SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Resotran 540 mg/ml suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml suspension for injection contains 540 mg ferucarbotran, equivalent to 28 mg or 0.5 mmol iron.

Each vial of 1.5 ml suspension for injection contains 810 mg ferucarbotran, equivalent to 42 mg or 0.75 mmol iron.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection
Reddish brown suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only. [Invented name] is a contrast agent to be used for magnetic resonance imaging (MRI) of the focal liver lesions when examination without contrast media has given uncertain findings.
[invented name] is indicated in adults.

4.2 Posology and method of administration

Diagnostic procedures that involve the use of contrast agents should be carried out under the direction of a physician with the requisite training and a thorough knowledge of the procedure to be performed.

Posology

Adults
The recommended dose of [invented name] for adults is:
For patients weighing less than 60 kg: 0.9 ml [invented name] (equivalent to 486 mg ferucarbotran or 0.45 mmol iron)
For patients weighing 60 kg or more: 1.4 ml [invented name] (equivalent to 756 mg ferucarbotran or 0.7 mmol iron)

Elderly and renal or hepatic impairment
No dose adjustment is considered necessary.

Repeated dose
No clinical information is available for repeated administration of [invented name] (see section 4.4 “Special warnings and precautions for use”). [invented name] should not be readministered before the signal loss in the liver has returned to the baseline levels. This will take at least 14 days.

Paediatric population
[invented name] should not be used in children and adolescents because of the absence of safety and efficacy data in patients under 18 years old.

Method of administration

[invented name] is a ready-to-use aqueous suspension for injection indicated for intravenous administration only. It is to be administered through a large-bore needle or indwelling catheter (18-20 gauge is recommended) with connection tube, if required.
To ensure proper placement of the injection needle, it is recommended to inject sterile 9 mg/ml (0.9%) saline solution before administration of [invented name].

After the injection of the contrast medium the connective tubing and the needle should be flushed using sterile 9 mg/ml (0.9%) saline solution.

For single use only, any unused suspension should be discarded in accordance with the local requirements.

For patient preparation, see section 4.4.

Image acquisition
Immediately after the bolus injection of [invented name] dynamic imaging is recommended using e.g. of T_2* -weighted or T_1-weighted gradient echo sequences (GRE).
Accumulation-phase imaging can be performed from 10 minutes to at least 8 hours post injection using T_2 or T_2* -weighted MR techniques, e.g. conventional T_2- spin echo (SE) or fast spin echo/ turbo spin echo (FSE /TSE)).

Diagnostic information about the intrahepatic vascular structure can be obtained by e.g. MR angiographic time-of-flight sequences (TOF) within 20 minutes post injection (p.i.) of [invented name].

4.3 Contraindications

Hypersensitivity to ferucarbotran or to any of the excipients, Hypersensitivity to dextran.
Known severe hypersensitivity to other parenteral iron products.

4.4 Special warnings and precautions for use

[Invented name] should only be administered when staff trained to evaluate and manage anaphylactic reactions is immediately available, in an environment where full resuscitation facilities can be assured. The patient should be observed for adverse effects for at least 30 minutes following each [invented name] injection.

Hypersensitivity
It has been observed that [invented name] induces anaphylactoid (hypersensitivity) reactions in dextran-sensitized dogs. Those reactions comparable to the Dextran Induced Anaphylactic Reaction (DIAR) might also occur in humans with hypersensitivity to dextran (see 4.3 “Contraindications”, 4.8 “Undesirable effects” and 5.3 “Preclinical safety data”). Appropriate drugs and equipment in order to deal with such adverse events should be at hand when [invented name] is used.

Severe hypersensitivity reactions to other parenteral iron products, have been reported.

As with other intravenous contrast agents, [invented name] can be associated with anaphylactoid/hypersensitivity or other idiosyncratic reactions, characterized by cardiovascular,

respiratory or cutaneous manifestations, and ranging to severe reactions including shock. Most of these reactions occur within one hour after the administration of [invented name]. However, delayed cutaneous reactions have occurred (hours later or up to several days) (see 4.8 Undesirable effects).

Monitor carefully patients for signs and symptoms of hypersensitivity reactions during and following each administration of [invented name].
Medication for the treatment of hypersensitivity reactions as well as preparedness for institution of emergency measures are necessary.

The risk of hypersensitivity reactions is higher in case of:

- previous reaction to contrast media
- history of bronchial asthma
- history of allergic disorders

In patients with an allergic disposition including a history of asthma, special caution should be exercised because among them a two-fold higher incidence of adverse events has been observed.

Hemosiderosis
In patients with disorders associated with iron overload (e.g., haemosiderosis, chronic haemolytic anaemia with frequent blood transfusions, or chronic iron replacement) it should be noted that a high iron content in the liver affects the signal intensity of the liver, therefore the benefit of [invented name] might be limited.

Paravenous injection
To avoid paravenous injections which may lead to long-lasting local discolouration of the skin (see 5.3 “Preclinical safety data”), it is necessary to ensure the correct placement of the injection needle by flushing with sterile 9 mg/ml (0.9%) saline solution before injection of [invented name] (see 4.2 “Posology and method of administration”).

Repeated administrations
No information is available about repeated use with [invented name]. [invented name] should not be readministered before the signal loss in the liver has returned back to the baseline levels. This will take at least 14 days.

Patient preparation
Nausea and vomiting are known side effects that may occur with the use of contrast media (see also section 4.8 “Undesirable effect”). Therefore, the patient should not eat for two hours before examination to avoid aspiration.

Specific warnings
This medicinal product contains less than 1 mmol sodium (23 mg) per 1.4 ml, i.e. essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions with other medicinal products have been observed. No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy
Clinical experience of [invented name] in pregnant women is limited. Animal studies have shown reproductive toxicity in doses far beyond the reocmmended diagnsotic doses (see section 5.3

"Preclinical safety data"). The potential risk for humans is unknown. [invented name] should not be used in pregnant women or women supsected of being pregnant, if not absolutely necessary.

Foetal bradycardia may occur following administration of parenteral irons. It is usually transient and a consequence of a hypersensitivity reaction of the mother. The unborn baby should be carefully monitored during intravenous administration of parenteral irons to pregnant women.

Breastfeeding
No transfer of ferucarbotran or metabolised iron into breast milk was observed in lactating rats, within 24 hours. It is not known if [invented name] is excreted into breast milk in humans. Therefore [invented name] only should be given during lactation after special consideration. Breastfeeding should be interrupted while milk should be drawn and discarded for a few days following [invented name] administration.

4.7 Effects on ability to drive and use machines

No effects have been observed. No studies on the effects on the ability to drive and use machines have been performed. Patients driving vehicles or operating machinery should take into account that nausea may incidentally occur.

4.8 Undesirable effects

Frequency of adverse reactions from clinical trial data:
During the clinical development phase the overall incidence of adverse reactions which were classified as related was 7.6%. In patients with an allergic disposition including a history of asthma, special caution should be exercised because among them a two-fold higher increase of adverse reactions has been observed. There is no difference with regard to severity or quality of the symptoms.

The most commonly reported adverse reactions were pain, vasodilation (feeling of warmth) and paraesthesia (feeling of coldness) which were reported in less than 2% of patients. Most of the adverse reactions were mild to moderate in intensity.

Based on the experience with more than 1000 patients, the following adverse reactions were observed and classified by investigators as drug-related, where a connection between the drug and the adverse event is judged to be possible, probable or certain.

The table below reports adverse reactions by MedDRA system organ classes (MedDRA SOCs).

System Organ Class	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Not known**
Immune system disorders			Hypersensitivity reaction	Anaphylactoid shock Anaphylactoid reaction
Psychiatric disorders			Anxiety	
Nervous system disorders	Paraesthesia	Headache Dysgeusia	Convulsion Dizziness Hypoesthesia Parosmia	Loss of consciousness Depressed level of consciousness
Eye disorders				Conjunctivitis
Cardiac disorders		Chest pain		Cardiac arrest Tachycardia
Vascular disorders	Vasodilatation		Hypertension Phlebitis	Circulatory collapse Hypotension

				Flushing
Respiratory, thoracic and mediastinal disorders			Dyspnea Cough increased Rhinitis	Respiratory arrest Bronchospasm Cyanosis Oropharyngeal swelling
Gastrointestinal disorders		Vomiting Nausea		Abdominal pain
Skin and subcutaneous tissue disorders		Pruritus Rash	Urticaria Eczema	Angioedema Hyperhidrosis Erythema
General disorders and administration site conditions	Pain	Asthenia Back pain Injection site reaction		Feeling hot Face edema
Investigations				Plasma iron and ferritin increased Factor XI activity decreased Prolonged activated partial thromboplastin time (aPTT)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.
In association with a decrease in factor XI activity (maximum decrease of the mean about 15%), occasionally a transient and slight increase of activated partial thromboplastin time (aPTT) may occur at 4 – 6 hours after injection time, not resulting in a relevant effect on the overall bleeding time, the coagulation system (Quick test) remains unaffected.

After administration of ferucarbotran a dose-dependent increase in plasma iron (mean and medium values at 2 to 4 hours in 24 hours follow up) and ferritin level (between 12 hours and 21 days) was observed in healthy volunteers, whereas the total iron-binding capacity was unaffected. As observed with other paramagnetic complexes, in rare cases hypersensitivity reactions and anaphylaxis have been reported including shock that requires immediate medical intervention.
Delayed cutaneous reactions have been rarely reported (see 4.4 Special warnings and precautions for use).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

4.9 Overdose

Acute toxicity studies showed no risk of acute intoxication on use of [invented name].

The drug has been proved to be safe up to 0.08 ml (equivalent to 40 micromol Fe)/ kg body weight in healthy volunteers (approx. 4 times of the diagnostic dose) (see section 4.2 “Posology and method of administration”).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Superparamagnetic contrast media, ATC code: V08CB03, Iron oxide, nanoparticles

[invented name] is a stable aqueous suspension of superparamagnetic iron oxide (SPIO) nanoparticles coated with carboxydextran. The coated iron oxide particle size is comparable to large biological proteins.
By virtue the superparamagnetic properties of the iron oxide, the contrast agent shortens predominantly the T2 relaxation time and causes distortion of local magnetic field, both mechanisms producing a pronounced signal loss in the neighbourhood of the iron oxide, particularly on T_2 and T_2* -weighted images. The T_2* effect is particularly pronounced after [invented name] is phagocytosed by the reticulo-endothelial cells (RES) during the accumulation phase.
By this the SPIO enhanced MRI is differentiating between benign and malign lesions based on their cellular composition and function (RES cells only in normal liver tissue and benign tumors).

In addition, the high T_1 relaxivity of [invented name] can be utilized for dynamic imaging during the vascular phase and for delineation vessels by Magnetic Resonance Angiography (MRA) sequences.

The physico-chemical characteristics of the ready-to-use suspension of [invented name] are:

Osmolality at 37°C (mOsm/kg H_2O)	314
Viscosity at 37°C (m Pas)	1.0
Density at 37°C (g/ml)	1.061
pH	5.5 – 7.0

5.2 Pharmacokinetic properties

Distribution and Elimination
After single intravenous administration ferucarbotran is distributed within the intravascular space and disappears quickly - in a bi-phasic manner - from the blood/ plasma by selective uptake by the reticuloendothelial system (RES), predominantly into the liver and spleen.

Biodegradation of the iron oxide core of ferucarbotran takes place within the cells of the RES. Biotransformation finally ends in incorporation of the iron of ferucarbotran into the “normal body iron pool”. Thus, the fate of the iron of ferucarbotran is finally identical to that of the normal biologically available iron.

At the maximum diagnostic dose of 1.4 ml of the medicinal product (equivalent to 756 mg ferucarbotran or 39 mg Fe) per patient, the total body iron will only increases very slightly (< 2%).

C_{max} increased proportionally in the dose range of 5-40 micomol Fe/kg. In clinical trials (Phase I) the half-life of ferucarbotran iron in serum for the initial phase, $t_{1/2\alpha}$ was found to be 0.26 ±0.19 hours or less and at the terminal phase, $t_{1/2\beta}$ 4.36 ±0.75 hours or less. The half-lives $t_{1/2\alpha}$ and $t_{1/2\beta}$ were not significantly related on the administered doses.

Elimination of Carboxydextran
In animal studies (rats) it was shown that the main portion (>70%) of the carboxydextran of ferucarbotran is subject to fast renal elimination. About 20% of carboxydextran showed a biodistribution very similar to that of the iron oxide core of ferucarbotran, suggesting that this fraction of carboxydextran accumulates in the organs of the RES (especially in the liver and spleen) without dislocation from the iron core of ferucarbotran. As for the iron oxide core there is a continuous elimination of carboxydextran from the liver.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Ferucarbotran showed no effects on fertility and general reproductive performance of male and female rats and was non-teratogenic in rats and rabbits. Only at high multiples of the diagnostic dose given daily over the period of organogenesis, ferucarbotran caused post-implantation and prenatal losses and delays in development of pups of rats (at 0.5 mmol/Fe/kg/day, representing about 50 times the diagnostic dose) and increased resorption rate and reduced the number of live foetuses in rabbits (at 0.8 mmol Fe/kg/day representing about 80 times the diagnostic dose).

In local tolerance studies paravenous, intramuscular or intracutaneous administration led to local inflammatory reactions at the site of administration. Inadvertent misplacement of the injection of [invented name] may result in a long-lasting pigment-like discolouration of the skin at the administration site as a result of local retention of the iron particles. Thus, intravenous administration should be strictly adhered to when [invented name] is applied in humans. [invented name] demonstrated no signs of sensitizing (contact-allergenic) potential in animal tests.

In dogs with dextran antibodies, [invented name] induced an immune response comparable to the Dextran Induced Anaphylactic Reaction (DIAR), indicating its potential to induce an anaphylactic reaction in humans with antidextran antibodies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

(S)-Lactic acid (E270)
Mannitol (E421)
Sodium hydroxide (E524) (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

Clear type I glass vial filled with 1.5 ml, sealed with a stopper of fluorinated bromobutyl rubber, crimped with crimping cap with coloured flip cap and packed in unit carton box.

1x 1.5 ml

6.6 Special precautions for disposal and other handling

After long standing of the preparation slight colour changes (dark to middle brown) may be observed, which disappear during normal handling. Inspect vial visually for damage and sediment before use. Use only those containing sediment-free homogeneous solution.

[invented name] is a ready-to-use aqueous suspension for injection and should not be diluted. Vial containing contrast agents are intended for single use only. [invented name] may not be drawn into the syringe until immediately before use.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

2024-09-24