IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0686/001/001
Case No: 2058562

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Guerbet

BP 57400, **95943 Roissy CdG cedex**, **France**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

ENDOREM, 11.2 mg Fe/mL, concentrate for suspension for infusion

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **23/08/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

ENDOREM, 11.2 mg Fe/mL, concentrate for suspension for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

- Per 1 mL:

Superparamagnetic iron oxide nanoparticles	15.8 mg
corresponding to an iron content	11.2 mg

After dilution in 100 mL of 5% isotonic glucose solution, 1 mL contains 0.112 mg of iron

- Per ampoule (8 mL):

Superparamagnetic iron oxide nanoparticles	126.500 mg
corresponding to an iron content	89.600 mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for suspension for infusion.
Dark brown to black dispersion of iron oxide nanoparticles

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

This product is for diagnostic use only.

Detection of liver tumours by MRI (Magnetic Resonance Imaging).

4.2 Posology and method of administration

The recommended single dose is 15 µmoles Fe/kg of body weight, i.e. 0.075 mL/kg body weight.

The product must be administered by slow infusion for a period of at least 30 minutes, after dilution in 100 mL of 5 % isotonic glucose solution.

Good practice of emergency resuscitation techniques is essential, and the appropriate medicinal products and equipment must be available.

The imaging is optimal between 30 minutes and 6 hours after the administration of ENDOREM.

The radiologist will choose the most effective method of imaging.

Dosage remains unchanged in subjects with liver or renal insufficiency.

The safety and efficacy in patients under 18 years old have not been established.

4.3 Contraindications

Hypersensitivity to active ingredient, Dextran or to any the other excipients

4.4 Special warnings and precautions for use

- Never administer the product without first diluting it.
- Since the risk of hypotension is decreased when the product is administered by slow IV injection, ENDOREM should only be administered by slow IV injection.
  Hypotension may nevertheless occur in rare instances.
- Particular attention must be paid to the quality of the intravenous injection since local irritation following paravenous administration may occur.
- Administration of ENDOREM must not be repeated within the 14 days following the examination, as the active ingredient (iron oxide) alters the biological parameters related to iron metabolism during this period.
- In the event of lumbar pain, chest pain, hypotension, or dyspnoea, the infusion must be stopped and the patient kept under medical surveillance until the symptoms disappear. The administration of ENDOREM can then be continued under medical supervision by reducing the infusion rate and spreading the infusion over at least 60 minutes.
- Although the Dextran contained in ENDOREM has a low molecular weight, its administration may induce immediate and severe anaphylactoid reactions. For this reason, particular attention must be paid during the administration of the product (oxygen equipment, adrenaline, antihistaminic medication and corticosteroids must be available for immediate treatment of such reactions).
- The use of ENDOREM is not justified in patients with haemochromatosis, due to the natural signal extinction in the liver of these patients.
- In case of blood disease associated with splenomegaly, the diagnostic efficacy may be reduced.
- The incidence of adverse drug reactions, particularly lumbar pain, is increased for cirrhotic patients: care is urged during the administration in such patients.
- The safety and efficacy in patients under 18 years old have not been established.

4.5 Interaction with other medicinal products and other forms of interaction

In the absence of specific studies, no other substances should be mixed with ENDOREM.

4.6 Pregnancy and lactation

Pregnancy :

Studies performed in animal demonstrated a teratogenic effect of ENDOREM in rabbit at doses 160 fold higher than the recommended therapeutic dose.
There are currently no human clinical data relevant enough to enable the assessment of a possible malformative or foetotoxic risk associated with the administration of ENDOREM during pregnancy.
Therefore, the use of ENDOREM is not recommended during pregnancy. This should not lead to the systematic advising of an induced abortion in the case of inadvertent exposure during pregnancy, but to a careful attitude with adapted prenatal monitoring.

Lactation :

No data are available on the passage of ENDOREM into breast milk. Therefore, breast feeding should be interrupted for a few days following Endorem administration.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Most side effects in association with ENDOREM are transient.
The frequency of the adverse effects reported is not known:

Immune system disorders: Not known (cannot be estimated from the available data)
Anaphylactoid reactions may occur: hypotension, dyspnoea, pruritus, urticaria, facial oedema, skin rash, anaphylactic shock and bronchospasm.

Nervous system disorders: Not known (cannot be estimated from the available data)
Headache

Cardiac disorders: Not known (cannot be estimated from the available data) Tachycardia

Vascular disorders: Not known (cannot be estimated from the available data)
Blood pressure fluctuation, flushing

Respiratory, thoracic and mediastinal disorders: Not known (cannot be estimated from the available data)
Dyspnoea

Gastrointestinal disorders: Not known (cannot be estimated from the available data)
Nausea, vomiting, abdominal pain.

Musculoskeletal and connective tissue disorders: Not known (cannot be estimated from the available data)
Back pain (especially lumbar pain).

General disorders and administration site conditions: Not known (cannot be estimated from the available data)
Chest pain, feeling hot, chills, hyperhidrosis.

4.9 Overdose

In case of overdosage (for example accidental bolus injection of the whole ampoule), vital signs should be monitored. Symptomatic treatment may be given if necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code : V08CB03 superparamagnetic iron oxide nanoparticles (superparamagnetic contrast agent for MRI).

The crystalline configuration of the solid iron oxide gives the product its superparamagnetic properties. The magnetic field disturbances generated around each particle reduce MRI signal intensity in the tissues which contain it.

Under the recommended clinical conditions, the product has shown a satisfactory tolerance profile in animals and in humans in terms of effects to the cardiovascular system, the kidney or the lung.

5.2 Pharmacokinetic properties

Pharmacokinetic studies have identified the liver as the organ showing the most uptake of the product. After intravenous injection, the blood is rapidly cleared of the product by the liver. The iron oxide particles disappear from the storage organs (liver, spleen, etc...) over a matter of days, which indicates that the product is metabolised and the iron is then incorporated into normal iron metabolism, specifically into haemoglobin.

5.3 Preclinical safety data

In the preclinical plan, ENDOREM has been found to have low toxicity after single and repeated dose administration except for effects at the injection site.

In case of accidental perivascular administration, a local effect has been observed such as erythema and skin pigmentation, which eventually reverted to normal. There is no specific data concerning intra arterial local tolerance. In rabbits, the product was teratogenic at a dose of 11.2 mg Fe/kg per day inducing particularly malformations of the heart, skull, brain, etc. In rats, daily doses of 11.2 mg Fe/kg per day caused no malformations. Higher doses were toxic to the mother and decreased growth rates (foetuses and neonates of lower weight). No fertility studies or peri-and post-natal toxicity studies have been carried out. The product was not found to be mutagenic in the in vivo and in vitro tests used. The passage of the product into milk has not been studied.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dextran
Citric acid
Mannitol
Water for injections

6.2 Incompatibilities

Based on the physico-chemical studies carried out, ENDOREM must not be diluted with a 0.9% sodium chloride solution.

6.3 Shelf Life

- Shelf life of the medicinal product as packaged for sale : 3 years.
- Shelf life after dilution : Chemical and physical in-use stability has been demonstrated for 7 days between +15°C and +25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 30°C.
Do not freeze.

6.5 Nature and contents of container

8 mL in 10 mL-ampoule (type I neutral glass) accompanied with an infusion set (PVC) including a 5 µ filter (polyamide) and a syringe (polypropylene) with a needle (stainless steel) for infusion preparation.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Before use, the ampoule must be inverted several times.
The product must be diluted before use. For single use only. Discard any unused solution.

Using the syringe and needle (supplied with the ampoule), the dose corresponding to the patient's weight must be diluted using aseptic technique in 100 mL of a 5% glucose solution exclusively before slow intravenous administration through the infusion set fitted with a filter (supplied with the ampoule) for at least 30 minutes.

Since the colour of the product prevents visual inspection, the filter guarantees the absence of large particles during the infusion.

7 MARKETING AUTHORISATION HOLDER

GUERBET
BP 57400
95943 Roissy CdG Cedex
France

8 MARKETING AUTHORISATION NUMBER

PA 686/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 March 1995
Date of last renewal: 23 August 2009

10 DATE OF REVISION OF THE TEXT

August 2009