Commentary on the clinical and preclinical dosage limits of interstitially administered magnetic fluids for therapeutic hyperthermia based on current practice and efficacy models:

SUPPLEMENTARY INFORMATION

S1. Manufacturer's Instructions for Use

In Section 3 of the paper we reference the published instructions for use (IFU) pamphlets for the commercial products Resovist®, Feraheme®, Sienna+®, and Nanotherm™. To ensure that these sources are readily available for the reader to examine in detail, we reproduce them herewith.

Reference 47: Ferucarbotran Resovist®: liver-specific contrast agent for MRI of focal liver lesions. Published by: Schering AG, Germany, 2002.

Schering AG, Germany

Resovist® Summary

Resovist® is safe and well tolerated:

- good cardiovascular tolerance side effects after fast bolus injection
- backache uncommon
- no relevant clinical lab changes

Resovist® is highly efficient:

- improves the detection of liver lesions significantly
- is superior compared to CTAP
- enables early and accumulation phase imaging (T1-, T2- and T2*-weighted)
- improves the characterisation of most liver lesions significantly

Resovist® is easy to use:

- ready to use solution, pre-filled syringe, fast injection
- patient does not need to be removed from the scanner
- total investigation only takes a few minutes longer than with extracellular gadolinium-chelates
- very convenient for the patient

Resovist® 0.5 mmol Fe/ml, solution for injection, prefilled syringe, Active ingredient: Ferucarbotran Composition: **Pharmacologically active ingredients:** 1 ml of solution for injection contains 540 mg ferucarbotran, corresponding to 0.5 mmol (28 mg) iron. **Excipients:** Lactic acid, mannitol, sodium hydroxide, water for injection. **Indications:** Resovist® is a contrast agent to be used for magnetic resonance imaging (MRI) of focal liver lesions when examination without contrast media has given uncertain findings. **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®. **Special warnings and special 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 Appropriate drugs and equipment in order to deal with such adverse events should be at hand when Resovist® is used. 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 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® 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. **Use during pregnancy and lactation:** Resovist® should not be used during pregnancy unless it is considered absolutely necessary. It is not known if Resovist® is excreted into breast milk in humans. Therefore Resovist® should only 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. **Undesirable effects:** Common (≥ 1% to < 10 %): pain at the injection site (< 2 %), vasodilatation (< 2 %), paresthesia (< 2 %). Uncommon (≥ 0.1 % to < 1 %): Asthenia, back pain, injection site reactions, chest pain, nausea, vomiting, headache, taste perversion, pruritus, rash. Rare (≥ 0.01 % to < 0.1 %): Hypersensitivity and anaphylaxis, hypertension, phlebitis, hyperesthesia, anxiety, dizziness, convulsion, parosmia, dyspnea, cough increased, rhinitis, eczema, urticaria. **Interactions:** No interactions with other medicaments have been observed. Formal drug interaction studies have not been carried out. **Dosage:** 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). **Additional information:** Please note! For current prescribing information refer to the package insert and/or contact your local Schering organization. Schering AG, 13342 Berlin, Germany, Status: February 2002

Schering Diagnostics

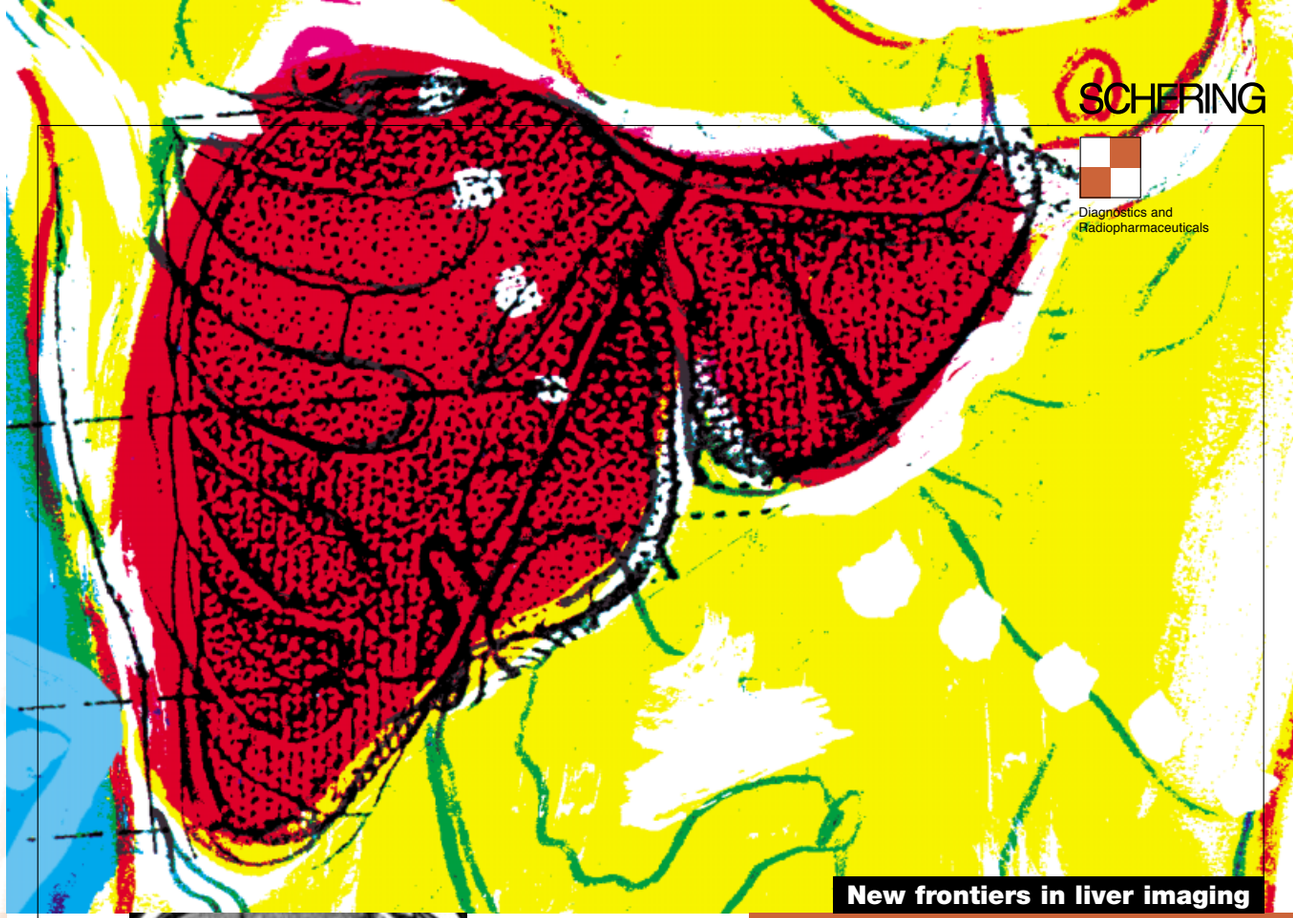
From seeing to understanding.

www.schering-diagnostics.de

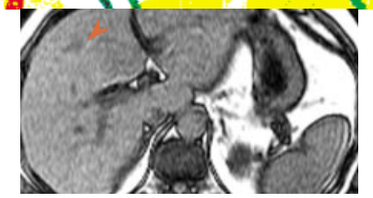
EU2002.0158

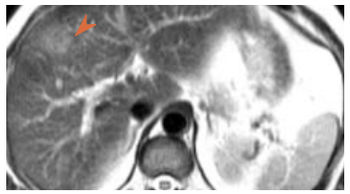
SCHERING

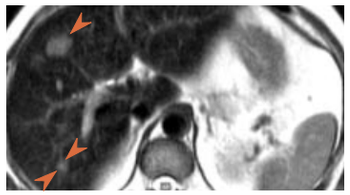
Diagnostics and Radiopharmaceuticals



New frontiers in liver imaging







Ferucarbotran

Resovist®

Liver-specific contrast agent for MRI of focal liver lesions: Detection and characterisation in a single diagnostic work-up.

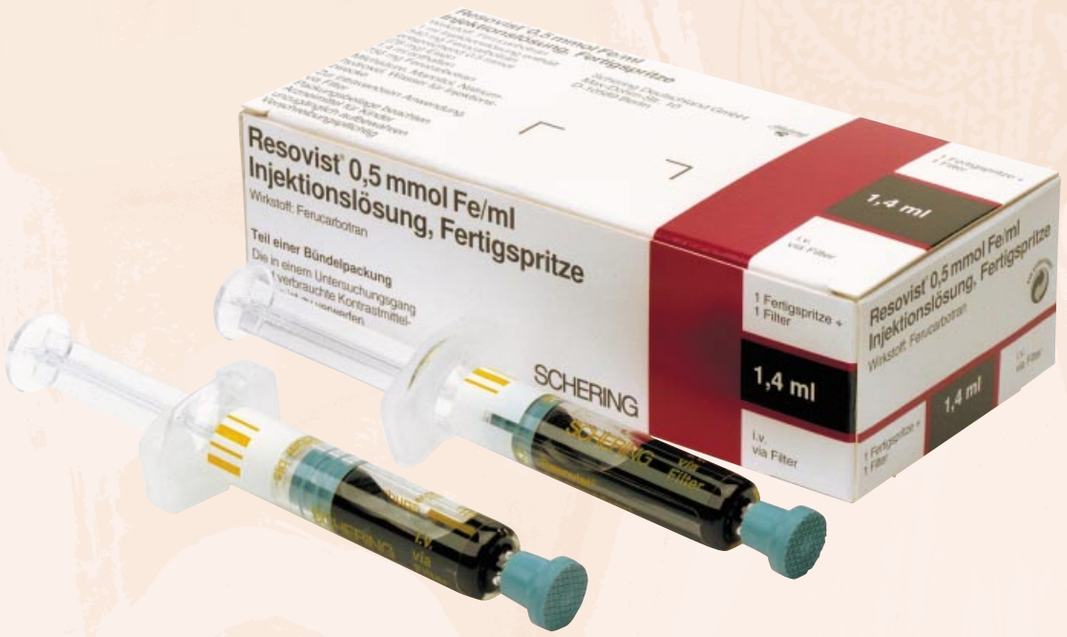
Information for radiologists

Product characteristics

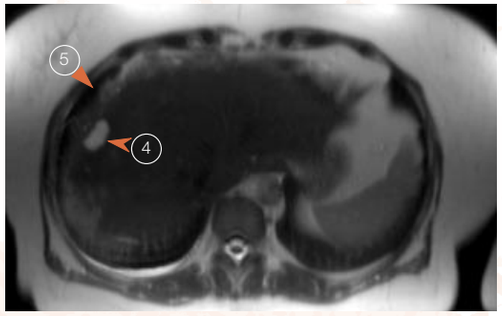
Resovist® is a liver-specific magnetic resonance (MR) contrast agent. The active ingredients are carboxydextran-coated superparamagnetic iron oxide (SPIO) particles (ferucarbotran). The coating prevents the iron-oxide particles from aggregating and makes the compound highly hydrophilic.

Resovist® exhibits a low viscosity and is isotonic to blood plasma. The hydrodynamic diameters of the coated particles range between 45 and 60 nm. The differing particle sizes determine the velocity of their uptake by cells of the RES (reticulo-endothelial system) – especially the Kupffer cells in the liver – as well as their relaxivity-related effects.

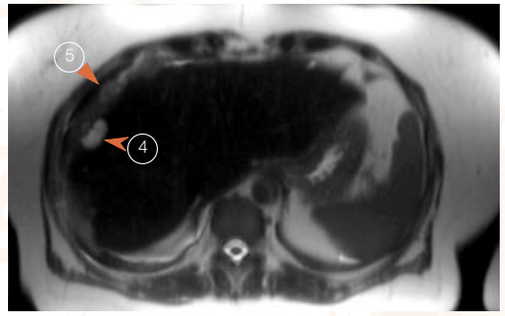
Resovist® has a strong effect on the shortening of both T1 and T2 relaxation times. The R1 and R2 relaxivities in blood (at 1.5 Tesla and 37°C) are 7.2 ± 0.1 and 82.0 ± 6.2 L/(mmol x sec) respectively. Due to the high R2 relaxivity, Resovist® is particularly suited to T2- and T2*-weighted imaging. Additionally, Resovist® enables T1-weighted imaging, with a tenth of the standard dose of Gd-DTPA ensuring a valuable although less pronounced T1-effect. Resovist® is ideal for the differentiation of benign versus malignant lesions as well as for proving or excluding multifocal liver lesions.



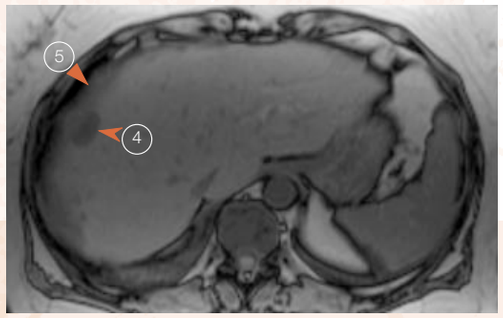
Case study



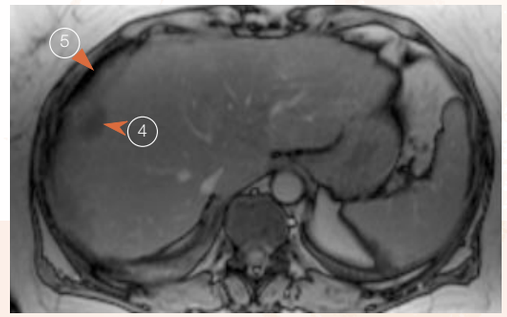
(g) HASTE-sequence: native



(h) HASTE-sequence: post Resovist®



(i)T1-GRE opposed phase: native



(j)T1-GRE opposed phase: post Resovist®

Courtesy of: Hammerstingl, MD, Vogl, MD; Frankfurt, Germany

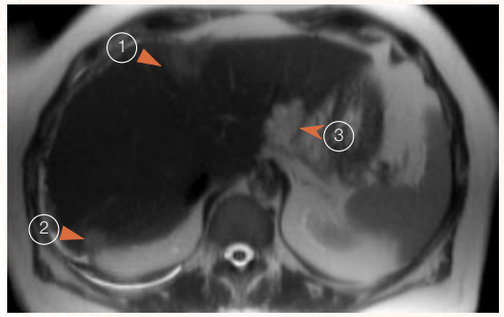
Answer:
Liver metastases (lesions 1 and 2)
Hemangioma (lesion 3)
Hepatic cyst (lesion 4)
Peritoneal carcinosis (lesion 5, multiple lesions at the liver periphery)

Produced by:
Schering AG, Region Europe MBD, 13342 Berlin, Germany

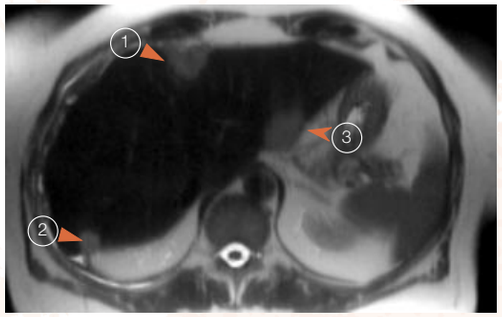
Scientific advice kindly provided by:
Dr. Renate Hammerstingl, MD, Dr. Wolfram Schwarz, MD, Prof. Thomas Vogl, MD,
Johann-Wolfgang-Goethe University, Frankfurt, Germany
Dr. Dominik Weishaupt, MD, University Hospital, Zurich, Switzerland
Dr. Stephan Schmitz, MD, Benjamin-Franklin University Hospital, Berlin, Germany

Case study

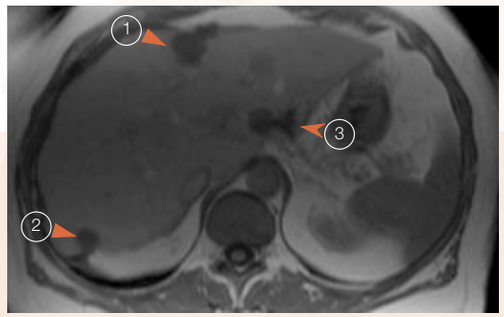
Female patient with breast carcinoma and multiple liver lesions



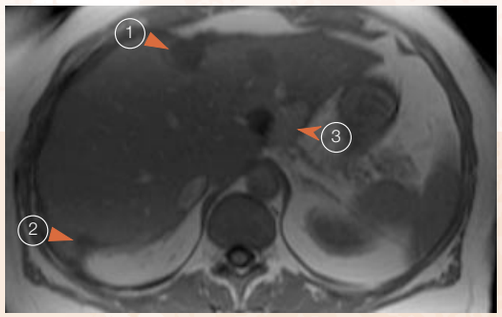
(a) HASTE-sequence: native



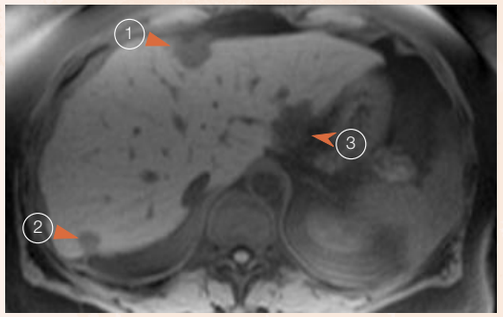
(b) HASTE-sequence: post Resovist®



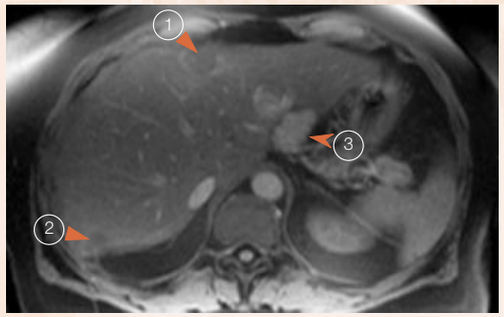
(c) T1-GRE in phase: post Resovist®
- arterial phase



(d) T1-GRE-sequence: post Resovist®
- portal-venous phase



(e) T1-GRE-FS: native



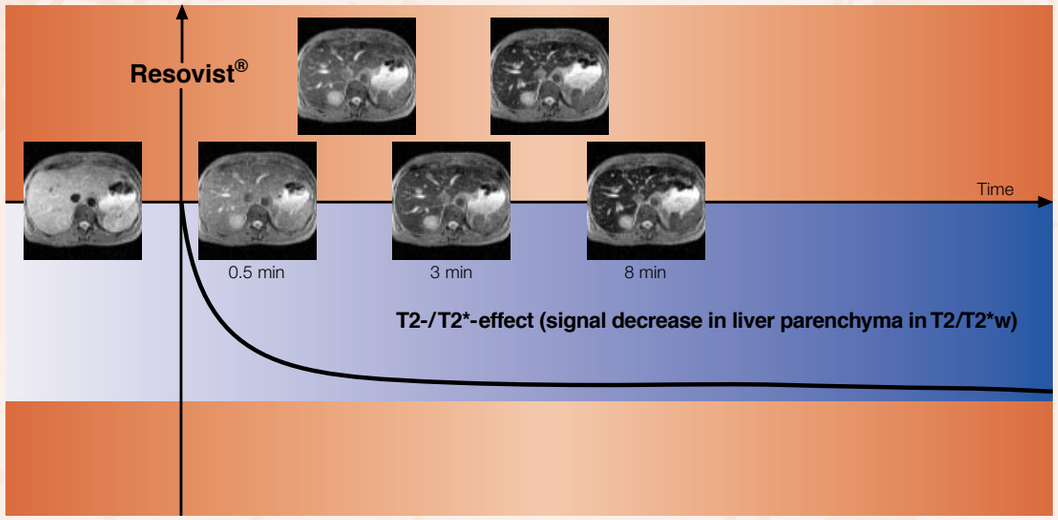
(f) T1-GRE-FS: post Resovist®

Resovist®: Mode of action

After intravenous injection, about 85 % of the administered Resovist® dose is taken up by Kupffer cells (the remaining amount is taken up by other RES cells). The larger particles are taken up faster than the smaller particles (with plasma half-lives of ~5 minutes and up to ~100 minutes respectively). Because the smaller particles stay in the vessels for longer they display a "blood-pool" characteristic.

T2/T2*-weighted imaging

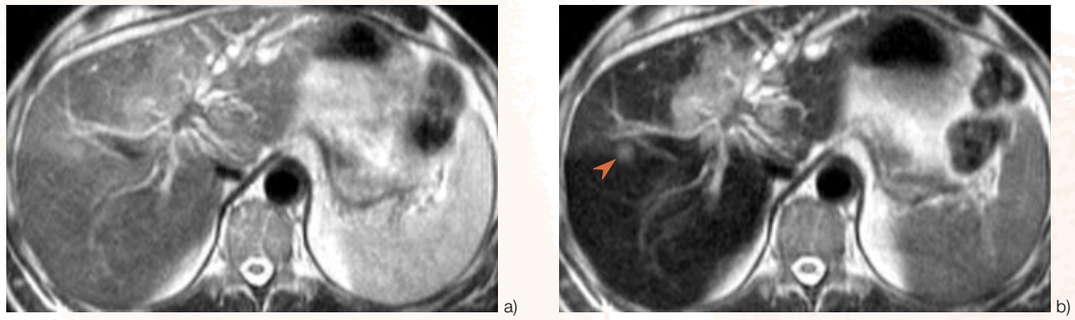
By virtue of the superparamagnetic properties of iron oxide, Resovist® shortens the T2 relaxation time very effectively and causes distortion of local magnetic fields (susceptibility effects). The effect of both mechanisms increases after the particles have been phagocytosed by the RES and stored in Kupffer cells (compartmentalisation). This results in a pronounced signal loss, particularly on T2- and T2*-weighted images, and to a lesser extent on some T1-weighted techniques (e.g. gradient echo sequences). Using T2- or T2*-weighted scans, a dramatic signal intensity (SI) decrease can be seen in tissues that take up Resovist®.



Time-dependent changes of signal intensities (SI) in liver parenchyma in T2/T2* weighted scans (black line). T2*-weighted images of the early and accumulation phase in a patient with liver metastasis. As early as 30 seconds after the injection of Resovist®, a signal intensity decrease of the liver can be noted. Further signal intensity decrease is displayed in this patient until 8 minutes post injection. Courtesy of: Brambs, MD; Ulm, Germany.

Resovist®: Mode of action

As most malignant tumours like metastases or hepatocellular carcinoma do not contain Kupffer cells or have impaired cell activity, Resovist® affects their native signal intensity to a lesser extent, if at all. This results in an improvement of the lesion to liver contrast.



Patient with a cholangiocellular carcinoma in the hepatic bifurcation. On the native T2-weighted image (a) the lesion is almost isointense and not clearly demarcated. Demarcation is clearly improved 10 minutes after fast intravenous bolus injection of 1.4 ml Resovist® (b). In addition, the Resovist® -enhanced MR image depicts a small satellite tumour nodule (arrow).
Courtesy of: Blakeborough et al., Radiology 1997, 203:759-765.

T1-weighted imaging

Shortening of the T2-relaxation time and susceptibility effects caused by the aggregation of iron oxide nanoparticles in the Kupffer cells result in a decrease in signal intensity of the liver parenchyma on T1-weighted images. In addition, as long as Resovist® particles are freely dispersed in the blood, a signal intensity increase from the vessels can be seen on T1-weighted images.

The signal from healthy liver tissue depends on the time post injection. It decreases in T1-weighted imaging due to the susceptibility of the clustered larger Resovist® particles, whereas the signal in the vessels stays bright – due to the smaller particles that are still circulating. Consequently the contrast between liver tissue and vessels is improved. Due to the specific pharmacodynamic properties of Resovist®, the peak of this contrast is at about 5 to 10 minutes post injection.

Typical changes of signal intensity

Benign lesions

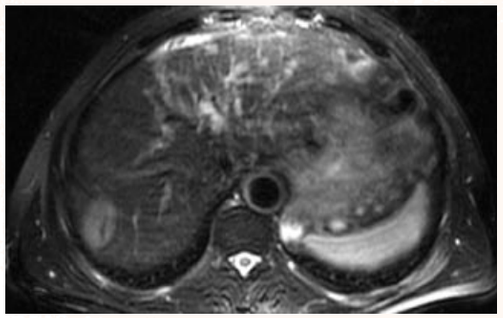
Sequence	FNH	Adenoma	Hemangioma
T2-native	iso-to mildly hyperintense nidus: hyperintense	heterogeneous signal due to blood, necrosis, lime	hyperintense, fibrous areas: hypointense
T2-post	signal decay homogeneous pattern iso-mildly hyperintense nidus: hyperintense	signal decay mildly hyperintense peripheral emphasis no nidus	signal decay more discrete than with FNH and adenoma
T1-native	iso-to mildly hypointense nidus: hypointense	heterogeneous signal due to blood, necrosis, lime pseudo capsule: hypointense	hypointense
T1 early phase	hypervascularized mildly hyperintense	mildly hypervascularized iso-hypointense	contrast take up increasing from the outside to the inside Iris aperture phenomenon
T1 accumulation phase	mildly hyperintense (according to degree of perfusion)	iso-hyperintense	homogeneously hyperintense

Malignant lesions

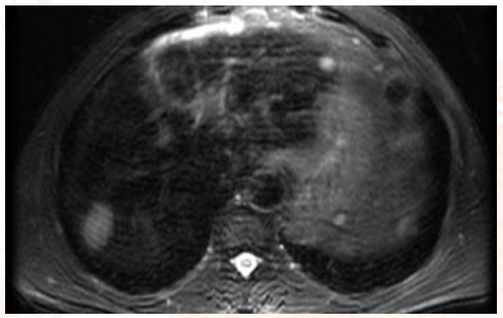
Sequence	HCC	CCC	Liver metastasis	
T2-native	hyper-to isointense inhomogeneous pattern central necrosis capsule: hyperintense	hyperintense inhomogeneous	often moderately hyperintense	
T2-post	no signal loss hyperintense	no signal loss hyperintense	no signal loss, hyperintense	
T1-native	iso-to hypointense central inhomogeneity	hypointense inhomogeneous	often hypointense	
T1 early phase	mostly hypervascularized in the beginning hyperintense followed by wash-out effect	rim-enhancement: peripheral hyper- vascularization central hypointensity	**hypovascular** rim enhancement: periph. hyper- vascularization wash-out effect otherwise hypointense	**hypervasc.** hyperintensi- ty due to vasculari- zation
T1 accumulation phase	mildly hyper-to isointense	mostly iso-to hypointense peripheral rim enhancement	mostly iso-to hypointense With peripheral rim enhancement	

Characterisation of lesions with Resovist®

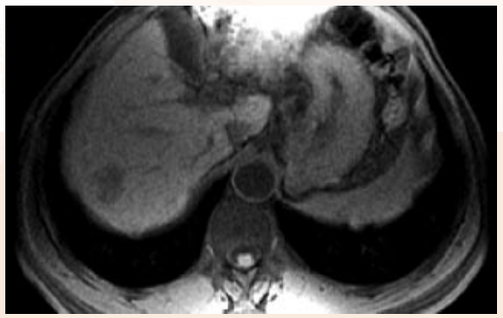
Hypervascular HCC



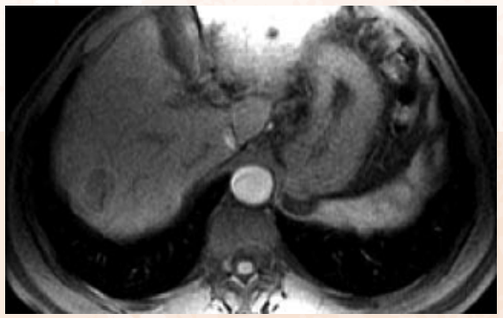
T2-FSE (TR/TE/flip angle = 3500 ms/100 ms/90°)
Hyperintense lesion in cirrhotic liver parenchyma.



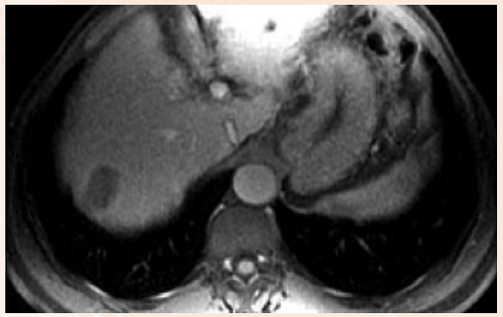
Post Resovist®
10 min after administration of Resovist® the lesion conspicuity is improved



T1-GRE (TR/TE/flip angle = 150 ms/1.4 ms/60°)
Hypointense signal of the HCC in the native scan.



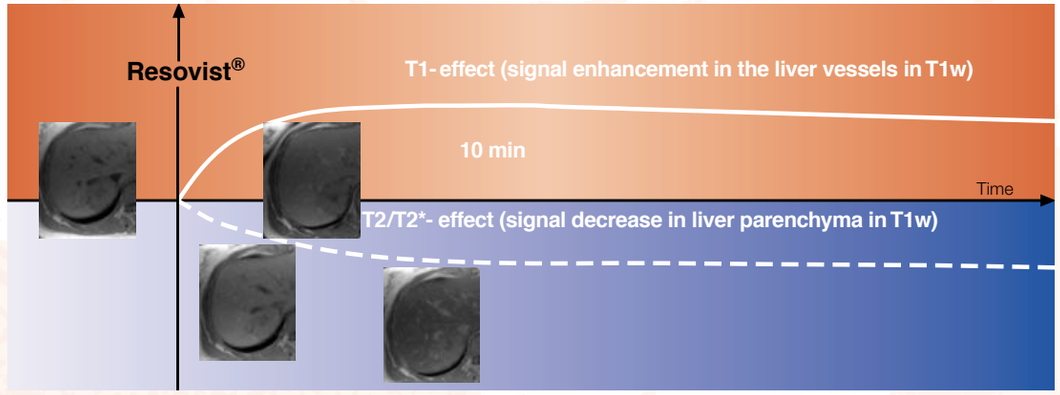
T1-GRE (TR/TE/flip angle = 150 ms/1.4 ms/60°)
During **arterial phase** (20 sec after administration of Resovist®), the hypervascular lesion shows marginal signal enhancement compared to the native scan.



T1-GRE (TR/TE/flip angle = 150 ms/1.4 ms/60°)
In the corresponding image during **portal-venous phase** (60 sec after administration of Resovist®), the hypervascular lesion shows a rapid wash-out. Note the enhancement of the vessels due to the T1-effect of Resovist®.

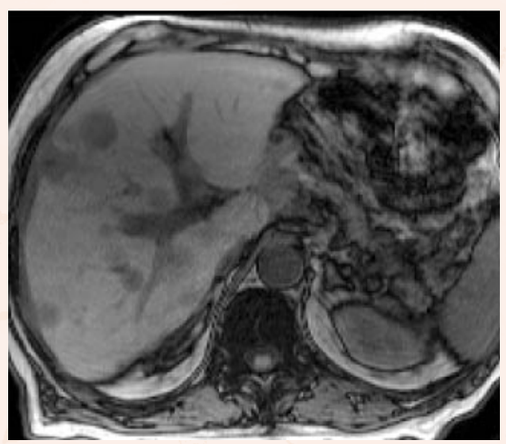
Courtesy of: Weishaupt, MD; Zurich, Switzerland

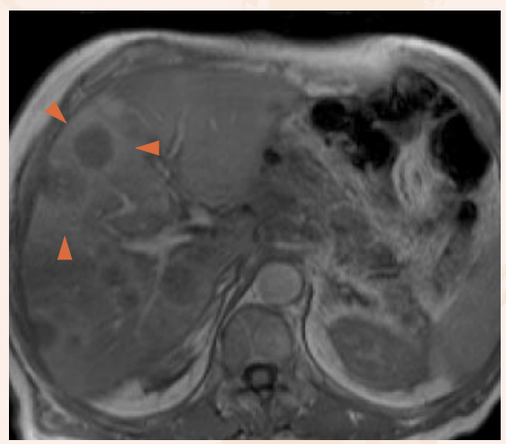
Resovist®: Mode of action



Time-dependent changes of signal intensities (SI) in liver vessels (white line) and liver parenchyma (white dotted line) in T1-weighted scans. In the arterial phase scan (20 sec p.i.) the SI of the parenchyma is slightly increased compared to the pre-contrast scan. (This is the perfusion effect i.e. all the Resovist® particles are still in the vessels). At 90 sec p.i. the SI of the parenchyma is slightly decreased compared to the pre-contrast scan due to the overlying T2/T2*-effect of the larger particles (fast uptake). Smaller particles are circulating in (and enhancing) the vessels. Images 10 min p.i. display further SI decrease of the parenchyma. Due to the enhancement of the vessels, the contrast between parenchyma and vessels is improved. As a result, the liver tissue accumulation and blood-pool distribution generates a "contrast inversion." That is, the high signal intensity of liver and low signal intensity of vessels of the unenhanced images change to a low signal intensity of liver and a high signal intensity of vessels on T1-weighted images 10 minutes p.i. of Resovist®. Courtesy of: Hammerstingl, MD; Frankfurt, Germany.

Early (arterial and portal-venous) and accumulation phase imaging (approximately 10 min p.i.) add helpful information regarding the characterisation of focal liver lesions and assessment of the vascular situation. For example, due to the blood-pool characteristics of the smaller Resovist® particles, the well known "ring enhancement" and "wedge sign" in metastatic lesions can be detected much more frequently than with liver imaging using extracellular contrast agents.


a)


b)

Patient with colon cancer and multiple liver metastases. Native (a) and Resovist®-enhanced (b) T1-weighted images. Note the ring enhancement and wedge sign (arrows) on the T1-weighted image 10 min after administration of Resovist®.
Courtesy of: Huppertz, MD, Munich, Germany.

Safety

Resovist® proved to have a very good safety profile in its class of contrast agents. Resovist®, is well tolerated when given by fast bolus injection. No significant cardiovascular side effects have been reported. The quantity and quality of adverse events is comparable to those seen with gadolinium agents. The following adverse events have been reported most frequently during the clinical development programme: paresthesia, headache, feeling of warmth, nausea, pain, anxiety, vomiting, backache and pain at injection site. All of these adverse events were of mild intensity and short duration.

Backache occurred in only 3 out of 1053 patients (0.3% – mild (2) and moderate (1) intensity) after administration of Resovist®. No backache required any treatment or interruption of the injection or scanning session.

Reactions comparable to Dextran Induced Anaphylactic Reaction (DIAR) might occur in patients with hypersensitivity to dextran. Appropriate drugs and equipment to deal with such adverse events should be at hand when Resovist® is used.

There is no contraindication to administer Resovist® to patients with impaired renal or liver function. No significant changes in urine chemistry or creatinine clearance were recorded in clinical studies. There is no evidence of any systematic effect of Resovist® on liver function.
The amount of iron in the recommended dose of Resovist® (0.9 ml in patients < 60 kg body weight, 1.4 ml in patients ≥ 60 kg body weight, corresponding to 5.8 –12.9 µmol Fe/kg BW) is equivalent to about 1% of normal whole-body iron content. This is equivalent to the normal dietary intake of iron in 2-3 days. Administration of this amount of iron will result in transient changes in serum iron, ferritin, and iron-binding capacity, but there is no danger of iron overload.

How to use Resovist®

Resovist® is a ready-to-use solution for intravenous injection and is provided in a pre-filled glass syringe.

- 1.4 mL prefilled syringe for patients with ≥ 60 kg body weight
- 0.9 mL prefilled syringe for patients with < 60 kg body weight

A 5 µm filter must be used for injection because visual inspection of the brownish solution before injection is not possible. The filter is included in the box.

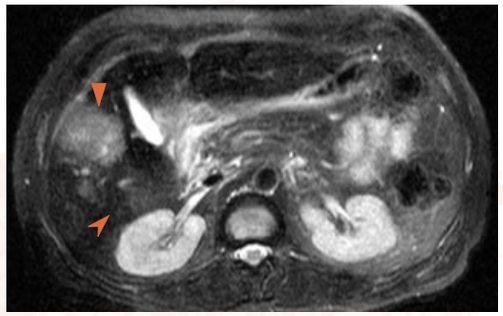
Resovist® can be injected without restriction to injection speed. Immediately after Resovist®'s injection a volume of 20–30 ml saline solution (0.9%) should be administered to flush the connecting line and veins.

There are several ways to prepare the injection of Resovist®. In order not to move the patient out of the magnet, a connecting line for the injection may be used. This line can be pre-filled with Resovist® and then be flushed with saline either by hand or by injector. Using a Medrad Spectris® Injection System, the saline cartridge must be in position "A." Then cartridge "B" on the display can be disabled. Injection volume, speed and start of the injection can be carried out in the usual way.

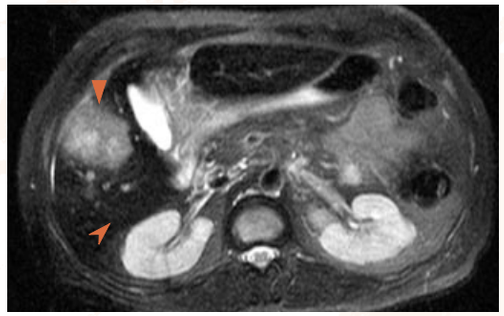
The unique properties of Resovist® enable a comprehensive pre- and post-contrast examination to be performed with a liver-specific contrast agent in a reasonable time period for the first time. The whole examination will only last a few minutes longer than a liver examination performed with an extracellular contrast agent.

Characterisation of lesions with Resovist®

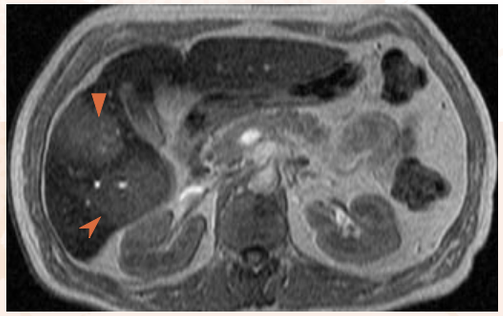
HCC and adenoma in the case of liver cirrhosis



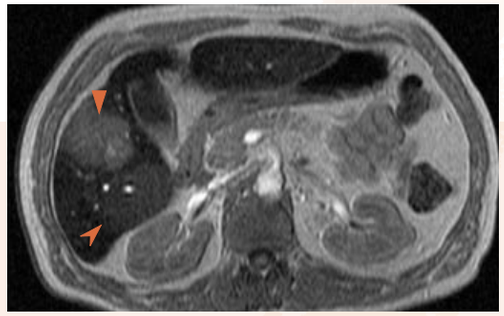
T2-TSE-FS: native
(TR/TE/Flip angle = 2000 ms/90ms/130°)
Hyperintense lesion in the right liver lobe segment 5. ►
Additional lesion of lower intensity detected. ➤



Post Resovist®
Unchanged hyperintense signal pattern of HCC ► without contrast agent uptake and signal loss respectively as an indication for maglinancy. Typical signal decay of the adenoma. ➤



T1-GRE: native
(TR/TE/flip angle = 150 ms/4.8ms/80°)
Hyperintense signal of HCC and adenoma.

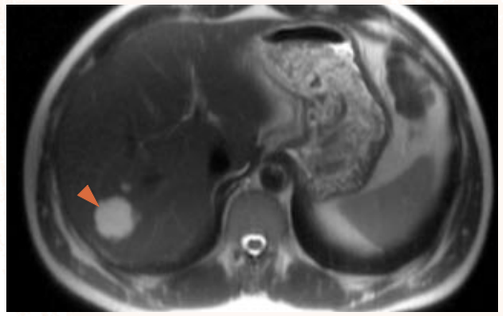


Post Resovist®
Unchanged signal texture of HCC-node. ►
Slight signal decay of adenoma. ➤

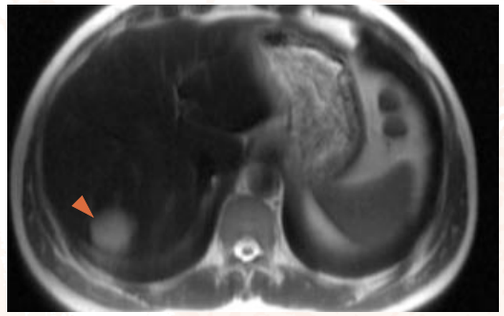
Courtesy of: Hammerstingl, MD, Schwarz, MD, Vogl, MD; Frankfurt, Germany

Characterisation of lesions with Resovist®

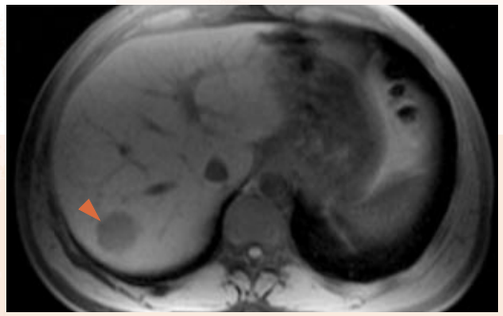
Hemangioma



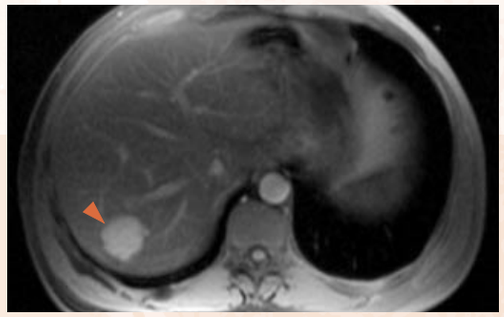
HASTE-Sequence: native
(TR/TE/flip angle = 1200 ms/63 ms/150°)
Hyperintense lesion in liver segment 6.



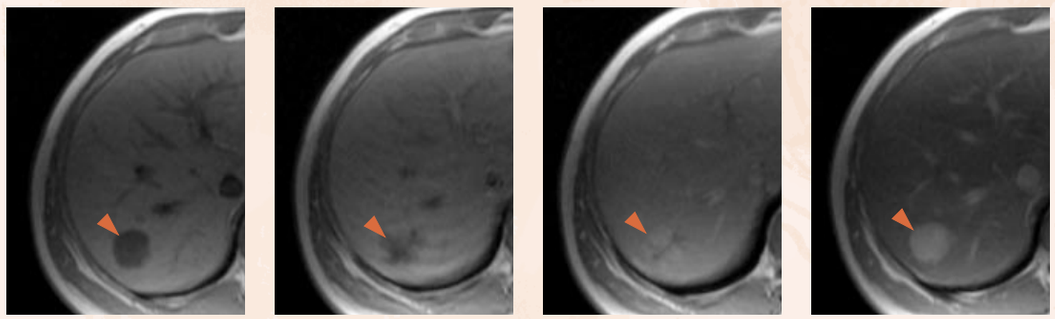
Post Resovist®
Typical signal loss of the lesion as a sign of the bloodpooling effect is an indication for a hemangioma.



T1-GRE-FS: native
(TR/TE/flip angle = 150 ms/4.8 ms/80°)
Hypointense lesion precontrast.



Post Resovist®
Typical change of signal intensity from hypointense to hyperintense as an indication for a hemangioma.



Native **15 s p.i.** **45 s p.i.** **120 s p.i.**

Early T1-weighted GRE sequence: bolus injection of Resovist®
(TR/TE/flip angle = 160 ms/4.8 ms/80°)
Centripedal filling of the lesion (iris phenomenon).

Courtesy of: Hammerstingl, MD, Vogl, MD; Frankfurt, Germany

Scanning Recommendations

Fast bolus injection of Resovist® makes it possible to observe the early perfusion characteristics of the liver using T1- or T2*-weighted sequences. The accumulation phase imaging can be performed as early as 10 minutes p.i. utilising T1, T2 and T2*-weighted sequences. The T2 and T2*-weighted accumulation phase imaging improves lesion detection by improving the visualisation, delineation and conspicuity of the lesions. Accumulation of Resovist® – or the lack of it – provides additional information regarding lesion characterisation.

As some of the benign tumors like focal nodular hyperplasia (FNH) contain functioning RES cells, this is helpful in differential diagnosis. Resovist®'s typical imaging properties result in specific time-dependent changes of signal intensities in T1-, T2- and T2*-weighted images.

The following recommendations should be regarded as starting points for your individual experience.

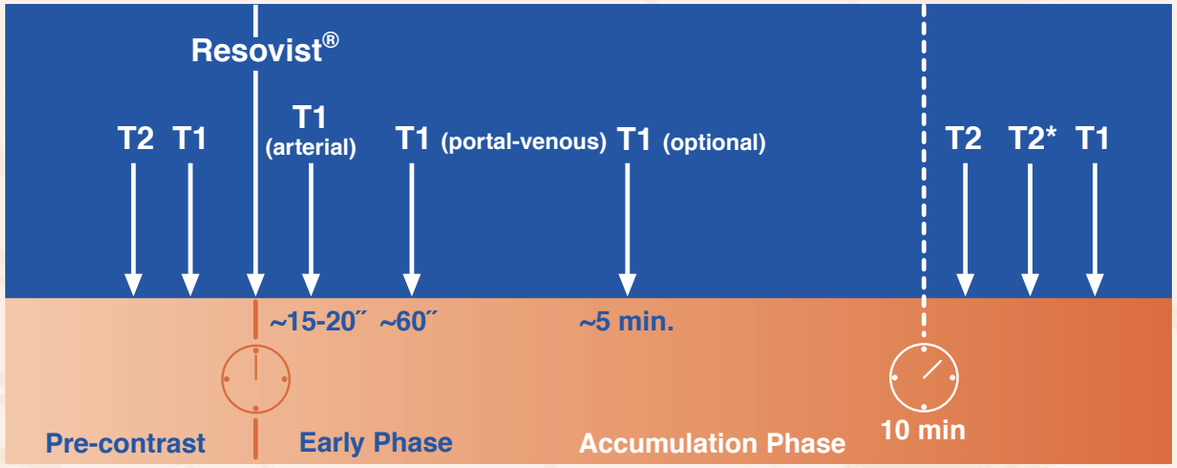
To achieve the optimal signal-to-noise ratio it is recommended to use body phased array coils, if available.

Pre-contrast imaging
- Localiser
- T1 gradient echo (with fat saturation) and breath-hold
- T2 turbo spin echo (with fat saturation) and respiratory triggering (preferable), or breath-hold

Post-contrast early phase imaging
- Early T1 gradient echo – or optional T2* gradient echo – (with fat saturation) and breath-hold (shortest possible TE). Scan times eg 15–20 sec (arterial phase) and 50–60 sec (portal-venous phase) p.i.

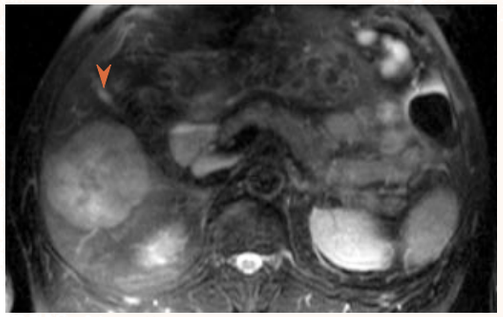
Post-contrast accumulation phase imaging
Optional 3-5 min after administration:
- T1 gradient echo (with fat saturation) and breath-hold (shortest possible TE)

10 min after administration
- T2 turbo spin echo (with fat saturation) and respiratory triggering (preferable) or breath-hold
- T1 gradient echo (with fat saturation) and breath-hold (shortest possible TE)
- T2* gradient echo (with fat saturation) and breath-hold

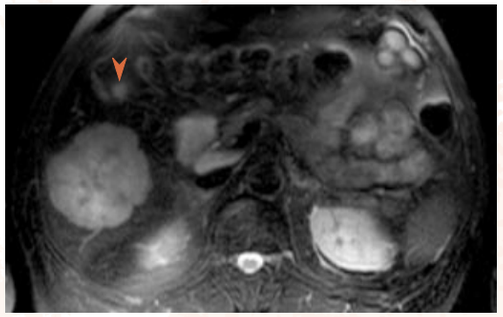


Detection

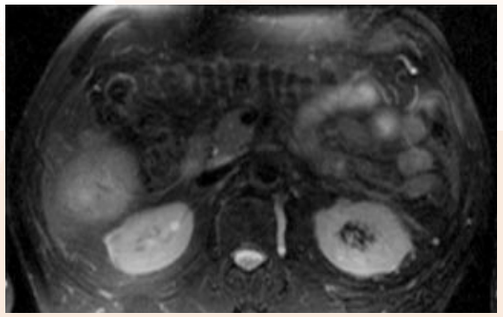
Leiomyosarcoma of the liver with satellites



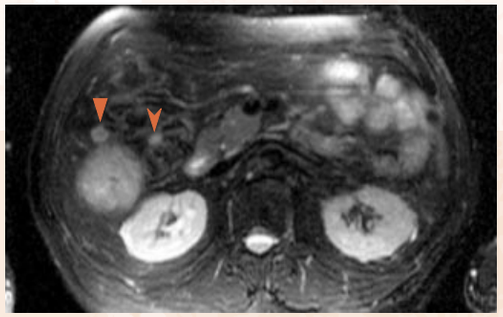
T2-TSE-FS: native
(TR/TE/flip angle = 2790 ms/90 ms/130°)
Hyperintense lesion in the right liver lobe, segment 6 with suspected satellite lesion ventrally (arrow).



Post Resovist®
No change of signal intensity post Resovist®. Typical sign of malignancy. Confirmation of the additional satellite lesion.

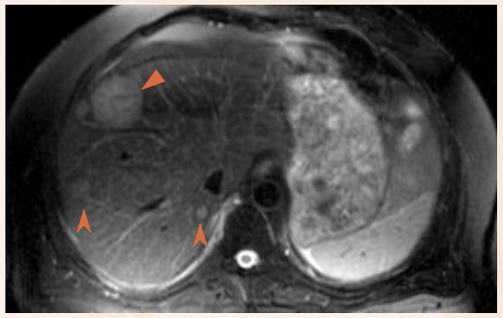


T2-TSE-FS: native
(TR/TE/flip angle = 2790 ms/90 ms/130°)

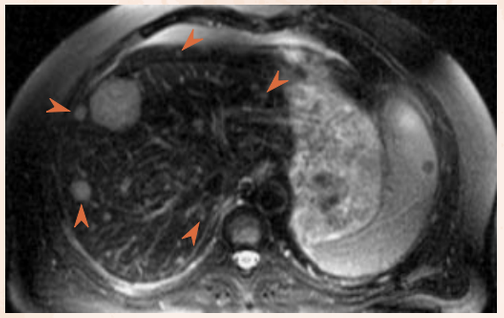


Post Resovist®
Better demarcation of lesion ► as compared to the native scan.
Detection of an additional satellite lesion. ➤

Liver metastases of a neuro-endocrine tumour



T2-TSE-FS: native
(TR/TE/flip angle = 2790 ms/90 ms/130°)
Neuro-endocrine tumour. ► Suspicion of further satellites. ➤



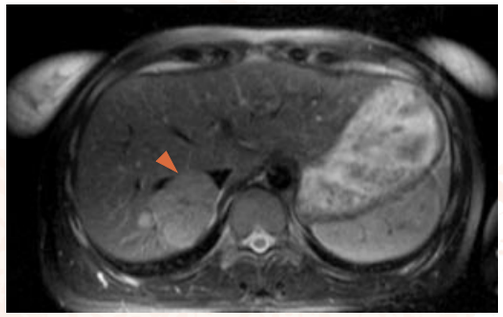
Post Resovist®
Clear demarcation of multiple satellites. ➤
Additionally, detection of a cyst in the splen.

In comparison to native images, T2-weighted images with Resovist® clearly increase the detection of liver lesions.

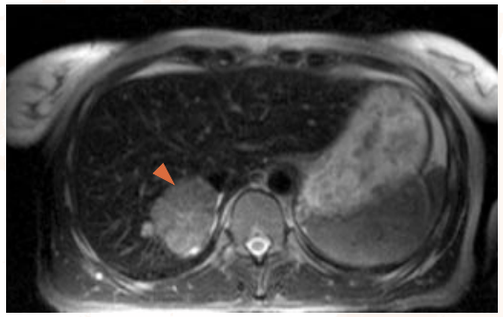
Courtesy of: Hammerstingl, MD, Vogl, MD; Frankfurt, Germany

Characterisation of lesions with Resovist®

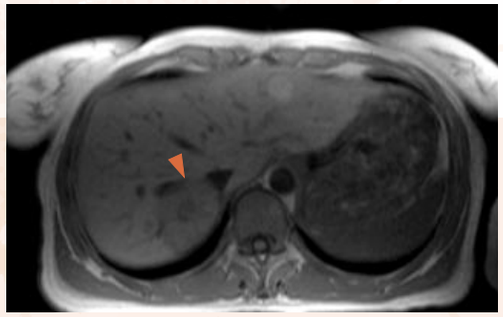
FNH



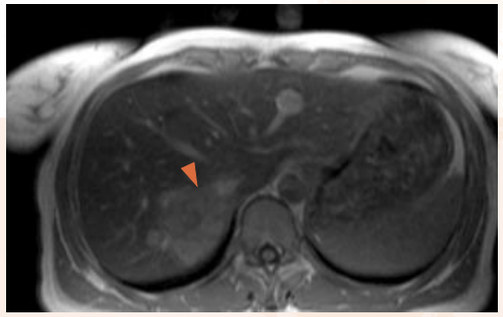
T2-TSE-FS: native
(TR/TE/flip angle = 2800ms/90ms/130°)
Hyperintense lesion in liver segment 7 with compression of VCI.



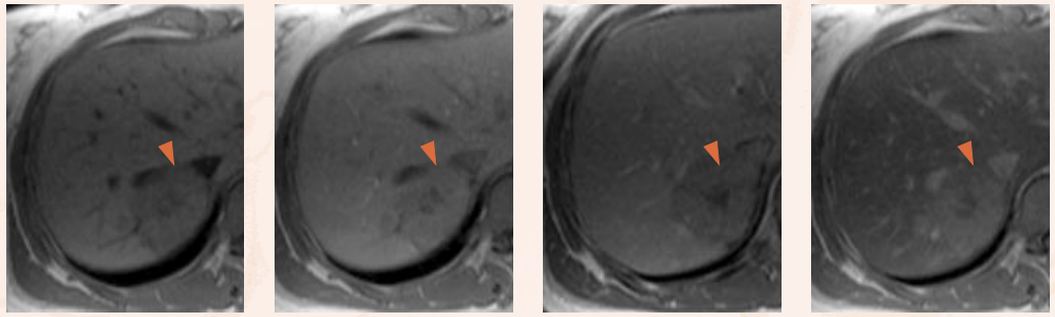
T2-TSE-FS: post Resovist®
(TR/TE/Flip angle = 2800 ms/90ms/130°)
Signal decay of lesion with improved deliniation of central nidus and shifted vascular structures in the right rim area as a typical sign for FNH.



T1-GRE-FS: native
(TR/TE/flip angle = 150 ms/4.8ms/80°)
Hypointensity of lesion with hypointense centre.



T1-GRE-FS: post Resovist®
Hyperintensity as a classical sign for a hypervascularisation of FNH. Pulsation artifact in the left liver lobe.



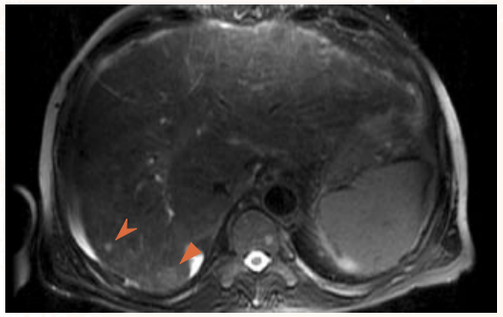
native | **15 s p.i.** | **90 s p.i.** | **9 min p.i.**

Early T1-weighted GRE-sequence: bolus injection of Resovist®
(TR/TE/flip angle = 160ms/4.8 ms/80°)
Hypervascularised FNH node in the early phase with successive decay of signal intensity and isointensity in the accumulation phase in comparison to the liver parenchyma. 9 min p. i. hyperintensity of FNH due to continuous decay of signal intensity of the liver.

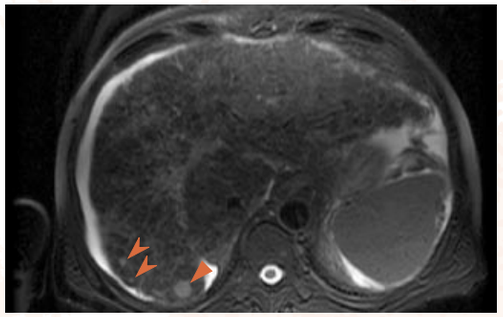
Courtesy of: Hammerstingl, MD, Vogl, MD; Frankfurt, Germany

Improved detection compared to unspecific MR contrast agent

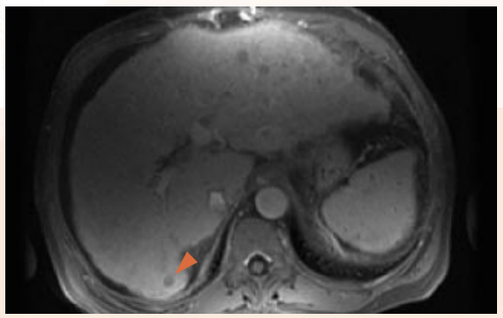
Multifocal HCC



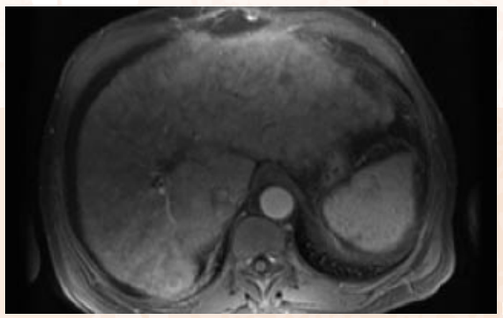
T2-FSE (R/TE/flip angle = 3500ms/100 ms/90°)
A mildly hyperintense lesion can be seen in segment VII. ►
A second smaller hyperintense lesion ➤ is noted in close proximity. Note the presence of perihepatic ascites.



Post Resovist®
10 min p. i. of Resovist® confirmation of the HCC. ►
In addition, two more HCCs ➤can be detected which would have been missed on Gd-DTPA-enhanced images (see below).



a)



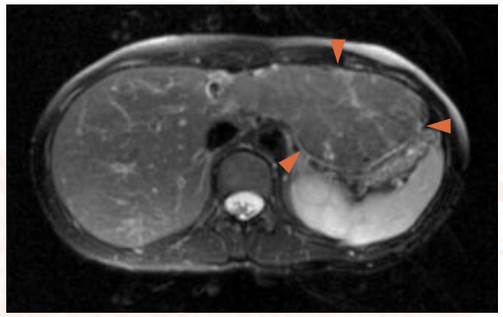
b)

T1-GRE (TR/TE/Flip angle = 150 ms/1.4ms/60°)
Gd-DTPA-enhanced arterial (a) and portal-venous phase (b) scans. The HCC ► shows typical signal enhancement in the arterial phase and wash-out in the portal-venous phase. Further lesions can not be detected.

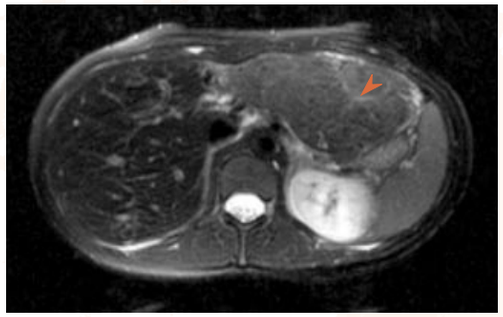
Courtesy of: Weishaupt, MD; Zurich, Switzerland

Detection

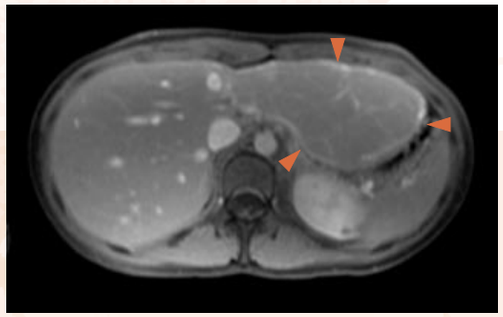
FNH (focal nodular hyperplasia)



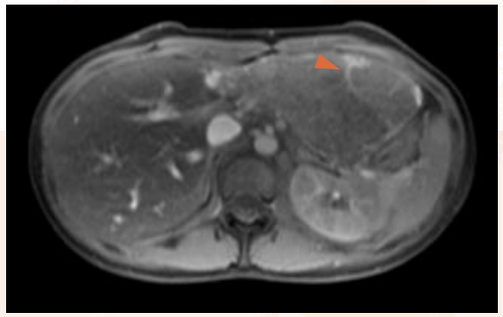
T2-TSE-FS: native
TR/TE/flip angle = 2790ms/90ms/130°
Isointense lesion in the left liver lobe with shifting of vascular structures and stomach compression.



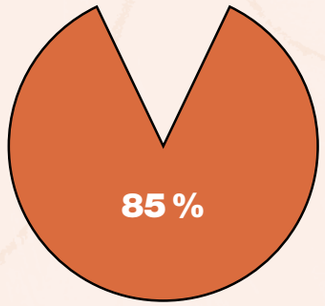
Post Resovist®
Significant decrease of signal intensity of the lesion with central nidus, typical for FNH.



T1-GRE-FS: Gd-DPTA
TR/TE/flip angle = 150ms/4.8ms/80°
Isointense lesion in the left liver lobe with shifting of vascular structures and stomach compression.



Post Resovist®
Discrete hypervascularisation of the FNH with enhanced display of vascular structures and central nidus.

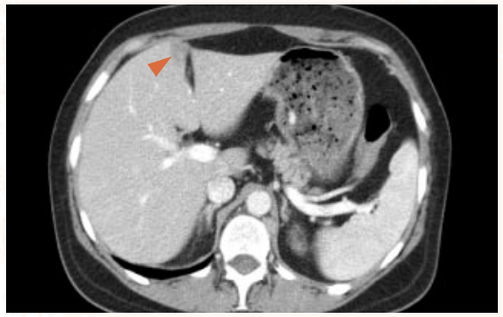


Accumulation of Resovist® in the Kupffer cells of the liver.

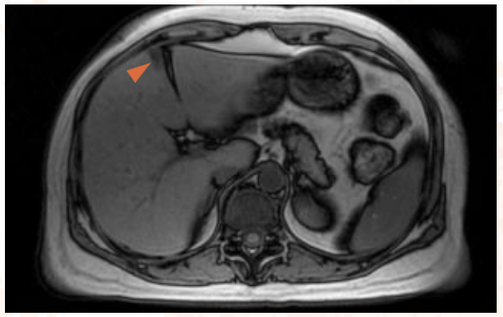
Courtesy of: Hammerstingl, MD, Vogl, MD; Frankfurt, Germany

Improved detection compared to CT

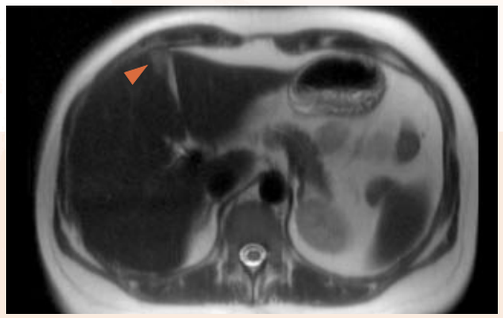
Focal fatty degeneration



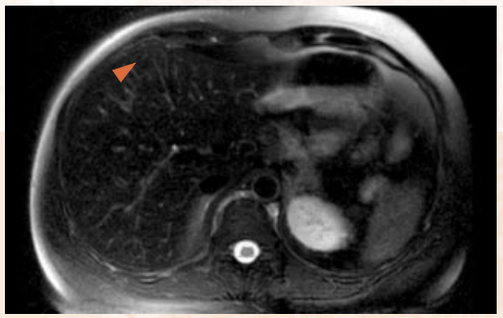
Spiral-CT: Portal phase
Hypodense lesion in the right liver lobe segment 4B.
Distinct central enhancement.



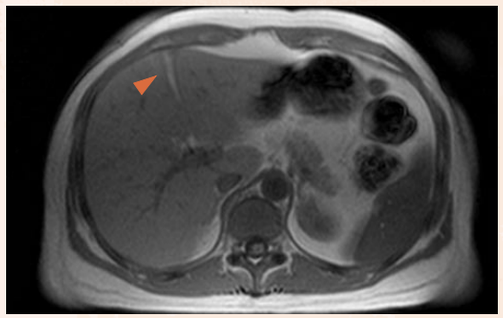
T1-GRE-opposed phase: native
(TR/TE/flip angle = 150ms/2.4 ms/70°)
Hypointense lesion in the right liver lobe segment 4B.



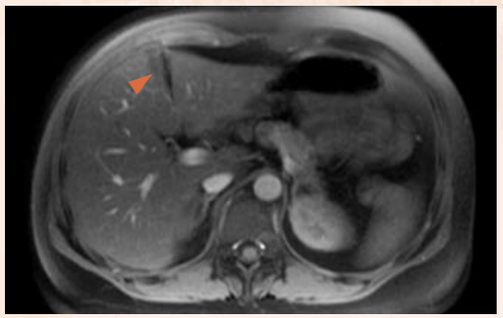
Haste: post Resovist®
(TR/TE/flip angle = 1200 ms/63ms/150°)
Discrete hyperintense lesion.



T2-TSE-FS: post Resovist®
(TR/TE/flip angle = 2800 ms/90ms/130°)
Homogeneous signal loss of liver parenchyma due to Resovist® uptake. No proof of a metastasis.



T1-GRE-in phase: native
(TR/TE/flip angle = 150 ms/4.8 ms/70°)
Discrete hyperintense lesion.

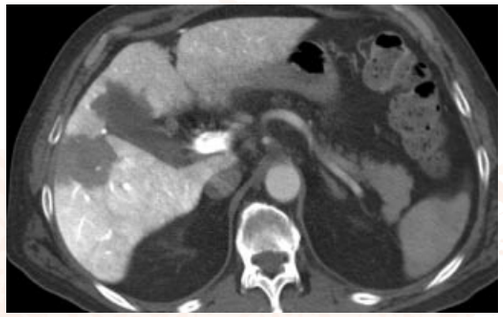


T1-GRE-in phase: post Resovist®
(TR/TRE/flip angle = 150 ms/4.8 ms/70°)
Homogeneous marginal drop of signal of liver parenchyma
Lower signal reduction of the lesion with hyperintensity (focal fatty degeneration).

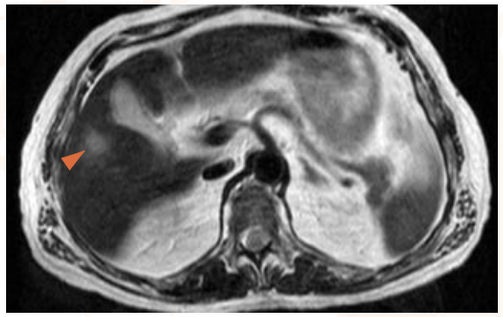
Courtesy of: Hammerstingl, MD, Schwarz, MD, Vogl, MD; Frankfurt, Germany

Improved detection compared to CTAP

Liver cirrhosis and HCC



CTAP: portal phase
Findings of large lesion in segment 5 with suspected satellites proximal to gall bladder and in segment 4B.



T2-TSE-FS: post Resovist®
(TR/TE/flip angle = 2000 ms/90ms/130°)
Detection of a solitary HCC focus with micronodular changes of liver parenchyma in a patient with cirrhosis.

With comparable sensitivity, Resovist® -enhanced MRI is superior to CTAP due to its higher specifity, since it leads to fewer false-positive findings.

Courtesy of: Hammerstingl, MD, Schwarz, MD, Vogl, MD; Frankfurt, Germany

Reference 48: Prescribing information: Resovist. Published by: Agis Commercial Agencies (1989) Limited, Israel, 2002.

Prescribing Information

RESOVIST

1. NAME OF THE MEDICINAL PRODUCT

Resovist

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of the MRI contrast agent Resovist contains 28 mg iron in the form of ferucarbotran. Ferucarbotran consists of superparamagnetic iron oxide nanoparticles coated with carboxydextran in an approximate ratio of 1 : 1.1 (w/w).

3. PHARMACEUTICAL FORM

Solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Resovist is a contrast agent for hepatic magnetic resonance imaging (MRI) when examining without contrast media has given uncertain findings.
It improves lesion detection (e.g. number, size, segmental distribution and conspicuity) and provides additional information regarding classification and characterization of focal liver lesions, thereby increasing diagnostic confidence.

4.2 Dosage and method of administration

· General information
The usual safety rules for magnetic resonance imaging must be observed, e.g. exclusion of cardiac pacemakers and ferromagnetic implants.

Nausea and vomiting are known possible adverse events of all extracellular MRI contrast media. The patient should therefore refrain from eating for two hours prior to investigation to avoid aspiration.
No clinical experience is yet available for patients younger than 18. Usage of Resovist in these patients can therefore not be recommended.

· Dosage
The ready-to-use solution is to be administered via the enclosed filter as an intravenous bolus injection followed by sterile physiological saline (10-20 ml) to flush the intravenous line (cf. 6.6 "Instructions for use/handling").

The following dosage guidelines apply to adults[3]
· For patients weighing 35 to less than 60 kg : 0.9 ml Resovist (equivalent to 25.2 mg Fe),
· for patients weighing 60 kg or more :1.4 ml Resovist (equivalent to 39.2 mg Fe).

The maximum dose tested in humans, 0.08 ml Resovist (equivalent to 2.24 mg Fe) per kg body weight, was well tolerated.

Immediately after the bolus injection of Resovist, dynamic imaging is recommended using 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., 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. angiographic time-of-flight sequences (TOF) within 20 min. p.i. of Resovist.

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

Known hypersensitivity to any of the ingredients.

4.4 Special warnings and special precautions for use

Diagnostic procedures that involve the use of contrast agents should be carried out under the direction of a physician with the prerequisite 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 4.3 “Contraindications”, 4.8 “Undesirable effects” and 5.3 “Preclinical safety data”). Drugs and equipment (e.g. endotracheal tube and oxygen respirator) should be close at hand when investigation is performed.

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 affect the signal intensity of the liver. Therefore, the expected benefit by an injection of Resovist might be limited.

To avoid paravenous injections which may lead to long-lasting local pigment-like discoloration of the skin (cf. 5.3 ”Preclinical safety data”), it is necessary to ensure the correct placement of the injection needle by sterile physiological saline injection before injection of Resovist (cf. 6.6 "Instructions for use/handling").

4.5 Interaction with other medicaments and other forms of interaction

No interactions with other medicaments have been observed. Formal drug interaction studies have not been carried out.

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 5.3 "Preclinical safety data"). 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

None known.

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.

Most of the undesirable effects were of mild to moderate intensity. Based on the experience in more than 1000 patients the following undesirable effects, classified by the investigators as related (possibly, probably, definitely) have been observed.

· Body as a whole: Pain, asthenia and back pain in less than 1% of cases.
· Cardiovascular: Vasodilation in less than 2%, chest pain in less than 1%, hypertension and phlebitis in less than 0.1%.
· Gastrointestinal: Nausea and vomiting in less than 1%.
· Nervous system: Paraesthesia in less than 2%, headache in less than 1%, hypesthesia, anxiety, dizziness and convulsion in less than 0.1%.
· Special senses: Taste perversion in less than 1%, parosmia in less than 0.1%.
· Respiratory system: Dyspnea, cough increased and rhinitis in less than 0.1%.
· Skin: Pruritus and rashes in less than 1%, eczema and urticaria in less than 0.1%.
· Local irritation: Injection site reactions in less than 1%.
· Hypersensitivity: in less than 0.1%.

In association with a decrease in factor XI activity occasionally a transient and slight increase of the partial thromboplastin time (PTT) may occur, whereas the Quick test remains unaffected.

After administration of Resovist, a dose dependent increase of the plasma iron and ferritin level was observed with a maximum level reached 24 hours later, whereas the total iron-binding capacity was unaffected.

As observed with other paramagnetic complexes, in very rare cases hypersensitivity reactions and anaphylaxis have been reported including shock that may need immediate medical intervention.

4.9 Overdose

Acute toxicity studies showed no risk of acute intoxication on use of Resovist.[4 7]

The drug has been proved to be safe up to 0.08 ml (equivalent to 2.24 mg Fe) per kg body weight in healthy volunteers (approx. 4 times the diagnostic dose) (see 4.2 ”Dosage”).[3]

In case of clinical symptoms due to overdose, observation of vital signs and symptomatic treatment is recommended.

4.10 Drug abuse and dependence

Not known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Resovist is a stable, aqueous solution of superparamagnetic iron oxide nanoparticles coated with carboxydextran. The coated iron oxide particle size is comparable to that of large biological proteins.

By virtue of the superparamagnetic properties of the iron oxide, the contrast agent shortens predominantly the T_2 relaxation time[7] and causes microscopic susceptibility effects (distortion of local magnetic field), both mechanisms producing a pronounced signal loss in the neighborhood of the iron oxide, particularly on T_2 and T_2* weighted images.
The T_2* effect is especially produced after Resovist is phagocytosed by the reticulo-endothelial system (RES) cells (accumulation phase). In addition, the high T_1 relaxivity of Resovist can be utilized for dynamic imaging during vascular phase and delineating vessels by magnetic resonance angiography (MRA) sequences.
The physico-chemical characteristics of the ready-to-use solution of Resovist listed below are:

Osmolality at 37 °C (mOsm per kg H_2O)	- 333[10]
Viscosity at 37 °C (mPa·s)	- 1.03[10]
Density at 37° C (g per ml)	- 1.057[10]
pH	- 5.0 - 7.0

[1]

5.2 Pharmacokinetic properties

· Distribution and metabolism
After single intravenous administration, Resovist is distributed within the intravascular space and disappears quickly (in a bi-phasic manner) from blood/plasma due to selective uptake by the reticulo-endothelial system (RES) predominantly in liver and spleen. Biodegradation of the iron oxide core of ferucarbotran takes place within the cells of the RES.[4]

About 20 % of carboxydextran showed a very similar biodistribution as 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.[11]

Biotransformation finally yields in incorporation of the ferucarbotran iron into the "normal body iron pool". Thus the fate of the Resovist iron is finally identical to that of the normal biologically available iron.

At the maximum diagnostic dose of 1.4 ml Resovist (equivalent to 39.2 mg Fe) per patient the total body iron will only increase very slightly (< 2 %).[4]

· Elimination
In clinical trials (Phase I) the half-life of Resovist iron in serum for the initial phase, $t_{½a}$, was found to be 0.257±0.190 hours or less and for the terminal phase, $t_{½b}$ 4.36±0.75 hours or less. The half-lives $t_{½a}$ and $t_{½b}$, were not significantly related to the administered doses.[3]

In animal studies (rat) it was shown, that the main portion (> 70 %) of Resovist carboxydextran is subject to fast renal elimination. As for the iron oxide core, there is 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 postimplantation 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 fetuses in rabbits (at 0.8mmol Fe/kg/day representing about 80 times the diagnostic dose.)

· Local tolerance and contact-sensitizing potential
The local tolerance studies paravenous, intramuscular and intracutaneous administrations led to focal inflammatory reactions at the application sites.
It was additionally shown that inadvertent misplacement of the injection of Resovist may result in a long-lasting pigment-like discoloration of the skin at the administration site.15
Thus intravenous administration should be strictly adhered to when Resovist is given to humans (cf. 4.4 "Special warnings").

Resovist showed no evidence of a sensitizing (contact-allergenic) potential using the maximization test in guinea-pigs.
It has been observed that Resovist induces anaphylactic (hypersensitivity) reactions in dextran-sensitized dogs. Those reactions might also occur in rare cases in humans (cf. 4.4 "Special warnings").

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients1
L-(+)- lactic acid
mannitol
sodium hydroxide
water for injection..

6.2 Incompatibilities
Must not be mixed with other drugs.

6.3 Shelf life

For the product as packaged for sale: 3 years for all presentations.

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

· 2.0 ml injection vials filled with 1.6 ml[21]
Injection vial: colorless glass
Stopper: chlorobutyl elastomer
Flanged cap: Snap cap flanged closure, aluminum with internal and external lacquer, with colored plastic cap made of polypropylene

· 2.25 ml prefilled syringes filled with 0.9, 1.1 and 1.4 ml[22]
Barrel: colorless glass siliconized with silicone oil emulsion
Plunger stopper: chlorobutyl elastomer, siliconized with silicone oil
Tip cap: chlorobutyl elastomer
Each pack contains a Sterifix Pury consisting of a male Luer Lock filter hub: acrylonitrile/butadiene/styrene copolymer with a liquid filter of 5 µm.
The filter material is made of polyamide 66.

6.6 Instructions for use / handling

Resovist is a ready-to-use aqueous solution. Vials containing contrast media are not intended for the withdrawal of multiple doses. The rubber stopper should never be pierced more than once. Resovist should not be drawn into the syringe until immediately before use.

The tip cap should not be removed from the prefilled syringe until immediately before use.

Resovist 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 connected tubing, if. required.To ensure proper placement of the injection needle, it is recommended that sterile physiological saline be injected before Resovist is administered. After the injection of the contrast medium, the connective tubing and the needle should be flushed using sterile physiological saline. A three-way stopcock connected to the tube can facilitate this procedure.

Any contrast agent medium not used in one examination must be discarded.

Manufacturer: Schering AG, Germany

Importer: Agis Commercial Agencies (1989) Ltd.

30.4.02

Reference 49: Feraheme™ ferumoxytol injection: highlights of prescribing information. Published by: AMAG Pharmaceuticals Inc., USA, 2015.

Feraheme™
ferumoxytol injection

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Feraheme safely and effectively. See full prescribing information for Feraheme.

FERAHEME® (ferumoxytol) Injection
For Intravenous (IV) use
Initial U.S. Approval: 2009

RECENT MAJOR CHANGES

Boxed Warning	03/2015
Dosage and Administration (2)	03/2015
Warnings and Precautions, Serious Hypersensitivity Reactions (5.1)	03/2015

WARNING: RISK FOR SERIOUS HYPERSENSITIVITY/ANAPHYLAXIS REACTIONS
See full prescribing information for complete boxed warning.

Fatal and serious hypersensitivity reactions including anaphylaxis have occurred in patients receiving Feraheme. Initial symptoms may include hypotension, syncope, unresponsiveness, cardiac/cardiorespiratory arrest.

- **Only administer Feraheme when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions. (5.1)**
- **Observe for signs or symptoms of hypersensitivity reactions during and for at least 30 minutes following Feraheme infusion including monitoring of blood pressure and pulse during and after Feraheme administration. (5.1)**
- **Hypersensitivity reactions have occurred in patients in whom a previous Feraheme dose was tolerated. (5.1)**

INDICATIONS AND USAGE

Feraheme is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease (CKD). (1)

DOSAGE AND ADMINISTRATION

- The recommended dose of Feraheme is an initial 510 mg dose followed by a second 510 mg dose 3 to 8 days later.
- Administer Feraheme as an intravenous infusion in 50-200 mL 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP over at least 15 minutes

DOSAGE FORMS AND STRENGTHS

Injection: 510 mg iron per17 mL (30 mg per mL) in single use vials. (3)

CONTRAINDICATIONS

- Known hypersensitivity to Feraheme or any of its components.
- History of allergic reaction to any intravenous iron product

WARNINGS AND PRECAUTIONS

- Greater risk of anaphylaxis in patients with multiple drug allergies. (5.1).
- Hypotension: Feraheme may cause hypotension. Monitor for signs and symptoms of hypotension following each administration of Feraheme. (5.2)
- Iron Overload: Regularly monitor hematologic responses during Feraheme therapy. Do not administer Feraheme to patients with iron overload. (5.3)
- Magnetic Resonance Imaging: Feraheme can alter magnetic resonance imaging (MRI) studies. (5.4)

ADVERSE REACTIONS

The most common adverse reactions (≥ 2%) following the administration of Feraheme are diarrhea, nausea, dizziness, hypotension, constipation, and peripheral edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS with Feraheme, contact AMAG Pharmaceuticals, Inc. at 1-877-411-2510, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 03/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK FOR SERIOUS HYPERSENSITIVITY/ANAPHYLAXIS REACTIONS

Fatal and serious hypersensitivity reactions including anaphylaxis have occurred in patients receiving Feraheme. Initial symptoms may include hypotension, syncope, unresponsiveness, cardiac/cardiorespiratory arrest.

- **Only administer Feraheme when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions** [*see Warnings and Precautions (5.1)*].
- **Observe for signs or symptoms of hypersensitivity reactions during and for at least 30 minutes following Feraheme infusion including monitoring of blood pressure and pulse during and after Feraheme administration** [*see Warnings and Precautions (5.1)*].
- **Hypersensitivity reactions have occurred in patients in whom a previous Feraheme dose was tolerated** [*see Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

Feraheme is indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease (CKD).

2 DOSAGE AND ADMINISTRATION

The recommended dose of Feraheme is an initial 510 mg dose followed by a second 510 mg dose 3 to 8 days later. Administer Feraheme as an intravenous infusion in 50-200 mL 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP over at least 15 minutes. Administer while the patient is in a reclined or semi-reclined position.

Feraheme, when added to intravenous infusion bags containing either 0.9% Sodium Chloride Injection, USP (normal saline), or 5% Dextrose Injection, USP, at concentrations of 2-8 mg elemental iron per mL, should be used immediately but may be stored at controlled room temperature (25°C ± 2°C) for up to 4 hours.

The dosage is expressed in terms of mg of elemental iron, with each mL of Feraheme containing 30 mg of elemental iron. Evaluate the hematologic response (hemoglobin, ferritin, iron and transferrin saturation) at least one month following the second Feraheme infusion. The recommended Feraheme dose may be readministered to patients with persistent or recurrent iron deficiency anemia.

For patients receiving hemodialysis, administer Feraheme once the blood pressure is stable and the patient has completed at least one hour of hemodialysis. Monitor for signs and symptoms of hypotension following each Feraheme infusion.

Allow at least 30 minutes between administration of Feraheme and administration of other medications that could potentially cause serious hypersensitivity reactions and/or hypotension, such as chemotherapeutic agents or monoclonal antibodies.

Inspect parenteral drug products visually for the absence of particulate matter and discoloration prior to administration.

3 DOSAGE FORMS AND STRENGTHS

Feraheme Injection is available in single use vials. Each vial contains 510 mg of elemental iron in 17 mL (30 mg per mL).

4 CONTRAINDICATIONS

Feraheme is contraindicated in patients with:

- Known hypersensitivity to Feraheme or any of its components
- History of allergic reaction to any intravenous iron product

5 WARNINGS AND PRECAUTIONS

5.1 Serious Hypersensitivity Reactions

Fatal and serious hypersensitivity reactions including anaphylaxis, presenting with cardiac/cardiorespiratory arrest, clinically significant hypotension, syncope, or unresponsiveness have occurred in patients receiving Feraheme [*see Boxed Warning*]. Other adverse reactions potentially associated with hypersensitivity have occurred (pruritus, rash, urticaria, and wheezing). These reactions have occurred following the first dose or subsequent doses in patients in whom a previous Feraheme dose was tolerated.

Patients with a history of multiple drug allergies may have a greater risk of anaphylaxis with parenteral iron products. Carefully consider the potential risks and benefits before administering Feraheme to these patients.

Only administer Feraheme when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions. Closely observe patients for signs and symptoms of hypersensitivity including monitoring of blood pressure and pulse during and after Feraheme administration for at least 30 minutes and until clinically stable following completion of each infusion [*see Adverse Reactions (6.2)*].

In clinical studies predominantly in patients with CKD, serious hypersensitivity reactions were reported in 0.2% (3/1,726) of subjects receiving Feraheme. Other adverse reactions potentially associated with hypersensitivity (e.g., pruritus, rash, urticaria or wheezing) were reported in 3.7% (63/1,726) of these subjects. In other trials excluding patients with Stages 4 and 5 CKD, moderate to severe hypersensitivity reactions were reported in 2.6% (26/1014) of patients treated with Feraheme.

In the post-marketing experience, fatal and serious anaphylactic type reactions presenting with cardiac/ cardiorespiratory arrest, clinically significant hypotension, syncope, and unresponsiveness have been reported. Elderly patients with multiple or serious co-morbidities who experience hypersensitivity reactions and/or hypotension following administration of Feraheme may have more severe outcomes [*see Boxed Warning, Adverse Reactions (6.2) and Use in Specific Populations (8.5)*].

5.2 Hypotension

Severe adverse reactions of clinically significant hypotension have been reported. In clinical studies, hypotension was reported in 1.9% (33/1,726) of subjects, including three patients with serious hypotensive reactions. Hypotension has also been reported in the post-marketing experience [*see Adverse Reactions from Post-marketing Spontaneous Reports (6.2)*]. Monitor patients for signs and symptoms of hypotension following each Feraheme administration [*see Dosage and Administration (2)* and *Warnings and Precautions (5.1)*].

5.3 Iron Overload

Excessive therapy with parenteral iron can lead to excess storage of iron with the possibility of iatrogenic hemosiderosis. Regularly monitor the hematologic response during parenteral iron therapy [*see Dosage and Administration (2)*]. Do not administer Feraheme to patients with iron overload.

In the 24 hours following administration of Feraheme, laboratory assays may overestimate serum iron and transferrin bound iron by also measuring the iron in the Feraheme complex.

5.4 Magnetic Resonance (MR) Imaging

Administration of Feraheme may transiently affect the diagnostic ability of MR imaging. Anticipated MR imaging studies should be conducted prior to the administration of Feraheme. Alteration of MR imaging studies may persist for up to 3 months following the last Feraheme dose. If MR imaging is required within 3 months after Feraheme administration, use T1- or proton density-weighted MR pulse sequences to minimize the Feraheme effects; MR imaging using T2-weighted pulse sequences should not be performed earlier than 4 weeks after the administration of Feraheme. Maximum alteration of vascular MR imaging is anticipated to be evident for 1 – 2 days following Feraheme administration [*see Clinical Pharmacology (12.3)*].

Feraheme will not interfere with X-ray, computed tomography (CT), positron emission tomography (PET), single photon emission computed tomography (SPECT), ultrasound or nuclear medicine imaging.

6 ADVERSE REACTIONS

Feraheme administration may cause serious hypersensitivity reactions and hypotension [*see Warnings and Precautions (5.1),(5.2)*].

In clinical studies, 1,726 subjects were exposed to Feraheme; 1,562 of these had CKD and 164 did not have CKD. Of these subjects 46% were male and the median age was 63 years (range of 18 to 96 years).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug may not reflect the rates observed in practice.

6.1 Adverse Reactions in Clinical Studies

Across the three randomized clinical trials [Trial 1, 2, and 3, *see Clinical Studies (14)*], a total of 605 patients were exposed to two injections of 510 mg of Feraheme and a total of 280 patients were exposed to 200 mg/day of oral iron for 21 days. Most patients received their second Feraheme injection 3 to 8 days after the first injection.

Adverse reactions related to Feraheme and reported by ≥ 1% of Feraheme-treated patients in the randomized clinical trials are listed in Table 1. Diarrhea (4.0%), constipation (2.1%) and hypertension (1.0%) have also been reported in Feraheme-treated patients.

Table 1: Adverse Reactions to Feraheme Reported in ≥1% of Patients with CKD

Adverse Reactions	Feraheme 2 x 510 mg (n = 605)	Oral Iron (n = 280)
Nausea	3.1%	7.5%
Dizziness	2.6%	1.8%
Hypotension	2.5%	0.4%
Peripheral Edema	2.0%	3.2%
Headache	1.8%	2.1%
Edema	1.5%	1.4%
Vomiting	1.5%	5.0%
Abdominal Pain	1.3%	1.4%
Chest Pain	1.3%	0.7%
Cough	1.3%	1.4%
Pruritus	1.2%	0.4%
Pyrexia	1.0%	0.7%
Back Pain	1.0%	0%
Muscle Spasms	1.0%	1.4%
Dyspnea	1.0%	1.1%
Rash	1.0%	0.4%

In clinical trials, adverse reactions leading to treatment discontinuation and occurring in ≥ 2 Feraheme-treated patients included hypotension, infusion site swelling, increased serum ferritin level, chest pain, diarrhea, dizziness, ecchymosis, pruritus, chronic renal failure, and urticaria.

Following completion of the controlled phase of the trials, 69 patients received two additional 510 mg intravenous injections of Feraheme (for a total cumulative dose of 2.04 g). Adverse reactions following this repeat Feraheme dosing were similar in character and frequency to those observed following the first two intravenous injections.

In a placebo-controlled, cross-over trial, 713 patients with CKD received a single 510 mg dose of Feraheme. Adverse reactions reported by these patients were similar in character and frequency to those observed in other clinical trials.

6.2 Postmarketing Experience

Because adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following serious adverse reactions have been reported from the post-marketing experience with Feraheme: fatal, life-threatening, and serious anaphylactic-type reactions, cardiac/cardiorespiratory arrest, clinically significant hypotension, syncope, unresponsiveness, loss of consciousness, tachycardia/rhythm abnormalities, angioedema, ischemic myocardial events, congestive heart failure, pulse absent, and cyanosis. These adverse reactions have usually occurred within 30 minutes after the administration of Feraheme. Reactions have occurred following the first dose or subsequent doses of Feraheme.

7 DRUG INTERACTIONS

Drug-drug interaction studies with Feraheme were not conducted. Feraheme may reduce the absorption of concomitantly administered oral iron preparations.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no studies of Feraheme in pregnant women. In animal studies, ferumoxytol caused fetal malformations and decreased fetal weights at maternally toxic doses of 6 times the estimated human daily dose. Use Feraheme during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of ferumoxytol during organogenesis, at doses of 31.6 mg Fe/kg/day in rats and 16.5 mg Fe/kg/day in rabbits, did not result in maternal or fetal effects. These doses are approximately 2 times the estimated human daily dose based on body surface area. In rats, administration of ferumoxytol during organogenesis at a maternally toxic dose of 100 mg Fe/kg/day, approximately 6 times the estimated human daily dose based on body surface area, caused a decrease in fetal weights. In rabbits, administration of ferumoxytol during organogenesis at a maternally toxic dose of 45 mg Fe/kg/day, approximately 6 times the estimated human daily dose based on body surface area, was associated with external and/or soft tissue fetal malformations and decreased fetal weights.

8.3 Nursing Mothers

It is not known whether Feraheme is present in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to avoid Feraheme, taking into account the importance of Feraheme to the mother and the known benefits of nursing.

8.4 Pediatric Use

The safety and effectiveness of Feraheme in pediatric patients (less than 18 years old) have not been established.

8.5 Geriatric Use

In controlled clinical trials, 330 patients ≥ 65 years of age were treated with Feraheme. No overall differences in safety and efficacy were observed between older and younger patients in these trials, but greater sensitivity of older individuals cannot be ruled out. In general, dose administration to an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients with multiple or serious co-morbidities who experience hypersensitivity reactions and/or hypotension following administration of Feraheme may have more severe outcomes. The potential risks and benefits of Feraheme administration should be carefully considered in these patients [*see Dosage and Administration (2) Serious Hypersensitivity Reactions (5.1) and Clinical Studies (14)*].

10 OVERDOSAGE

Limited data are available regarding overdosage of Feraheme in humans.

Excessive dosages of Feraheme may lead to accumulation of iron in storage sites potentially leading to hemosiderosis. Do not administer Feraheme to patients with iron overload [*Warnings and Precautions (5.3)*].

11 DESCRIPTION

Feraheme, an iron replacement product, is a non-stoichiometric magnetite (superparamagnetic iron oxide) coated with polyglucose sorbitol carboxymethylether. The overall colloidal particle size is 17-31 nm in diameter. The chemical formula of Feraheme is $Fe_{5874}O_{8752}$-$C_{11719}H_{18682}O_{9933}Na_{414}$ with an apparent molecular weight of 750 kDa.

Feraheme Injection is an aqueous colloidal product that is formulated with mannitol. It is a black to reddish brown liquid, and is provided in single use vials containing 510 mg of elemental iron. Each mL of the sterile colloidal solution of Feraheme Injection contains 30 mg of elemental iron and 44 mg of mannitol, and has low bleomycin-detectable iron. The formulation is isotonic with an osmolality of 270-330 mOsm/kg. The product contains no preservatives, and has a pH of 6 to 8.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Feraheme consists of a superparamagnetic iron oxide that is coated with a carbohydrate shell, which helps to isolate the bioactive iron from plasma components until the iron-carbohydrate complex enters the reticuloendothelial system macrophages of the liver, spleen and bone marrow. The iron is released from the iron-carbohydrate complex within vesicles in the macrophages. Iron then either enters the intracellular storage iron pool (e.g., ferritin) or is transferred to plasma transferrin for transport to erythroid precursor cells for incorporation into hemoglobin.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a randomized, positive- and placebo-controlled, parallel-group study, healthy subjects received a supratherapeutic regimen of Feraheme (1.02 g given as two 510 mg doses within 24 hours), placebo or a single dose of 400 mg moxifloxacin (positive control). Results demonstrated no effect of Feraheme on QT interval durations. No clinically meaningful effect of Feraheme on heart rate was observed.

12.3 Pharmacokinetics

The pharmacokinetic (PK) behavior of Feraheme has been examined in healthy subjects and in patients with CKD stage 5D on hemodialysis. Feraheme exhibited dose-dependent, capacity-limited elimination from plasma with a half life of approximately 15 hours in humans. The clearance (CL) was decreased by increasing the dose of Feraheme. Volume of distribution (Vd) was consistent with plasma volume, and the mean maximum observed plasma concentration (C_{max}) and terminal half-life ($t_{1/2}$) values increased with dose. The estimated values of CL and Vd following two 510 mg doses of Feraheme administered intravenously within 24 hours were 69.1 mL/hr and 3.16 L, respectively. The C_{max} and time of maximum concentration (t_{max}) were 206 mcg/mL and 0.32 hr, respectively. Rate of infusion had no influence on Feraheme PK parameters. No gender differences in Feraheme PK parameters were observed. Feraheme is not removed by hemodialysis.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Ferumoxytol was not tested for carcinogenic effects. In standard genotoxicity tests, ferumoxytol showed no evidence of mutagenic activity in an *in vitro* Ames test or clastogenic activity in either an *in vitro* chromosomal aberration assay or an *in vivo* micronucleus assay.

No adverse effects on fertility or general reproductive performance were noted in animal studies. Ferumoxytol had no effect on male or female fertility or general reproductive function in rats.

14 CLINICAL STUDIES

The safety and efficacy of Feraheme for the episodic treatment of iron deficiency anemia in patients with CKD were assessed in three randomized, open-label, controlled clinical trials (Trial 1, 2 and 3). These trials also included an uncontrolled, follow-up phase in which patients with persistent iron deficiency anemia could receive two additional 510 mg intravenous injections of Feraheme. The major efficacy results from the controlled phase of each study are shown in Table 2.

In all three trials, patients with CKD and iron deficiency anemia were randomized to treatment with Feraheme or oral iron. Feraheme was administered as two 510 mg intravenous single doses and oral iron (ferrous fumarate) was administered as a total daily dose of 200 mg elemental iron daily for 21 days. The major trial outcomes assessed the change in hemoglobin from baseline to Day 35. Trial 1 and 2 enrolled patients with non-dialysis dependent CKD and Trial 3 enrolled patients who were undergoing hemodialysis.

In Trial 1, the mean age of patients was 66 years (range, 23 to 95); 60% were female; 65% were Caucasian, 32% were Black, and 2% were other races. In the Feraheme and oral iron groups, 42% and 44% of patients, respectively, were receiving erythropoiesis stimulating agents (ESAs) at baseline.

In Trial 2, the mean age of patients was 65 years (range, 31 to 96); 61% were female; 58% were Caucasian, 35% were Black, and 7% were other races. In the Feraheme and oral iron groups, 36% and 43% of patients, respectively, were receiving ESAs at baseline.

In Trial 3, the mean age of patients was 60 years (range, 24 to 87); 43% were female; 34% were Caucasian, 59% were Black, and 7% were other races. All patients were receiving ESAs.

Table 2 shows the Baseline and mean change to Day 35 in hemoglobin (Hgb, g/dL), transferrin saturation (TSAT, %) and ferritin (ng/mL) in each treatment group for Trial 1, 2, and 3.

Table 2: Changes from Baseline to Day 35 in Hemoglobin, Transferrin Saturation and Ferritin (Intent to Treat Population)

	Trial 1 Non-Dialysis CKD		Trial 2 Non-Dialysis CKD		Trial 3 CKD on Dialysis	
ENDPOINT	Feraheme n = 226	Oral Iron n = 77	Feraheme n = 228	Oral Iron n = 76	Feraheme n = 114	Oral Iron n = 116
Baseline Hgb (mean ± SD, g/dL)	**9.9** ± 0.8	**9.9** ± 0.7	**10.0** ± 0.7	**10.0** ± 0.8	**10.6** ± 0.7	**10.7** ± 0.6
Hgb change from Baseline at Day 35 (mean ± SD, g/dL)	**1.2*** ± 1.3	**0.5** ± 1.0	**0.8*** ± 1.2	**0.2** ± 1.0	**1.0*** ± 1.1	**0.5** ± 1.1
Baseline TSAT (mean ± SD, %)	**9.8** ± 5.4	**10.4** ± 5.2	**11.3** ± 6.1	**10.1** ± 5.5	**15.7** ± 7.2	**15.9** ± 6.3
TSAT change from Baseline at Day 35 (mean ± SD, %)	**9.2** ± 9.4	**0.3** ± 4.7	**9.8** ± 9.2	**1.3** ± 6.4	**6.4** ± 12.6	**0.6** ± 8.3
Baseline ferritin (mean ± SD, ng/mL)	**123.7** ± 125.4	**146.2** ± 136.3	**146.1** ± 173.6	**143.5** ± 144.9	**340.5** ± 159.1	**357.6** ± 171.7
Ferritin change from Baseline at Day 35 (mean ± SD, ng/mL)	**300.7** ± 214.9	**0.3** ± 82.0	**381.7** ± 278.6	**6.9** ± 60.1	**233.9** ± 207.0	**-59.2** ± 106.2

* $p \leq 0.001$ for main efficacy endpoint

Following completion of the controlled phase of each of the Phase 3 trials, patients who were iron deficient and anemic could receive two additional 510 mg intravenous injections of Feraheme for a total cumulative dose of 2.04 g. Overall, 69 patients received two additional 510 mg intravenous injections of Feraheme, and on Day 35 following these additional injections, the majority of these patients (70%) experienced an increase in hemoglobin and iron parameters (TSAT and ferritin). The mean change (±SD) in hemoglobin level from the retreatment baseline for patients with an increase in hemoglobin was 0.86 (± 0.68) g/dL and was 0.5 (± 0.8) g/dL for all patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Feraheme is available in single use vials in the following package sizes (Table 3).

Table 3: Feraheme Packaging Description

NDC Code	Dose / Total volume per vial	Vials / Carton
NDC 59338-775-01	510 mg/ 17 mL	1
NDC 59338-775-10	510 mg/ 17 mL	10

16.2 Stability and Storage

Store at 20° to 25°C (68° to 77°F). Excursions permitted to 15° – 30°C (59° – 86°F) [see USP controlled room temperature].

17 PATIENT COUNSELING INFORMATION

Refer patients to the FDA approved Patient Package Insert.

Prior to Feraheme administration:

- Question patients regarding a history of allergy to intravenous iron or any medications.
- Advise patients of the serious risks associated with Feraheme.
- Advise patients to immediately report any signs and symptoms of hypersensitivity that may develop during and following Feraheme administration, such as rash, itching, dizziness, lightheadedness, swelling and breathing problems. Advise patients to seek immediate medical attention if these occur [*see Warnings and Precautions (5)*].

U.S Patents: 6,599,498 B1; 7,553,479 B2; 7,871,597 B2; 8,501,158 B2

Distributed by: AMAG Pharmaceuticals, Inc. Waltham, MA 02451

AMAG Pharmaceuticals®, Inc.
1100 Winter Street
Waltham, MA 02451

Reference 50: Sienna+® for use with Sentimag®. Published by: Endomag Limited, Cambridge, UK, 2015.

Sienna+® for use with Sentimag®

The information contained in this manual is subject to change without notice. Please visit www.endomag.com for the latest version.

Indications for Use

Sienna+® is a magnetic tracer intended and calibrated for use with the Sentimag® device ONLY as part of an overall system to mark and locate lymph nodes in cancer patients prior to their surgical removal.

According to its Intended Use, Sienna+® must be detected within seven days after injection. Sienna+® is classified as a class IIa medical device by Medical Device Directive 93/42/EEC.

Description

Sienna+® is a blackish-brown sterile aqueous suspension of superparamagnetic carboxydextran-coated iron oxide particles in injectable water, supplied aseptically in single-use vials containing circa 2.2 ml. Each millilitre of Sienna+® contains circa 28 milligrams of iron.

Dosage and Administration

Recommended dose is 2 ml with the equivalent iron content of 55 mg +/- 4 mg per dose. Inspect the seal of the vial before use to ensure it is unbroken. Do not use if the vial cap is broken, the vial is leaking, or if the expiry date has passed.

For Breast: Draw 2 ml of Sienna+® via a sterile needle and 5 micron syringe filter into an appropriate sterile hypodermic syringe of minimum volume 5 ml and check the quantity. Replace the needle and syringe filter with a fresh sterile needle and draw 3 ml of 0.9% sterile saline into the syringe and briefly shake the syringe to mix. Administer Sienna+® by subcutaneous injection into either subareolar or peritumoral interstitial tissue, and follow with 5 minutes vigorous massage at the injection site. For subareolar injection, surgeons should wait at least **20 minutes** before attempting transcutaneous measurement of the axilla. Peritumoral injection may require a longer wait. Proceed with incision only after obtaining a **clear transcutaneous** signal with the Sentimag®. Migration may be slower in older or larger patients.

For other indications: Draw 2 ml of Sienna+® via a sterile needle and 5 micron syringe filter into an appropriate sterile hypodermic syringe and check the quantity. Administer Sienna+® by subcutaneous injection into peritumoral interstitial tissue and, where appropriate, follow with 5 minutes massage at the injection site. Proceed as above.

Contraindications

1. Sienna+® is contraindicated in any patient with hypersensitivity to iron oxide or dextran compounds.
2. Do not administer to any patient with an iron overload disease.
3. Do not administer to any patient with a metal implant close to the expected sentinel lymph node location.

Warnings and Precautions

1. Sienna+® is intended ONLY for use with the Sentimag® device, and is therefore subject to the Warnings and Precautions of the Sentimag® device including the precaution that the system should not be used in patients with pacemakers.
2. For injection into interstitial tissue ONLY.
3. For use ONLY by appropriately trained clinicians for detection of sentinel lymph nodes during surgical procedures.
4. Sienna+® can alter magnetic resonance imaging (MRI) studies of the injection and drainage site. Some amount of alteration may be long-term. Because of this, surgeons should consider whether Sienna+® is appropriate for a patient on a case by case basis.
5. Sienna+® is not intended for treatment of iron deficiency anaemia in patients or any other medicinal applications.
6. If inadvertently administered intravenously, anaphylactoid or cardiovascular reactions may occur.
7. Some transient or long-term brownish skin coloration may occur
8. Do not reuse, sterility cannot be guaranteed if the rubber seal on the vial has already been punctured.

Adverse Reactions

When similar material to that used in Sienna+® has been injected **intravenously**, the following undesirable effects have been reported: Common (<2%) – pain at the injection site, vasodilation, paresthesia. Uncommon (≥0.1% to <1%) – asthenia, back pain, injection site reactions, chest pain, nausea, vomiting, headache, taste perversion, pruritus, rash. Rare (≥0.01% to <0.1%) - hypersensitivity & anaphylaxis, hypertension, phlebitis, hyperesthesia, anxiety, dizziness, convulsion, parosmia, dyspnea, increased cough, rhinitis, eczema, urticaria. There have been a small number of reports of inflammatory and hypersensitivity response with intradermal injection. There is no evidence of adverse reaction following interstitial injection. **Sienna+® is intended for interstitial injection ONLY** and the majority of the dose is intended to be surgically removed leaving only a small interstitial residue.

Overdose

Overdose is unlikely if used as specified with a single 2 ml volume of Sienna+ administered as an interstitial injection.

Non-Clinical Toxicology

Sienna+® has been reviewed and tested as specified in EN 10993-1:2009 based on the specified site of injection and duration.

Use in Specific Populations

There have been no studies of Sienna+® in pregnant women, nursing mothers or paediatric patients.

Mechanism of Action

The lymphatic system comprises a network of vessels that drain tissue fluid (lymph) including the injected Sienna+® into lymph nodes and then the specialized organs involved in the immune system. The lymph nodes act as a filter, removing invading organisms or abnormal cells and other materials such as bacteria and cancer cells from the lymph fluid. Sienna+® particles are also trapped in the filter. They therefore become physically trapped in the node, allowing them to be used as a superparamagnetic marker which can be identified by the Sentimag® device.

The Sienna+® particles are trapped by the natural physical filtration action of the lymph node and are not part of a medicinal action.

Magnetic Fields

When the Sienna+® material is exposed to the excitation field of the Sentimag® the Sienna+® material responds with a temporarily induced magnetic field.

Storage

Store between 2°C and 30°C and such that temperature variations will be minimised.
DO NOT FREEZE.
Do not use after expiry date specified on vial.

Patient Counselling

1. Question patient regarding any prior history of reactions to iron oxide or dextran products.
2. Inform patient to report any signs and symptoms of hypersensitivity that may develop during and/or following administration, such as rash, itching, dizziness, lightheadedness.
3. Advise patient that some long-term brownish skin coloration may occur.
4. Advise patient that Sienna+ may alter post-operative magnetic resonance imaging (MRI) scans. Some alteration may be long-term.

Symbols

 Single Use

 Expiry Date specified on vial

 Lot or batch number specified on vial

 Catalogue Number

 Aseptically Filled

 Read Instructions

 Warnings and Cautions specified in instructions

 Do not use if vial is open or damaged

 Store between temperatures indicated

 Manufacturer

 CE mark for Medical Device as specified by the Medical Device Directive 93/42/EEC

Sienna+® for use with Sentimag®

Endomagnetics Ltd
The Jeffreys Building
Cowley Road, Cambridge
CB4 0WS, United Kingdom

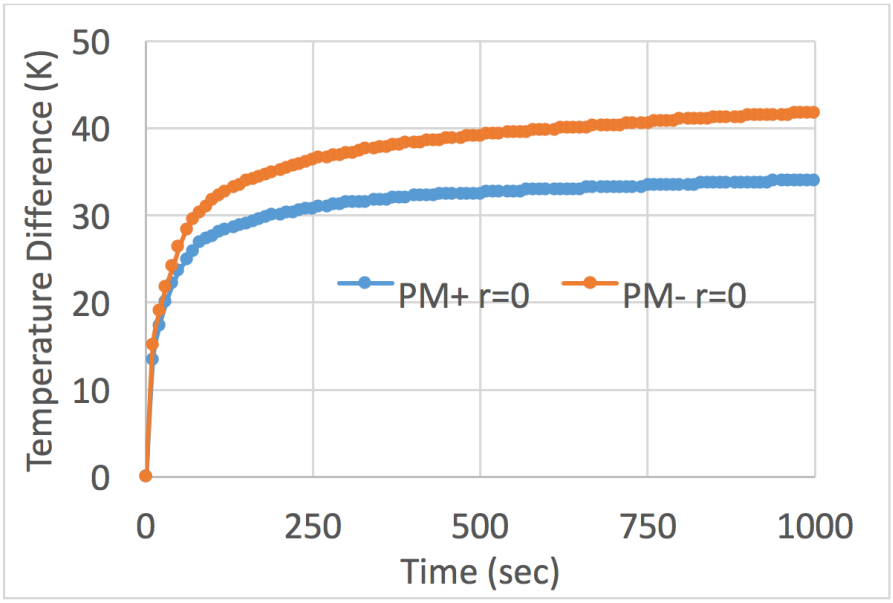
SIE-006, Issue 18.0, 05/10/15

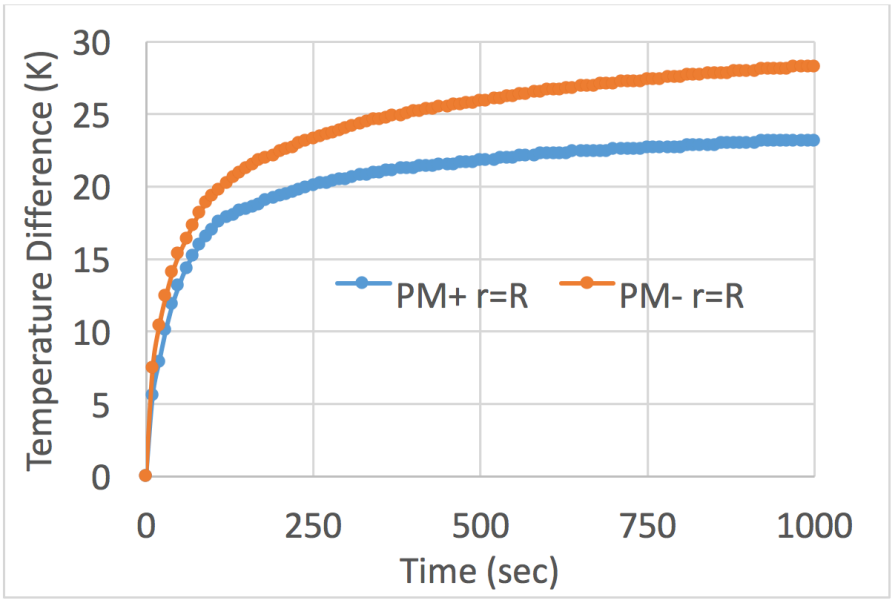
S2. Influence of perfusion and metabolism on bioheat model predictions for homogeneous spherical sources

In Section 4 of the paper we introduce the time-dependent, zero perfusion, zero metabolic heat generation bioheat model of Andrä et al. for the case of a homogeneous dispersion of magnetic hyperthermia agents over a sphere [1]. We note there that although this model is extremely simple, it has the advantage of being entirely analytical, which allows for facile manipulation of the model outcomes, as exemplified in the data presented in Figures 2 and 3 of the paper.

However, the question of how significant are the absence of perfusion and metabolism effects from the model is a very pertinent one. Fortunately, Cheng & Liu have published a comprehensive paper describing the results of their numerical analyses of the Pennes bioheat equation in spherical coordinates [2], in which they directly compare their results to those obtained using the Andrä model. After having shown that their numerical method gave them the same radial temperature profiles (ΔT as a function of the radius r) as the Andrä model at all time points, Cheng & Liu compared the time-dependence of the predicted ΔT values at the origin ($r = 0$) and at the boundary of the magnetic-particle infused spherical region ($r = R$).

Their reported data is shown in the figures below, which are adapted from their Figure 3 [2]. The red lines correspond to the predicted temperature evolution in the case that there is zero perfusion and zero metabolic heat generation, as per the Andrä model. The blue lines correspond to the predicted $T(t)$ curves for breast tumour and normal tissue, using a Pennes-type model in which the perfusion and metabolic rates in the tumour were estimated to be $\omega_{\mathrm{b1}} = 0.009$ m^{3}s^{-1}m^{-3} and $Q_{\mathrm{met1}} = 29$ kWm^{-3}; and in the healthy tissue, the lower figures of $\omega_{\mathrm{b2}} = 0.0018$ m^{3}s^{-1}m^{-3} and $Q_{\mathrm{met2}} = 450$ Wm^{-3}. The blood temperature was taken to be $T_{\mathrm{b}} = 37$ °C, and the product of the density and specific heat capacity of blood was taken to be $\rho_{\mathrm{b}} C_{\mathrm{b}} = 4.18 \times 10^6$ Jm^{-3}K. The thermal conductivities, densities, and specific heats of the tumour tissues and normal tissues were taken to be: $k_1 = 0.778$ WK^{-1}m, $\rho_1 = 1660$ kgm^{-3}, and $C_1 = 2540$ Jkg^{-1}K; and $k_2 = 0.642$ WK^{-1}m, $\rho_2 = 1000$ kgm^{-3}, and $C_2 = 3720$ Jkg^{-1}K respectively.

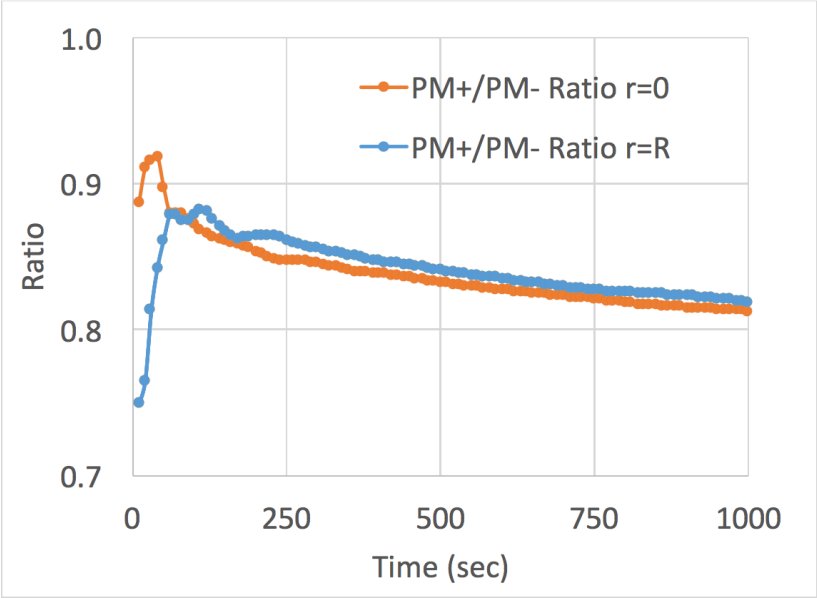




On inspection it is clear that the effect of perfusion and metabolism is to suppress the ΔT elevation. However, it is also clear that the difference between the two models is not huge, and, as shown in the figure below, is reasonably well approximated as a simple scaling factor of:

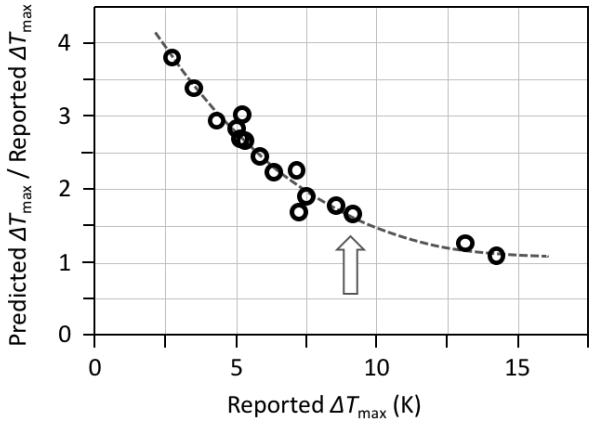
$$\Delta T(t)_{\text{with perfusion \& metabolism}} / \Delta T(t)_{\text{without perfusion \& metabolism}} \approx 0.84 \pm 0.02$$

over the range from $t = 250$ sec to $t = 1000$ sec.


1.0
0.9
0.8
0.7
Ratio
PM+/PM- Ratio r=0
PM+/PM- Ratio r=R
0
250
500
750
1000
Time (sec)

S3. Evaluation of the accuracy of the first-approximation Andrä model compared to reported *in vivo* values of $\Delta T_{\max}$

In Section 5 of the paper we briefly describe how we derive the data that is presented in Figure 4, *viz.*



by comparing the predicted $\Delta T_{\max}$ values determined using the analytical model described in Equation (12) with the reported clinical $\Delta T_{\max}$ values from the 2007 Johannsen et al. paper [3]. Here we describe in more detail how this figure was generated.

Looking first at the predicted values, we start with the assumption that the $\Delta T_{\max}$ value equates to the value of $\Delta T(\mathrm{r})$ at the centre of the magnetic-nanoparticle-infused region, i.e. at $r = 0$. From Equation (8) we see that:

$$\Delta T(r = 0) = \left[1 + \frac{k_2}{2k_1}\right] \Delta T(r = R) \,,$$

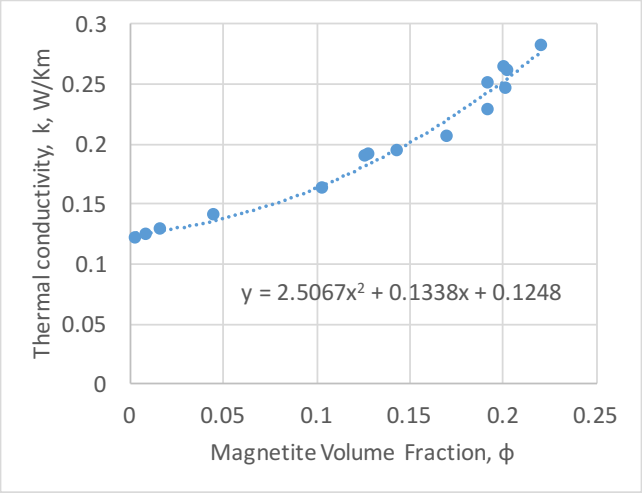
so that, as per the definition in Equation (10), $\Delta T_{\max} = \left[1 + \frac{k_2}{2k_1}\right] \Delta T_{\mathrm{R}}$. This then raises the question of what value to take for the thermal conductivity k_1 of the MNP-infused core region.

We can estimate this with reference to the data presented in Figure 1 of the paper by Fertman et al. (1987) on 'Thermal conductivity of magnetite magnetic fluids' [4], which shows the concentration dependence of a series of Fe_3O_4-based ferrofluids with Fe_3O_4-to-carrier-fluid volumetric fractions φ ranging from 0 to 22%. Digitising and reanalysing their data as per the figure below, we can see that:

$k_{\text{measured}} = k_{\text{carrier fluid}} + k_{\text{magnetite}}$, where

$k_{\text{carrier fluid}} = 0.125$ W/Km , and

$$k_{\text{magnetite}} = 0.134\,\varphi + 2.507\,\varphi^2 \ .$$



We can convert between the v/v fraction φ and the corresponding Fe concentration [Fe] in mg_{Fe}/ml via the molecular weights of Fe and O, and the density of magnetite (ca. 5240 mg/ml). For example, for $\varphi = 0.1$, in 1 ml we have 0.1 ml Fe_3O_4, which equates to 524 mg Fe_3O_4, and ca. (168/232)*524 = 380 mg of Fe. More generally:

$$\varphi = \frac{(232/168) \times [\text{Fe}]\ (\text{mg}_{\text{Fe}}/\text{ml})}{5240\ (\text{mg}_{\text{Fe}_3\text{O}_4}/\text{ml})} \ ; \qquad \text{and}$$

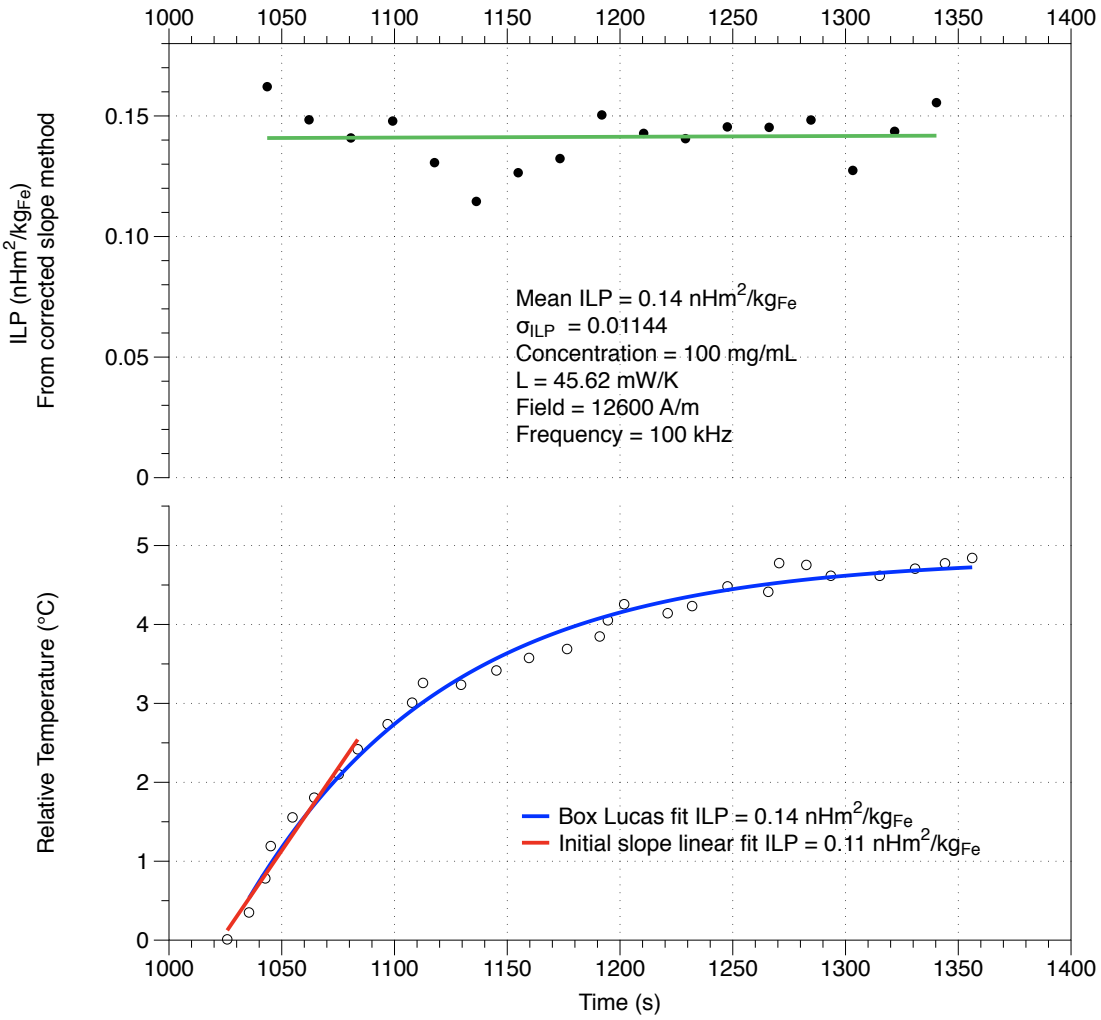
$$[\text{Fe}]\ (\text{mg}_{\text{Fe}}/\text{ml}) = \frac{5240\ (\text{mg}_{\text{Fe}_3\text{O}_4}/\text{ml}) \times \varphi}{(232/168)} \ .$$

From this we can see that even for a local Fe concentration of [Fe] = 100 mg_{Fe}/ml, the corresponding volume fraction is small, at $\varphi = 0.026$, and the contribution to the thermal conductivity, $k_{\text{magnetite}} = 0.134 \times 0.026 + 2.507 \times (0.026)^2 = 0.005\ \text{W/Km}$, is also small. This is the figure that is referred to in the text.

Regarding the *ILP* parameter, this is not stated explicitly in the Johannsen 2007 paper, and nor is the associated *SAR* specific absorption rate parameter. However, we can obtain an estimate of the *ILP* from an earlier paper from the same group [5], where they reported on preclinical (rat) experiments using the same 'MFL AS' material. In this paper Johannsen et al. note that the initial concentration of the magnetic fluid was 120 mg/ml of ferrite, which, assuming that the ferrite in question was magnetite, Fe_3O_4, corresponds to an initial concentration of 87 mg_{Fe}/ml. They also state that in their rat tumour model they chose how much to inject on the basis that 0.5 ml of their injectate would disperse over a tumour volume of 1 cm^3. This equates to a dispersion factor of

$V_d/V_i = 2.0$. However, they also note from their biodistribution experiments that they found a retention factor of approximately 80% in the treated group of rats. Combining these results, we deduce that the average iron concentration in the treated tumours was of order 87 mg_{Fe}/ml (the original injectate concentration) × 0.8 (the retention factor) / 2.0 (the dispersion factor) ≈ 35 mg_{Fe}/ml_{tissue}.

Having thus estimated the intratumoural iron concentration, it is therefore possible to deduce the *ILP* of the particles by analysing the magnetic heating data presented in Figure 1 of the paper. In particular, the data recorded from 17 to 22 minutes is especially well defined, and it is explicitly noted in the figure caption that the field amplitude was constant in that period at 12.6 kA/m. Applying the corrected slope method [6] to analyse the data, we obtained the fit shown below, with an *ILP* of ca. 0.14 nHm^2/kg assuming a nominal concentration of 100 mg_{Fe}/ml_{tissue}.



Scaling this to the adjusted concentration of 35 mg_{Fe}/ml_{tissue}, we obtain the figure quoted in the text, *viz.* an *ILP* of ca. 0.40 nHm^2/kg.

We are now in a position to address the clinical dataset presented in Table 1 of Johannsen 2007 [3]. The key reported data values are reproduced in the table on the following page, *viz.* the injectate volume, the CT-based retained volume (i.e. the volume of tissue in which measurable amounts of magnetic nanoparticles were retained), and the thermal-probe-measured maximum achieved temperatures.

The columns of derived data are as follows. The dispersion factor v was taken to be equal to the ratio of the CT-based retained volume V_r divided by the injectate volume V_i, with an important proviso being applied, in that it was assumed that v should not be less than 1.0, and that in the event that the measured V_r was less than the injected V_i (as in the cases of patients 1, 2, 3, 6, and 8), the explanation should lie in a less-than-unity retention of the injected fluid. For that reason, for those patients with $v = 1.00$ in the table, the retention factor retention $\mathcal{R}$ is less than one. Furthermore, it was assumed that any changes to the observed V_r volume between the first and last heating session would be either interpreted as an increase in dispersion factor (if the V_r increased, as for patients 1, 2, 3, 4, 6, 7, and 10), or a decrease in the retention factor (if the V_r decreased, as for patients 5, 8, and 9). The reported T_{max} values were converted to ΔT_{max} values by subtracting 37 °C.

	REPORTED DATA						*DERIVED DATA*				
Intrinsic loss power, ILP, nHm2 per kg_Fe	**Patient no.**	**Heat session**	**Injectate volume, V_i, ml**	**CT-based retained volume, V_r, ml**	**Applied magnetic field amplitude, H, kA/m**	**Reported T (max), C**	**Dispersion factor (ratio of V_r to V_i), v, unitless**	**Retention, R**	**Reported Delta-T (max), K**	**Predicted Delta-T (max), K**	**Ratio predicted deltaT_max / reported deltaT_max**
0.40	1	1	12.00	11.20	4.4	44.2	1.00	0.93	7.2	16.1	2.23
0.40		6	12.00	15.90	4.4	42.1	1.42	0.93	5.1	14.3	2.80
0.40	2	1	9.50	7.90	4.3	44.3	1.00	0.83	7.3	12.2	1.67
0.40		5	9.50	8.10	4.3	40.6	1.03	0.83	3.6	12.1	3.35
0.40	3	1	4.00	0.80	4.7	40.7	1.00	0.20	3.7	3.2	0.85
0.40		6	4.00	0.90	4.7	40.5	1.13	0.20	3.5	3.0	0.87
0.40	4	1	12.00	16.40	4.5	42.3	1.37	1.00	5.3	15.9	3.0
0.40		6	12.00	22.30	4.5	42.4	1.86	1.00	5.4	14.3	2.7
0.40	5	1	11.60	18.60	4.5	44.0	1.60	1.00	7.0	14.7	2.1
0.40		6	11.60	2.80	4.5	42.2	1.60	0.15	5.2	4.2	0.8
0.40	6	1	10.00	8.40	4.5	42.2	1.00	0.84	5.2	13.9	2.67
0.40		6	10.00	10.60	4.5	41.4	1.26	0.84	4.4	12.8	2.92
0.40	7	1	13.50	17.90	4.2	45.6	1.33	1.00	8.6	15.1	1.75
0.40		6	13.50	21.00	4.2	44.6	1.56	1.00	7.6	14.3	1.88
0.40	8	1	10.50	8.80	4.5	42.9	1.00	0.84	5.9	14.3	2.43
0.40		6	10.50	5.60	4.5	39.8	1.00	0.53	2.8	10.6	3.78
0.40	9	1	14.00	30.70	4.7	50.2	2.19	1.00	13.2	16.4	1.24
0.40		6	14.00	27.00	4.7	51.3	2.19	0.88	14.3	15.0	1.05
0.40	10	1	11.20	15.80	4.5	46.2	1.41	1.00	9.2	15.0	1.63
0.40		6	11.20	19.10	4.5	43.4	1.71	1.00	6.4	14.1	2.20

The predicted $\Delta T_{\max}$ values were obtained by applying Equation (12),

$$\Delta T_{\max} \simeq 1.5\ (48\pi^2 v)^{-\frac{1}{3}} \left(\frac{ILP\ H^2\ f}{k_2}\right)\ c\ (\mathcal{R}V_{\mathrm{i}})^{\frac{2}{3}} \quad ,$$

with $\Delta T_{\max} \approx 1.5 \times \Delta T_{\mathrm{R}}$ on the basis that the thermal conductivity of the composite core is very similar to that of the surrounding tissue, and with the injectate volume V_{i} scaled by the retention factor $\mathcal{R}$.

Thus, for example, for Patient 1, session 1:

v = 1.00 is the dispersion factor

ILP = 0.40 nHm^2/kg as derived above

H = 4.4 kA/m is the field intensity

f = 100 kHz is the alternating field frequency

k_2 = 0.52 W/Km is the thermal conductivity of the prostate tissue

c = 112 mg$_{\mathrm{Fe}}$/ml is the concentration of the injected magnetic fluid

V_{i} = 12.0 ml injected and the scaled by the retention factor $\mathcal{R}$ = 0.93

Bringing these all together we obtain:

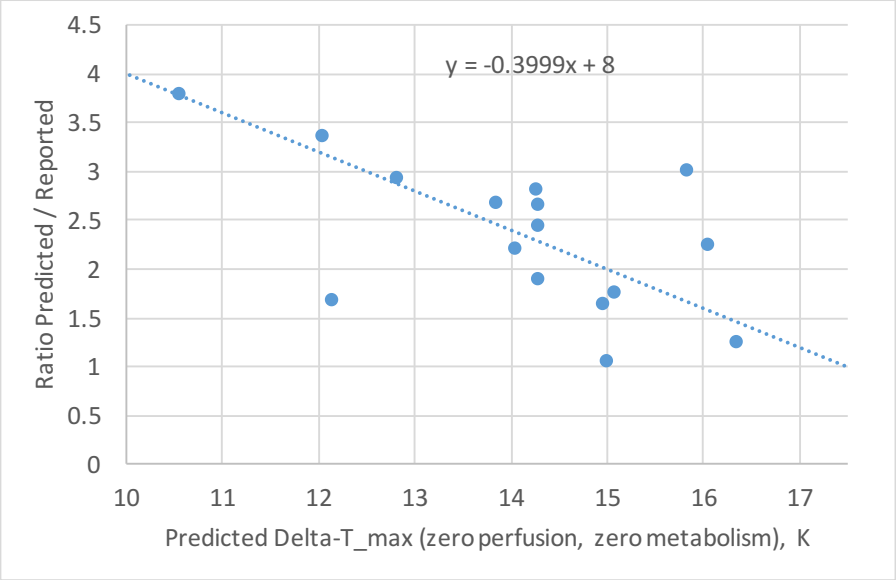
$$\Delta T_{\max} = 1.5 \times (48\pi^2)^{-\frac{1}{3}} \times \left(\frac{0.4 \times 4.4^2 \times 100\ \mathrm{W/kg}}{0.52\ \mathrm{W/Km}}\right)$$

$$\times\ (112\ \mathrm{kg/m^3})\ (0.93 \times 12 \times 10^{-6}\ \mathrm{m^3})^{\frac{2}{3}} \quad ,$$

which computes to 16.07 K, which is listed in the table as the predicted $\Delta T_{\max}$.

It should be noted that on analysing the data from Table 1 in Johannsen et al. 2007, it was found that the data recorded for patients 3 and 5 were anomalous. For patient 3 the injectate volume and the retention factors were both exceptionally small, and for patient 5 the retained volume after the first treatment fell dramatically to an $\mathcal{R}$ of ca. 0.15. For these reasons the datapoints corresponding to both of these cases were excluded from the set used for the preparation of Figure 4 in the paper.

Lastly, we note with some caution that it may be feasible, in the case of prostate cancer tissue, to utilise the data in Figure 4 to apply a post-hoc correction to the predicted $\Delta T_{\max}$ values, as a way of at least partially accounting for the effect of perfusion and metabolism. This should be thought of only as a very crude approximation, and no substitute for proper modelling and analysis, but nevertheless it is interesting to look at it. We do this by plotting the data as follows:



where we have manually superimposed a linear approximation to the data. Taking this at face value we might therefore apply the following corrections:

$$\Delta T_{\max}\ (\text{corrected}\ ) = \frac{\Delta T_{\max}\ (\text{predicted})}{8.0 - 0.4 \times \Delta T_{\max}\ (\text{predicted})}$$

for $\Delta T_{\max}\ (\text{predicted}) \leq 17.5$ K; and

$$\Delta T_{\max}\ (\text{corrected}\ ) = \Delta T_{\max}\ (\text{predicted})$$

for $\Delta T_{\max}\ (\text{predicted}) > 17.5$ K.

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