IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Previron 200 mg/ml solution for injection for pigs

PRODUCT SUMMARY

EU Procedure number	IE/V/0357/001
Name, strength and pharmaceutical form	Previron 200 mg/ml solution for injection for pigs
Active substances(s)	Iron (as gleptoferron)
Applicant	Laboratorios Hipra S.A. Avda. La Selva 135 17170 - Amer (Girona) Spain
Legal basis of application	Well-established use application (Article 13a of Directive No 2001/82/EC)
Date of completion of procedure	21/09/2016
Target species	Pigs
Indication for use	For the prevention of iron deficiency anaemia in piglets.
ATCvet code	QB03AC
Concerned Member States	AT, BE, BG, CZ, CY, DE, DK, EE, EL, ES, FI, FR, HR, HU, IT, LT, LU, LV, NL, NO, PL, PT, RO, SE, SK, UK

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

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 benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A.Qualitative and Quantitative Particulars
The product contains 200 mg/ml iron (as gleptoferron complex) as the active substance and the excipients phenol and water for injections.
The container/closure system consists of coloured Type II glass vials of 100 ml and 250 ml which are closed with Type I polymeric elastomer stoppers with aluminium caps.

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

B.Method of Preparation of the Product
The product is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.
Process validation data for the manufacturing process has been presented in accordance with the relevant European guidelines.

C.Control of Starting Materials
The active substance is iron (as gleptoferron complex), an established active substance.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 has been provided.
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.

D.Control on Intermediate Products
The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

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.
Satisfactory validation data for the analytical methods has been provided.
Batch analytical data from the proposed production site has been provided demonstrating compliance with the specification.

F.Stability
Stability data on the active substance has been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.
Stability data on the finished product has been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

G.Other Information
Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.ASafety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show that iron is an essential micronutrient. It plays a major role in the oxygen transport of haemoglobin and myoglobin, as well as a key role in enzymes, such as cytochromes, catalases, and peroxidases.
Iron has a high recovery rate from metabolism and food ingested. Thus, deficiency occurs only very rarely in adult animals.

The applicant has also provided bibliographical data which shows that after intramuscular injection, the iron complex is absorbed into the lymphatic tissue of piglets within 3 days. Here, the complex is split to release Fe^{3+} which is stored as ferritin in the main storage organs (e.g. liver, spleen and the reticuloendothelial system). In the blood, free Fe^{3+} binds to transferrin (transport form) and is mainly used for the synthesis of haemoglobin.

Toxicological Studies

The applicant has provided bibliographical data which show that iron dextran is of low acute toxicity when administered intraperitoneally or intravenously. As the product is intended for administration as a single dose administration to neonatal piglets, repeat dose and reproductive toxicity were not investigated in detail.

The available genotoxicity data does not indicate a risk for the consumer.

The applicant has provided bibliographical data investigating the carcinogenic potential of iron-dextran. No conclusive evidence of tumour formation at sites distant from the injection site has been obtained in animals. Taking into account that the target species are neonatal piglets subject to a single treatment, it is accepted that there is no safety risk for the target animal. In addition, these data were considered in the context of a maximum residue limit (MRL) application and, given the no MRL required status of the substance, it can be accepted that the available carcinogenicity data did not indicate a risk for the consumer.

Other Studies

According to the published literature acute overload or repeat administration of iron leading to iron overload can lead to oxidative stress. Transient inhibition of the immune system following large amounts of parenterally administered iron has been reported. This potential effect on the immune system is of limited relevance to the target animal under normal conditions of use; however, it may increase susceptibility for systemic infectious disease when administered in overdose.

Observations in Humans

It is known that excess iron or iron overload may cause iron poisoning. The lethal dose is 80 to 250 mg $iron^{2+}$/ kg body weight. Severe iron poisoning is characterised by damage to the intestinal epithelial lining, which can cause blood containing diarrhoea and vomiting. Acidosis, liver and/or kidney failure and cardiovascular collapse may follow. Iron in doses of 100 to 400 mg per day can cause symptoms in the gastrointestinal tract.

Studies on Metabolites, Impurities, Other Substances and Formulation

The formulation of the product only contains conventional excipients commonly used in veterinary pharmaceuticals.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the recommended dose for an individual piglet is multiples below the dose that a human patient would receive during treatment of iron deficiency. As a consequence adverse systemic effects are unlikely following accidental exposure. Regardless, it is recommended that care should be taken to avoid accidental self-injection as well as mucous membrane contact, especially people with known hypersensitivity to iron dextran, as anaphylactoid reactions are possible.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

Phase I
The environmental risk assessment can stop in Phase I because the product contains a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment.

Conclusion
Based on the data provided, the ERA can stop at Phase I. The product is not expected to pose an unacceptable risk for the environment when used according to the SPC.

III.B Residues Documentation

Residue Studies

No residue depletion studies were conducted because:

- Iron is an essential element and a normal constituent of the diet in man,
- Treated animals are unlikely to be sent for slaughter during or immediately after treatment,

It is accepted that the concentration of iron expected in the edible tissues from treated animals will not pose a health risk for the consumer.

MRLs

Iron dextran and iron glucoheptonate are listed in Table I of the Annex to Commission Regulation (EU) No 37/2010 as 'No MRL required' in all food producing species.

It is accepted that the MRL entries for iron dextran and iron glucoheptonate are applicable to the gleptoferron complex.

Withdrawal Periods

Given that:

- Iron is an essential element and a normal constituent of the diet in man,
- Residues of concern to the consumer are not expected in edible tissues,
- The product will be administered to piglets between days 1 and 3 of life, with little likelihood that treated animals will be sent for slaughter during or immediately after treatment,
- The active substance has 'No MRL required' status,

A withdrawal period of zero days for meat in piglets is justified.

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

Bibliographical data have been provided which shows that the administration of 200 mg Fe^{3+} (as iron(III)-hydroxide-dextran-gluco heptonic acid complex) to neonatal piglets is generally well-tolerated (both local and systemic tolerance). Any reactions observed were considered to be minor. Occasionally discolouration of the tissue and/or slight, soft swelling may be observed at the site of injection. It was noted that hypersensitivity reactions can occur. Data provided also demonstrates that the vitamin E and selenium status of the piglets is important in minimising adverse effects following treatment. Large amounts of iron administered by the parenteral route may result in transient reduced capacity of the immune system due to iron overload of lymph macrophages.

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

IV.B Clinical Studies

In support of the efficacy of the product, the applicant has provided:
1)Information from the published literature, and
2)The reports of studies investigating the safety and efficacy of an authorised product containing 200 mg/ml iron (as gleptoferron complex), to which similarity with Previron has been demonstrated.
It is accepted that the findings (in terms of safety and efficacy of gleptoferron/iron dextran) as presented in the study reports provided reflect what is known from the published literature.

Based on the totality of data provided, it is accepted that intramuscular administration of iron dextran/gleptoferron at a dose of 200 mg Fe^{3+} between the 1st and 3rd day of life to piglets has been shown to increase the number of erythrocytes, serum Fe, haemoglobin, haematocrit and mean corpuscular volume when compared to untreated controls. The data package presented supports the indication for prevention of iron deficiency anaemia in piglets and the proposed posology (200 mg Fe^{3+} on a single occasion between the 1st and 3rd day of life).

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 for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

VI. 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 HPRA website.

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.

Changes:
None.