MINISTERIO
DE SANIDAD, SERVICIOS SOCIALES
E IGUALDAD

agencia española de
medicamentos y
productos sanitarios

DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

C/Campezo 1, Edificio 8
28022 – Madrid
España
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

GLEPTAFER 200 mg/ml solution for injection for pigs

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0284/001/MR
Name, strength and pharmaceutical form	GLEPTAFER 200 mg/ml solution for injection for pigs.
Applicant	Laboratorios SYVA S.A.U. Avda. Párroco Pablo Díez, 49-57 (24010) León Spain
Active substance(s)	Iron(III)-Ions as Gleptoferron
ATC Vet code	QB03AC
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 Medicines Agencies website (http://www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual Recognition application in accordance with Article 13 a of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	26/07/2017
Date product first authorised in the Reference Member State (MRP only)	30/05/2016
Concerned Member States for original procedure	PL, PT, RO

I. SCIENTIFIC OVERVIEW

***For public assessment reports for the first authorisation in a range**:*

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 is a solution for injection containing 200 mg/ml of Iron (III) (as gleptoferron complex) and phenol and water for injections as excipients .

The container/closure system consists on HDPE vials with bromobutyl type I stoppers. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the preservative is justified.

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 from a licensed manufacturing site.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is Gleptoferron, a known active substance not described in the European Pharmacopoeia. Its synthesis cannot be separated from the formation of an intermediate product in the manufacture of the finished product, so the supporting documentation of its quality is submitted jointly.

Both the active substance and the intermediate have been manufactured in accordance with the principles of good manufacturing practice.

The specifications of both the active substance and the intermediate are considered adequate to control the quality of the materials. Batch analytical data demonstrating compliance with these specifications 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 (pharmaceuticals)

The controls performed during manufacture have been properly described. As mentioned before, it is not possible to separate the active substance synthesis of the intermediate product manufacture, so the documentation is submitted in conjunction in Part 2C.

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 sites have been provided demonstrating compliance with the specification.

G. Stability

Stability data on the intermediate product have been provided in accordance with applicable European guidelines, and justified the holding time of the intermediate prior to the sterilization and the subsequent packaging.

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.

H. Genetically Modified Organisms

None

J. Other Information

None

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show that iron is an essential micronutrient. It takes a major role in the oxygen transport of haemoglobin and myoglobin, as well as it has a key role in enzymes, such as cytochromes, catalases, and peroxidases.

Iron has a high recovery rate from metabolism and food ingested. Iron deficiency occurs only very rarely in adults animals.

After intramuscular injection, the iron complex is absorbed into lymphatic tissue 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, as transport form, and is mainly used for the synthesis of haemoglobin.

Toxicological Studies

- Single Dose Toxicity

The applicant has provided bibliographical data about the acute toxicity that show a low acute toxicity of iron compounds except for iron sulphate which can be considered moderately acute toxic after oral administration. The administration of high doses of iron causes irritations of the gastrointestinal tract and has a toxic effect on the vasculature and the liver parenchyma.

The applicant present a set of values of acute oral LD_{50} of iron-containing compounds:

Iron: Rat LD_{50} = 30 000 mg/kg
Ammonium iron sulphate: Rat LD_{50} = 3 250 mg/kg p.v.
Iron (II) ammonium sulphate: Rat LD_{50} = 3 250 mg/kg p.v.
Iron (III) chloride: Mouse LD_{50} = 1 280 mg/kg p.v.
Iron (III) dextran: Mouse LD_{50} = 1 000 mg/kg p.v.
Iron (II) fumarate: LD_{50} = 1 570 mg/kg p.v. (mouse); 3 850 mg/kg p.v. (rat).
Iron pentacarbonyl: Rabbit LD_{50} = 12 mg/kg p.v.
Iron (II) sulphate: LD_{50} = 680 mg/kg p.v. (mouse); 319 mg/kg p.v. (rat); 600 mg/kg p.v. (rabbit)

They have also submitted documentation on single dose toxicity studies using other administration routes (i.v. in mice, i.p. in rats and mice), however a LD_{50} could not be determined.

- Repeated Dose Toxicity

Since the medicinal product is administered only once, as well as based on the low toxicity seen in the single dose experiments, the presentation on data of repeated dose injection is not necessary and does not contribute to the safety characterization of the preparation.

- Reproductive Toxicity, including Teratogenicity:

No data were submitted about the reproductive toxicity. The exclusive usage of the preparation as single dose administration in neonatal piglets becomes unnecessary to submit investigations of the reproductive potential, and no data were submitted by the applicant.

- Mutagenicity

No data were submitted about the mutagenicity. The necessity for the determination of the preparation's mutagenic potential can be regarded as unnecessary. In addition, the chemical nature of the active substance it appears to be highly unlikely that an inherent mutagenic potential in piglets is present.

- Carcinogenicity

As the product is only indicated for piglets and is intended to be administered only once, the carcinogenicity is negligible.

- Other Studies

There are no studies on other effects included in the dossier. It is the opinion of the expert that there is also no need for such studies since the therapeutic and prophylactic usage of iron, or more specific the parenteral usage of Fe-dextran in humans and animals has a long tradition.

The expert presents some studies concerning the single toxicity of the product conducted in rats and mice injected intraperitoneally or intravenously, but at much higher dose than the toxic dose for humans. These studies demonstrated that the toxicity of this product is low.

Other reports are described by the expert in different non-target species, like mouse, rat, rabbit, gerbil and cattle.

- Studies in Humans

A risk concomitant with parenteral substitution of larger amounts of iron may be seen in a transient inhibition or reduced capacity of the immune system due to a momentary iron overload of lymph macrophages (during the acute phase or transportation/absorption from the injection site).

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the product does not pose an unacceptable risk for the user.

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. The assessment concluded that the product has an acceptable risk for the environment.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues documentation

Residue Studies

No residue depletion studies were conducted. The withdrawal period was based on bibliographic studies.

MRLs

Iron glucoheptonate as well as iron dextran are listed in the Table 1 of the Comission Regulation (EU) No 37/2010, and no MRL is required for all food producing animal species; other iron compounds (listed in Commission Regulation (EU) No 37/2010 no MRL are required. Therefore, this is also applicable for Iron -(ill)-hydroxyd-Dextran-Glucoheptanoacid-Complex used as active ingredient in GLEPTAFER 200 mg/ml solution for injection for pigs.

MRLs are listed below:

Pharmacologically active substance	Marker residue	Animal species	MRL	Target tissues
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

Concerning MRL status of the excipients, the following is noted: phenol is included also in Table 1 of the Commission Regulation (EU) No 37/2010, and no MRL is required, and water for injections is included in the list of substances considered as not falling within the scope of Regulation (EC) No. 470/2009.

Withdrawal Periods

Based on the data provided above and the low toxicity of iron, a **withdrawal period** of **Zero days** for meat and offal in pigs is justified to ensure consumer safety.

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IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographical data to show an overall view of the kinetic behaviour of iron after administration of gleptoferron complex in piglets.

Pharmacological effects of iron after its injection are also reviewed. Data submitted refer to iron dextran instead of gleptoferron but pharmacodynamics can be considered comparable with both substances taking into account that the iron from iron dextran and gleptoferron has been shown to be used with similar efficiency in different comparative clinical studies.

Tolerance in the Target Species of Animals

The applicant has provided data regarding the tolerance under normal conditions of use in piglets 1 to 4 days old. These data came from several clinical efficacy studies and seem to confirm the good local and general tolerance of the product at the proposed dose.

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

IV.B Clinical Studies

The applicant has provided a number of clinical study reports (dose confirmation and field studies). In these trials, a similar efficacy was statistically demonstrated in comparison to reference products authorized for the same indication. Efficacy was based on adequate parameters such as plasma iron concentration, erythrocytes, haemoglobin or haematocrit.

As supportive data, a number of references from the published scientific literature were provided showing the efficacy of the formulation to prevent iron deficiency/anaemia in piglets.

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.

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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 veterinary Heads of 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.

None