suckling piglets on the 3rd day of life. Ursoferran was administered as claimed, i.e. at a single dose of 200 mg iron intramuscularly. The positive control, which contains an iron (III)-hydroxide-dextran complex, was given at the same dosage. Relevant haematological parameters like erythrocytes, haemoglobin and haematocrit clearly showed an effect of iron supplementation in both treatment groups. Further evidence was given by increasing serum iron levels. Development of body weight and daily weight gain were within a normal range. Based on all available data it was agreed that Ursoferran 200 mg/ml pro inj. and the positive control product can be assumed comparable with regard to efficacy and that both products were well tolerated.

In addition the applicant provided another field study (Schmidt, 2011) which was performed according to current standards including GLP-compliance with regard to the laboratory part of the investigations. The study included 4 treatment groups, i.e. a negative control group treated with isotonic saline solution (injection volume 1 ml), a group treated with Ursoferran 200 mg pro inj. as it is currently marketed, a group treated with a new Ursoferran formulation not yet marketed and a positive control group treated with an authorised veterinary medicinal product containing iron (III)-hydroxide-dextran complex. Piglets were treated once at an age of 1 to 2 days. The Ursoferran formulations were given at the claimed dose of 200 mg iron/animal (corresponding to an injection volume of 1 ml), while the positive control was administered according to the label, i.e. at a dose of 100 mg iron/kg bodyweight. For the proof of efficacy the applicant had chosen the area under the plasma iron concentration curve (AUC) between day 0 and 24 using changes to baseline value as the primary outcome variable. This parameter was considered acceptable. It was proven that the respective AUCs of the iron-treated animals were superior compared to saline treated animals. Also other relevant haematological parameters like haemoglobin, haematocrit, MCV and MCH showed statistically significantly higher values compared to the negative control group. In addition the haematological data corresponded well with the clinical chemistry response, i.e. increase in plasma iron concentration and lower iron binding capacity in iron-treated animals. Consequently, the efficacy of Ursoferran 200 mg/ml pro inj. was adequately proven. All piglets were necropsied at day 24 for a general macroscopic post-mortem examination with specific attention to injection sites and local lymphnodes. The clinical examination of

the injection sites and the necropsy examinations were appropriate to confirm that Ursoferran 200 mg/ml pro inj. has a good local tolerance under normal use conditions. Also the general tolerance can be regarded as good as no untoward treatment-related clinical signs or other findings have been reported. In consequence the results on efficacy and tolerance of this study, which has been performed according to current standards, principally confirm the results of older 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 risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

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 Heads of Veterinary Medicinal Agencies website (www.hma.eu).

This section 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.

Summary of change **(Application number)**	**Section updated in Module 3**	**Approval date**
A.2 Change in the (invented) name of the medicinal product b) for Nationally Authorised Products (DE/V/149/IB/002/G)	N/A	1 November 2013
B.II.e.5.c) – Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/immunological medicinal products (DE/V/0149/001/II/017)	N/A	28/04/2017