Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Resovist 0.5 mmol Fe/ml, solution for injection, prefilled syringe.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 540 mg Ferucarbotran, corresponding to 0.5 mmol (28 mg) iron.
0.9 ml of the solution contains 486 mg Ferucarbotran and 1.4 ml contains 756 mg Ferucarbotran.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection, prefilled syringe,
reddish brown liquid

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Resovist 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.

4.2 Posology and method of administration

General information
Nausea and vomiting are known possible adverse events of all contrast media (see section 4.8). The patient should therefore refrain from eating for two hours prior to the investigation to avoid aspiration.

Method of administration
Resovist is a ready-to-use aqueous solution which is to be administered via the 5-µm filter included in the package through a large-bore needle or indwelling catheter (18-20 gauge is recommended) with connecting 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 the administration of Resovist.

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. A three-way stopcock connected to the tube can facilitate this procedure.
The tip cap should be removed from the syringe immediately before use.
For single-use only, any unused product should be discarded in accordance with the local requirements.
Immediately after the bolus injection of Resovist dynamic imaging is recommended using e.g. T_2*-weighted or T_1-weighted gradient echo sequences (GRE).

Accumulation-phase imaging can be performed from 10 min to at least 8 hours p.i. (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 vasculature can be obtained by e.g. MR-angiographic time-of-flight sequences (TOF) within 20 min. p.i. of Resovist.

The recommended dose of Resovist to adults is :
For patients weighing less than 60 kg : 0.9 ml Resovist (equivalent to 0.45 mmol iron).

For patients weighing 60 kg or more: 1.4 ml Resovist (equivalent to 0.7 mmol iron).

Dosage in elderly, renal or hepatic impaired patients:
No dosage adjustment is necessary.

Repeated Use:
No clinical information is available about repeated use with Resovist (see 4.4 “Special warnings and special precautions for use”)

Children and adolescents
No clinical experience is available with patients under 18 years of age. Usage of Resovist in these patients can therefore not be recommended.

4.3 Contraindications

Hypersensitivity to Ferucarbotran or to any of the excipients, Hypersensitivity to dextran.
The usual safety requirements for magnetic resonance imaging, especially the exclusion of ferromagnetic materials (e.g. pacemaker, vascular clips), also apply when using Resovist.

4.4 Special warnings and precautions for use

No clinical experience is available with patients under 18 years of age. Usage of Resovist in these patients can therefore not be recommended.

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.

It has been observed that Resovist 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 sections 4.3, 4.8 and 5.3). Appropriate drugs and equipment in order to deal with such adverse events should be at hand when Resovist is used.

Anaphylactoid /hypersensitivity reactions have been observed after the use of Resovist (see section 4.8). Serious reactions including anaphylactoid/allergic shock are possible. Most of these reactions occur within one hour after the administration of Resovist. However, delayed cutaneous reactions may occur (after hours to days).

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.

In patients with disorders associated with iron overload (e.g. hemosiderosis) it should be noted that a high iron content in the liver affects the signal intensity of the liver, therefore the benefit of Resovist might be limited.
To avoid paravenous injections which may lead to long-lasting local discolouration of the skin (see section 5.3), 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 Resovist (see section 4.2).
No clinical information is available about repeated use with Resovist. Resovist 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.

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 medicaments have been observed. No interaction studies have been performed.

4.6 Pregnancy and lactation

Clinical experience of Resovist in pregnant women is limited. Animal studies have shown reproductive toxicity in doses far beyond the recommended diagnostic doses (see section 5.3). The potential risk for humans is unknown. Resovist should not be used during pregnancy unless it is considered absolutely necessary.
No transfer of Ferucarbotran or metabolised iron into breast milk was observed in lactating rats, within 24 h. It is not known if Resovist is excreted into breast milk in humans. Therefore Resovist only should be given during lactation after special consideration. Breast feeding should be interrupted while milk should be drawn and discarded for a few days following Resovist administration.

4.7 Effects on ability to drive and use machines

No effects have been observed.

4.8 Undesirable effects

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 incidence of adverse reactions has been observed. There were no difference with regard to severity or quality of the symptoms.

The most commonly reported adverse reactions were pain, vasodilatation (feeling of warmth) and paraesthesia (feeling of coldness) which were reported in less than 2 % of the patients. Most of the adverse reactions were of mild to moderate intensity. Based on the experience with more than 1000 patients the following adverse reactions were observed, 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)
Immune system disorders			Hypersensitivity reaction
Psychiatric disorders			Anxiety
Nervous system disorders	Paraesthesia	Headache Dysgeusia	Convulsion Dizziness Hypoesthesia Parosmia
Cardiac disorders		Chest pain	
Vascular disorders	Vasodilatation		Hypertension Phlebitis
Respiratory, thoracic and mediastinal disorders			Dyspnea Cough increased Rhinitis
Gastrointestinal disorders		Vomiting Nausea	
Skin and subcutaneous tissue disorders		Pruritus Rash	Urticaria Eczema
General disorders and administration site conditions	Pain	Asthenia Back pain Injection site reaction	

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 (max decrease of the mean about 15%), occasionally a transient and slight increase in partial thromboplastin time (PTT) may occur, whereas the Quick test remains unaffected.
After administration of Resovist a dose-dependent increase in plasma iron and ferritin level was observed with a maximum level reached after 24 hours, 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 may need immediate medical intervention.

Post-Marketing
Anaphylactoid reactions/hypersensitivity

Anaphylactoid reactions/hypersensitivity have been reported uncommonly after the use of Resovist.

These reports include the clinical spectrum of signs and symptoms associated with allergy mediated reactions including cutaneous, cardiovascular, gastrointestinal and respiratory manifestations. Delayed cutaneous reactions have been rarely reported (see section 4.4). Severe immediate reactions such as anaphylactoid shock requiring emergency treatment have been rarely reported.

4.9 Overdose

Acute toxicity studies showed no risk of acute intoxication on use of Resovist.
The drug has been proved to be safe up to 0.08 ml (equiv. 40 micromol Fe)/kg body weight in healthy volunteers (approx. 4 times the diagnostic dose) (see section 4.2).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Superparamagnetic contrast media,
ATC-code: V08CB03, Iron oxide, nanoparticles
Resovist is a stable aqueous solution of superparamagnetic iron oxide nanoparticles coated with carboxydextran. The coated iron oxide particle size is comparable to large biological proteins.
By virtue of the superparamagnetic properties of the iron oxide, the contrast agent shortens predominantly the T_2 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 especially pronounced after Resovist is phagocytosed by the reticulo-endothelial system (RES) cells during the accumulation phase.
In addition, the high T_1 relaxivity of Resovist can be utilized for dynamic imaging during vascular phase and for delineating vessels by Magnetic Resonance Angiography (MRA) sequences.

The physico-chemical characteristics of the ready-to-use solution of Resovist are:

Osmolality at 37 °C (mOsm/kg H_2O)	333
Viscosity at 37 °C (mPa x s)	1.03
Density at 37° C (g/ml)	1.057
pH	5.5 - 7.0

5.2 Pharmacokinetic properties

Distribution and elimination
After single intravenous administration Resovist is distributed within the intravascular space and disappears quickly – in a bi-phasic manner - from blood/plasma by selective uptake by the 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 Resovist is finally identical to that of the normal biologically available iron.

At the maximum diagnostic dose of 1.4 ml Resovist (equiv. 39 mg Fe) per patient the total body iron will only increase very slightly (< 2 %)
C_{max} increased proportionally in the dose range 5-40 micromol Fe/kg. In clinical trials (Phase I) the half-life of Resovist iron in serum for the initial phase, $t_{½\alpha}$, was found to be 0.26 ± 0.19 hours or less and for the terminal phase, $t_{½\beta}$ 4.36 ± 0.75 hours or less. The half-lives $t_{½\alpha}$ and $t_{½\beta}$, were not significantly related to the administered doses.

Elimination of carboxydextran
In animal studies (rat) it was shown that the main portion (> 70 %) of Resovist carboxydextran 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 organs of the RES (especially in liver and spleen) without dislocation from the iron core of Resovist. 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 in rats (at 0.5mmol Fe/kg/day representing about 50 times the diagnostic dose) and increased resorption rate and reduced the number of live foetuses in rabbits (at 0.8mmol 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 Resovist 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 Resovist is applied in humans. Resovist demonstrated no signs of sensitizing (contact-allergenic) potential in animal tests.

In dogs with antidextran antibodies, Resovist 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

Lactic acid
Mannitol
Sodium hydroxide
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

This medicinal product does not require any special storage condition.

6.5 Nature and contents of container

- 2.25-ml prefilled syringe filled with 0.9 ml; carton of 1,5 or 10
- 2.25-ml prefilled syringe filled with 1.4 ml; carton of 1,5 or 10

Barrel: colourless glass Type I siliconized
Plunger stopper: chlorobutyl elastomer, siliconized
Tip cap: chlorobutyl elastomer Type I

Each package contains a Sterifix Pury filter consisting of a male Luer lock filter hub: acrylonitrile/butadiene/styrene copolymer with a liquid filter of 5 micrometer
The filter material is made of polyamide 66.

Not all pack sizes may be marketed.

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

After long standing of the preparation slight color changes (dark to middle brown) may be observed, which disappear during normal handling.

Resovist is a ready-to-use aqueous solution for single use only. The tip cap should be removed from the syringe immediately before use.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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72, Heather Road
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8 MARKETING AUTHORISATION NUMBER

PA 0012/093/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 February 2002
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July 2006