LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Defixopzyl
(iron dextran, iron (III) ion)

SE/V/124/01/MR

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

PRODUCT SUMMARY

EU Procedure number Asp no	SE/V/124/01/MR 2021-0269
Name, strength and pharmaceutical form	Defixopzyl, 200 mg/ml, Solution for injection
Applicant	Pharmacosmos A/S, Rørvangsvej 30 DK-4300 Holbæk Denmark
Active substance(s)	iron dextran, iron (III) ion
ATC Vetcode	QB03AC
Target species	Piglets, calves
Indication for use	Prevention and treatment of iron deficiency anaemia in piglets and calves.

Product name Defixopzyl	Application number SE/V/124/01/MR
Applicant Pharmacosmos A/S	MRP
Publicly available assessment report	

PRODUCT INFORMATION

The Summary of Product Characteristics (SPC), the labelling and package leaflet for this veterinary medicinal product (VMP) is available in the Union Product Database (UPD).

SUMMARY OF ASSESSMENT

Legal basis of original application*	Well established veterinary use application application in accordance with Article 22 of Regulation (EC) 2019/6 as amended.
Date of completion of the original mutual recognition procedure	2023-05-03
Date veterinary medicinal product first authorised in the Reference Member State (MRP only)	2022-06-21
Concerned Member States for original procedure	N/A (national procedure)
Concerned Member States for subsequent recognition procedure	N/A
Withdrawn CMS during original <mutual recognition> <decentralised><subsequent recognition> procedure	N/A

*Please be aware that certain parts of the dossier may be varied and consequently be subject to protection of technical documentation – for these and other changes of referenceability to parts of the dossier, please see chapter POST-AUTHORISATION PROCEDURES

1. SCIENTIFIC OVERVIEW

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

The veterinary medicinal product (VMP) is produced and controlled using validated methods and tests, which ensure the consistency of the VMP released on the market.

It has been shown that the VMP can be safely used in the target species; the reactions observed are indicated in the SPC.

The VMP 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 VMP was demonstrated according to the claims made in the SPC.

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

2. QUALITY DOCUMENTATION (physicochemical, biological or microbiological information)

A. Product description

The VMP contains Iron (III) hydrogenated dextran complex equivalent to 200 mg elementary iron and the excipients phenol as preservative, hydrochloride acid or sodium hydroxide as pH adjustment, sodium chloride as an excipient and water for injection as a diluent.

The primary packaging materials for Defixopzyl 200 mg/ml consist of either 100 ml and 200 ml collapsible vials (LDPE) covered in aluminium sachets, or glass vials. The vials are closed with rubber stoppers. The glass vial is a standard pharmacopoeial item (Ph.Eur. type II).

The primary packaging materials all conform to Ph.Eur. and have been selected for quality reasons as well as for suitability and compatibility with the product.
Phenol is used as a preservative and the choice of the phenol as a preservative is justified.

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

B. Description of the manufacturing method

The VMP is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.

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

C. Production and control of starting materials

The active substance is Iron (III) hydrogenated dextran 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 have been provided.

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

D. Control tests carried out on isolated intermediates during the manufacturing process

N/A

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 VMP.

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.

F. Stability tests

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.

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

G. Other information

N/A

3. SAFETY DOCUMENTATION (safety and residues tests)

A. Safety tests

Pharmacological and toxicological studies

The applicant has provided bibliographical data which show that iron (III)hydroxide is a well-established used substance to treat iron deficiency anaemia and to correct haemoglobin deficit and to regenerate iron storage. The pharmacodynamic, pharmacokinetic and toxicology is well known. Iron-containing products have been associated to anaphylactic reactions after injection. Iron dextrans have been shown to be teratogenic and embryocidal in animals. In addition, parenteral iron dextran may also cause exacerbation of inflammatory synovitis in affected joints in anaemic rheumatoid patients. Furthermore, the veterinary medicinal product may cause skin and eye irritation.

User safety

The applicant has provided a user safety assessment in compliance with the relevant guideline, which shows that there is a risk associated with accidental self-injection. In addition, a potential risk was identified following dermal and eye exposure. People hypersensitive to iron should avoid contact with this product. This product is not recommended to be handled by pregnant women or women planning to be pregnant due to the risk of unintended self-injection.

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

Environmental Risk Assessment

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

Phase I:

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because:

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment.

B. Residues documentation

Residue tests

No residue depletion studies were conducted because since piglets are treated in the first week of life, and calves with a much smaller dose compared to piglets, no residues will be detectable at the time of slaughter. Phenol, used as a preservative, has a rapid metabolism and is therefore not an issue for consumer's safety. EU commission regulation 37/2010 requires no maximum residue levels and no marker residue to be established for iron dextran and phenol in any food producing species.

Maximum Residue Limits

Iron dextran and phenol are included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 as follows:

Pharmaco-logically active substance	**Marker residue**	**Animal species**	**MRLs**	**Target tissues**	**Other provisions**	**Therapeutic classification**
Iron dextran	NOT APPLICABLE	All food producing species	No MRL required	NOT APPLICABLE	NO ENTRY	NO ENTRY
Phenol	NOT APPLICABLE	All food producing species	No MRL required	NOT APPLICABLE	NO ENTRY	NO ENTRY

Withdrawal Periods

Based on the data provided above, a withdrawal period of 0 days for meat in piglets and calves are justified.

4. EFFICACY DOCUMENTATION (preclinical studies and clinical trials)

This application was submitted in accordance with Article 22 of Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018, a so called well established veterinary use application.

The proposed indication was:
Treatment and prevention of iron deficiency anaemia in piglets and calves.

The proposed dose was:
Defixopzyl is administered as a single intramuscular or subcutaneous injection. The treatment may be repeated once.

Piglets: Prophylactic at 1-4 days of age and curative 1 ml per pig.
Calves: 5 ml.

The applicant submitted scientific literature from the public domain, as well as studies which appear to be unpublished studies or studies that are not published in peer-review papers, to fulfil part IV of the dossier. A description of the strategy used for literature search was provided. In the literature provided, a number of different products were used. In all studies except one, iron dextran was the active pharmaceutical ingredient. In 40 % of the studies the product used was manufactured by the applicant. In consideration of the fact that this concerns injectables where any differences in excipients may have limited effect on exposure, the products can be considered sufficiently comparable to Defixopzyl.

With regards to the appropriateness of the legal base, the applicant provided several published references which are older than 10 years. The active substance has been used as a veterinary medicinal product in the community for more than ten years.

During the procedure it was suggested by CMS that the indication should start with prevention. The indication was therefore amended to “Prevention and treatment of iron deficiency anaemia in piglets and calves.”.

Regarding section 3.9 of the SPC (Administration routes and dosage) some amendments were made during the procedure to address concerns raised by CMS. Objections to include the subcutaneous administration routes were raised and the applicant agreed to delete this route of administration from the SPC.

Concerns were raised regarding the safety and efficacy of a second injection, and it was suggested to include information on when a second dose may be safely administered to piglets and calves. It was also suggested to include information on when a first injection should be administered to calves.

The applicant submitted references to support that a second injection can be safely administered to piglets after a minimum of five days. A second injection may be administered to calves after a minimum of eight days, in line similar approved products. In calves, the need for a second injection should be determined by e.g., haemoglobin screening.

The final approved dosage regimen is:

Intramuscular use.

Piglets: 200 mg of iron per piglet corresponding to 1 ml per piglet at 1-4 days of age.
Calves: 1000 mg of iron per calf corresponding to 5 ml per calf at 1-10 days of age.

If needed, treatment may be repeated once after a minimum of 5 days in piglets and after a minimum of 8 days in calves. In calves, the need for a second injection should be determined by e.g., haemoglobin screening.

A. Pre-Clinical Studies

Pharmacology

Data on pharmacodynamics and pharmacokinetic properties of iron dextran were provided from public literature. The applicant also submitted literature to describe the toxicological profile of iron in more general terms, by use of data from both animals and humans.

Iron is an essential component of every cell in the body. Without a sufficient supply of iron, haemoglobin cannot be synthesized and the number of erythrocytes in the blood cannot be maintained at an adequate level. Iron deficiency anaemia can occur in young animals that are mainly confined to a milk diet. This condition is well-known in piglets but have also been reported to occur in calves, particularly under certain management conditions. Concerns about the neonatal iron status have also been raised in pre-weaned dairy calves fed on whole milk. Modern dairy calves may grow at a rate which leads to an increased iron demand.

Iron deficiency anaemia can also occur secondary to chronic blood loss which may in some instances be a result of particular infections or parasitic infestations. The use of the product under these conditions can be regarded covered by an indication for the prevention and treatment of iron deficiency anaemia. Iron deficiency anaemia can result in negative consequences such as increased incidence of disease and reduced growth

Dose determination and confirmation

Published literature were presented in support of the efficacy at the selected dose, see below.

Tolerance in the target species of animals

A number of published studies, as well as unpublished reports of older studies performed by the applicant, were presented in support of tolerance in piglets. The latest Period Safety Update Report (PSUR) for Uniferon and Solofer was also provided.

Administration of iron dextran to piglets is normally well-tolerated. Adverse reactions, sometimes with fatal outcome, may very rarely occur in piglets. These types of reactions were not reported in the references provided by the applicant but are known side effects of iron dextran. Appropriate warnings are included in the product information. Mild local reactions (staining) at the injection site were observed in one of the studies.

Tolerance in cattle has not been extensively investigated in specific studies. However, the presented studies do not raise any concerns regarding tolerance in cattle and iron dextran are already approved for use in calves at similar dosages in the EU.

B. Clinical trials

No clinical studies were performed. Instead, published literature were presented in support of the efficacy at the selected dose.

Studies in pigs

A large number of references (peer-reviewed papers and what appears to be unpublished trial reports) were provided by the applicant in support of the proposed indication.

Literature of studies performed within the EU as well as outside the EU were provided. In several of the studies, Uniferon was used. This product is considered equivalent to Defixopzyl. In most of the studies, 200 mg was the administered dose, and product was administered subcutaneously or intramuscularly to piglets during the first days of life. Taken together, the studies presented are considered to provide sufficient support for the indication prevention of iron deficiency anaemia and the proposed dose of 200 mg in piglets aged 1–4 days. This indication and the proposed dose of 200 mg in piglets is considered well-established. In clinical practice, piglets are administered iron routinely during the first days of life since anaemia otherwise develops rapidly. Identifying piglets that are already anaemic from those that have developed some degree of anaemia at time of this routine treatment is neither feasible nor necessary. Although the main objective with administering iron to newborn piglets is to prevent anaemia, in clinical practise this will be a mixture of prevention and treatment. Consequently, it can be accepted that the claim includes both prevention and treatment.

Results from some of the references indicate that administrating a second dose of iron may be beneficial in some instances. The statement in 4.9 of the SPC that treatment may be repeated once is therefore considered justified. The applicant provided references supporting that a second injection can be safely administered after a minimum of five days.

Studies in calves

A number of references has been provided in support of the proposed indication in calves. Two studies are considered to provide support for the indication prevention of iron deficiency anaemia at the proposed dose of 1000 mg in calves.

In a study by Mohri *et al.* 2010 (Effects of parenteral supply of Iron on RBC parameters, performance, and health in neonatal dairy calves. Biological Trace Element Research, 136(1), 33–39) ten calves, aged two days, were administered 1000 mg of iron as iron dextran. Haematological parameters were numerically improved in calves administered iron up to six weeks after treatment, but no statistically significant difference was demonstrated (possibly due to lack of power). Daily weight gain was increased compared to controls.

In a multi-center study by Allan *et al.* 2020 (The effect of iron dextran injection on daily weight gain and haemoglobin values in whole milk fed calves. *Animals*,10(5), 853.), 237 dairy calves (Holstein, Friesian, and Jersey crosses) fed on whole milk were randomly allocated to either receive an intramuscular injection of 1000 mg iron as iron dextran (Uniferon 20% Injection, Pharmacosmos) or no injection. Calves had the iron injection between one and ten days of life. Treated calves showed a significantly higher daily live weight gain within the first six weeks compared to controls (difference 78 g/day, $p<0.001$, total difference over 6 weeks 3.3 kg). There was no significant effect on weight gain between week six and twelve weeks. Injected calves had higher haemoglobin levels at six weeks compared to controls (110.7 vs 94.9 g/L, $p<0.001$). Number of calves with Hb levels under 90 g/L (classified as low) at six weeks was six in injected group, compared to 40 in control group ($p<0.001$). At week 6, haemoglobin levels in the treatment group had increased by 3.4 g/l compared to a decrease in the control group of 12.1 g/l. Calves with a higher growth rate from one to six weeks were more likely to have low Hb levels at six weeks. There was farm variation in both Hb levels and weight gain, with more pronounced differences between groups at some of the farms.

5. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The applicant has provided documentation in support that the active substance has been in well-established use within the Union for over 10 years. The product has been shown to be efficacious for the “Prevention and treatment of iron deficiency anaemia in piglets and calves.” This use can be considered well-established according to Article 22 of Regulation (EU) 2019/6.

The data submitted in the dossier demonstrate that when the VMP 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 VMP for humans and the environment is acceptable.

POST-AUTHORISATION PROCEDURES

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the VMP. The current SPC is available in the Union Product Database (UPD).

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 VMP.

None

or

Complete this section for significant variations, using the table shown below.

Some examples of significant changes in safety or efficacy data are:

- Changes to pharmacokinetic data leading to a change in the SPC
- Changes to toxicological data leading to a change in the SPC
- Changes to user safety warnings
- Changes to ecotoxicological information as given in the SPC or changes to disposal warnings
- New residue studies in new target species or tissues
- Reassessment of residue data or new studies resulting from changes to MRL
- Changes to withdrawal period
- Changes to target species
- Changes to target species tolerance data leading to change in warnings/precautions for target species
- New or changed indications
- Any change affecting the referenceability of the dossier

Significant changes in quality data include any variation requiring assessment (VRA), which affects the initial report and/or the SPC.

Sequence of significant variations

Changes to Part 2 of the dossier (quality)

Summary of change (Application number)	Approval date
<Example: Change in shelf-life> (MS/V/XXX/X/A/XX)	

Changes to Part 3 and/or Part 4 of the dossier (safety/efficacy)

Summary of change (Application number)	Supporting information	Approval date
<Example: Addition of target species - pigs> or <addition of indication <xxx>> (MS/V/XXX/X/….) *etc.*	*<Please choose relevant information and delete all information not needed>* <proprietary> <bibliographic> data> *<In case of proprietary/bibliographic data please outline if there is an impact on the protection period; otherwise delete>* Qualified for data protection: <yes><no> <Update according to the reference product> <Reference to <proprietary><bibliographic> data of a <linked> VMP: *<Please state the details of the product referred to.>* <Product name> <strength> <pharmaceutical form> <MAH><MS where the Product is/ has been authorised*<if not authorised in the RMS>*> *<In case reference to a linked VMP is made, please specify:>* *<For originally full dossiers referring to a linked VMP, e.g. a generic/hybrid of the present VMP>*	

	<The product referred to is a generic/hybrid VMP of the present product> *<For originally generic/hybrid dossiers>* <The product referred to is a VMP belonging to the same MA as the reference veterinary medical product of the present product> *<For originally generic/hybrid dossiers>* <The product referred to is a generic/hybrid VMP of the same reference veterinary medical product used for the present product>	