ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTH OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
DE - Germany	Schering Deutchland GmbH Max-Dohrn-Strasse 10 D-10589 Berlin	Gadograf	1 mmol/ml	Solution for injection	Intravenous use
DE - Germany	Schering Deutchland GmbH Max-Dohrn-Strasse 10 D-10589 Berlin	Gadograf	1 mmol/ml	Solution for Injection in prefilled syringe	Intravenous use
ES - Spain	Schering España, S.A. c/ Mendez Alvaro, 55 28045 Madrid	Gadograf	1 mmol/ml	Solution for injection	Intravenous use
ES - Spain	Schering España, S.A. c/ Mendez Alvaro, 55 28045 Madrid	Gadograf	1 mmol/ml	Solution for Injection in prefilled syringe	Intravenous use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF GADOBUTROL

1. Introduction and background

Gadograf contains gadobutrol, a neutral macrocyclic gadolinium complex with contrast-enhancing properties, which is used for magnetic resonance imaging (MRI). MRI is a widely used technique for the evaluation and detection of diffuse liver disease as well as for further characterization of focal liver disease. Gd-based contrast agents are frequently administered prior to contrast-enhanced dynamic liver MRI and may improve both detection and classification of focal liver lesions.

In renal pathologies, MRI techniques have become increasingly important, particularly in combination with a contrast agent that enables the assessment of different states of renal perfusion. Following intravenous bolus injection of Gadograf, important information on hyper- or hypoperfusion of the organ and lesions can be obtained with MRI, which allow a better differentiation of pathological processes and the characterization of the renal mass as well as staging of renal neoplasms.
Gadograf consists of nonspecific, low-molecular-weight, extracellular gadolinium-chelates and is presented in the formulation l.0 mmol gadolinium/ml and an osmolality of 1603 mosmol/kg H_2O at 37°C. Gadograf was the first paramagnetic contrast agent developed in a 1.0 molar solution thus requiring a smaller application volume in a higher dosage.

Gadograf 1.0 mmol/ml (INN gadobutrol) was approved for "***Contrast enhancement in cranial and spinal magnetic resonance imaging***" (MRI) in Germany in January 2000 and subsequently in July 2001 in Spain via the mutual recognition procedure. A label extension to the indication "***Contrast-enhanced Magnetic resonance angiography***" (CE-MRA) followed in November 2003.

2. Referral Procedure

In June 2005 a MR procedure started with Germany as the RMS for a Type II variation to add the indication of "***Contrast enhanced MRI of other body regions: liver, kidneys***" and the following posology and method of administration/dosage: "***CE-MRI of other body regions: The recommended dose for adults is 0.1 mmol per kilogram body weight (mmol/kg BW). This is equivalent to 0.1 ml/kg BW of the 1.0 M solution***".

The MRP procedure was finalised on Day 221 of the procedure on 09.05.2006 with approval of the proposed indication and inclusion of the liver and kidney imaging studies' results under Section 5.1. Further to the approval Spain raised a major objection related to the wording of the indication as Spain considered that the approved indication neither reflected the studied population in the two pivotal studies submitted for this variation of Gadograf nor the clinical context for which Gadograf has demonstrated to have the same diagnostic accuracy than its comparator.
After finalisation of the procedure the Spanish Agency for Medicines and Health Products initiated a referral for Arbitration under Article 36.1 of Directive 2001/83/EC to the CHMP.

Having considered the grounds for the referral, the CHMP, during its May 2006 plenary meeting, requested the MAH to address the major objection to public health and adopted a List of Questions. The MAH was requested to reply to the following Questions:

1) The current indication does neither reflect the studied population in the two pivotal studies submitted for this variation of Gadograf nor the clinical context for which Gadograf has demonstrated to have the same diagnostic accuracy than its comparator. As only those patients with high suspicion or evidence of having a focal disease of liver or kidneys obtained by other diagnostic tests or histopathology were included in the two pivotal studies, the indication approved must reflect the studied population and not in general for any patient undergoing a contrast enhanced MRI of liver or kidneys. Moreover, the wording of the indication should also reflect the clinical context for which Gadograf has demonstrated to have the same diagnostic

accuracy than its comparator, that is to correctly localise at least one malignant lesion of liver or kidney in an individual patient using combined pre- and post-contrast MR images.
*"**Contrast-enhanced magnetic resonance imaging (MRI) in patients with high suspicion or evidence of having a focal disease of liver or kidneys, obtained by other diagnostic tests or histopathology, to correctly localise malignant lesions of liver or kidney**."*

2) The requested indication cannot be approved for paediatric population aged less than 18 years since there is no data on the efficacy and safety of the use of Gadograf for contrast-enhancement MRI in this population in the submitted pivotal studies. The MAH must include in section 4.2 the following sentence:
"Gadograf is not recommended for use in population below age 18 due to a lack of data on efficacy and safety."

3). The MAH is asked to provide information on the clinical utility of this product for the requested indication (directly or indirectly), according to the Points of Consider on the evaluation of diagnostic agents (CPMP/EWP/1119/98). One of the requirements for a diagnostic agent to be authorised is to demonstrate relevant impact on diagnostic thinking in the clinical context in which the test is to be used, unless such impact can be shown indirectly or historically. It is not clearly obvious that accurate diagnostic information per se is beneficial, so the application for authorisation should provide support that the information is clinically useful by direct evaluation of this aspect in the clinical trials provided or being drawn historically from published scientific evidence.

3. Discussion

The MAH submitted its response to the CHMP List of Questions on 29 September 2006. In the response the MAH acknowledges with reference to Question 1) that the patient population studied in the pivotal trials has some limitations in comparison to the overall anticipated patient population undergoing CE-MRI, but these limitations are the result of methodological requirements to adequately demonstrate the diagnostic efficacy of Gadograf-enhanced MRI in the pivotal studies. With reference to Question 2) the MAH acknowledged that Gadograf has not been adequately studied for any of its approved indications (including the new indication "contrast-enhanced MRI of liver and kidneys") in patients aged less than 18 years.

Having considered the response provided by the MAH and assessed by the Rapporteurs, on 16 November 2006, the CHMP adopted a Request of Supplementary Information, in which the MAH was asked to further expand on the issue of clinical utility and to comment on a proposed wordings regarding the Indication in 4.1 and the Posology in 4.2 of the SPC.
In its response the MAH addressed the issue of clinical utility by comparing Gadograf-enhanced with Magnevist-enhanced MRI and underlined the diagnostic efficacy of Gadograf. The MAH further agreed to the proposed wording by the CHMP as follows:
Section 4.1 (Indication):

"Contrast enhanced MRI of liver or kidneys in patients with high suspicion or evidence of having focal lesions to classify these lesions as benign or malignant".

Section 4.2 (Posology):
"Gadograf is not recommended for use in population below age 18 due to a lack of data on efficacy and safety."

4. Conclusions

Since the issue of clinical utility was satisfactorily addressed and the MAH agreed to the proposed wording, the CHMP is of the opinion that the data provided allow the conclusion that, on basis of the pivotal clinical studies comparing Gadograf-enhanced with Magnevist-enhanced MRI, diagnostic efficacy of Gadograf for the classification of focal liver or renal lesions as benign or malignant, as well as clinical safety of Gadograf has been adequately established.
The MAH has updated SPC sections 4.1 and 4.2 in accordance with the requests of the CHMP.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS

Whereas,

- the Committee considered the referral made under Article 36(1) of Directive 2001/83/EC, as amended for Gadograf detailed in Annex I;

  - the CHMP recommended that the following additional indication: *"Contrast enhanced MRI of liver or kidneys in patients with high suspicion or evidence of having focal lesions to classify these lesions as benign or malignant."* can be granted for Gadograf.

The CHMP has recommended the variation (extension of indication) of the Marketing Authorisation in accordance with the Summary of Product Characteristics set out in Annex III for Gadograf (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gadograf 1.0 mmol/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 604.72 mg of gadobutrol (equivalent to 1.0 mmol gadobutrol containing 157.25 mg gadolinium).

For a full list of excipients, see section 6.1.

Physico-chemical properties:
Osmolality at 37°C: 1603 mOsm/kg H_2O
Viscosity at 37°C: 4.96 mPa·s

3. PHARMACEUTICAL FORM

Solution for injection
Clear, colourless to pale yellow liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Contrast enhancement in cranial and spinal magnetic resonance imaging (MRI).
Contrast enhanced MRI of liver or kidneys in patients with high suspicion or evidence of having focal lesions to classify these lesions as benign or malignant.
Contrast enhancement in magnetic resonance angiography (CE-MRA).

4.2 Posology and method of administration

Gadograf should only be administered by physicians experienced in the field of clinical MRI practice.

- General information

The dose required is administered intravenously as a bolus injection. Contrast-enhanced MRI can commence immediately afterwards (shortly after the injection depending on the pulse sequences used and the protocol for the examination).
Optimal opacification is observed during arterial first pass for CE-MRA and within a period of about 15 minutes after injection of Gadograf for CNS indications (time depending on type of lesion/tissue). Tissue enhancement generally lasts up to 45 minutes after injection of Gadograf.

T1 -weighted scanning sequences are particularly suitable for contrast-enhanced examinations.

Intravascular administration of contrast media should, if possible, be done with the patient lying down. After the administration, the patient should be kept under observation for at least half an hour, since experience shows that the majority of undesirable effects occur within this time.

- Dosage
- Adults

CNS indications:
The recommended dose for adults is 0.1 mmol per kilogram body weight (mmol/kg BW). This is equivalent to 0.1 ml/kg BW of the 1.0 M solution.
If a strong clinical suspicion of a lesion persists despite an unremarkable MRI or when more accurate information might influence therapy of the patient, a further injection of up to 0.2 mmol/kg BW within 30 minutes of the first injection may be performed.

CE-MRI of liver and kidneys:
The recommended dose for adults is 0.1 mmol per kilogram body weight (mmol/kg BW). This is equivalent to 0.1 ml/kg BW of the 1.0 M solution.

CE-MRA:
Imaging of 1 field of view (FOV): 7.5 ml for body weight below 75 kg; 10 ml for body weight of 75 kg and higher (corresponding to 0.1-0.15 mmol/kg BW).
Imaging of >1 field of view (FOV): 15 ml for body weight below 75 kg; 20 ml for body weight of 75 kg and higher (corresponding to 0.2-0.3 mmol/kg BW).

- Paediatric patients

Gadograf is not recommended for use in population below age 18 due to a lack of data on efficacy and safety.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Gadograf should not be used in patients with uncorrected hypokalemia. In patients with severe cardiovascular disease Gadograf should only be administered after careful risk benefit assessment because only limited data are available so far.

Gadograf should be used with special care in patients

- with known congenital long QT syndrome or a family history of congenital long QT syndrome
- with known previous arrhythmias after taking medicinal products that prolong cardiac repolarisation
- who are currently taking a medicinal product that is known to prolong cardiac repolarisation e.g. a Class III antiarrhythmic (e.g. amiodarone, sotalol).

The possibility that Gadograf may cause torsade de pointes arrhythmias in an individual patient cannot be excluded (see section 5.3 Preclinical safety data).

Since contrast medium elimination is delayed in patients with severely impaired renal function, the benefits must be weighed very carefully against the risks in such cases. In particularly severe cases, it is advisable to remove Gadograf from the body by extracorporeal haemodialysis: For removal of the agent from the body, at least 3 dialysis sessions within 5 days of the injection should be performed.

No impairment of renal functions has been observed during clinical trials performed on a limited number of patients. Data are too limited to exclude the possibility of renal toxicity or aggravation of renal impairment.

The usual safety requirements for magnetic resonance imaging, especially the exclusion of ferromagnetic materials, also apply when using Gadograf.

Hypersensitivity reactions, as have been reported for other contrast media containing gadolinium, have also been observed after administration of Gadograf. To be able to react immediately to an emergency, medicinal products and equipment (e.g. endotracheal tube and respirator) should be within hand reach.

In patients with an allergic disposition the decision to use Gadograf must be made after particularly careful evaluation of the risk-benefit ratio. In rare cases delayed anaphylactoid reactions (after hours to days) have been observed.

Like with other gadolinium containing contrast agents special precaution is necessary in patients with a low threshold for seizures.

While injecting Gadograf into veins with a small lumen there is the possibility of adverse effects such as reddening and swelling.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Pregnancy and lactation

There are no adequate data from the use of gadobutrol in pregnant women. In animal studies repeated dosing of gadobutrol only at maternally toxic dose levels (8 to 17 times the diagnostic dose) caused retardation of the embryonal development and embryolethality but no teratogenicity. The potential risk of single administration for humans is unknown.

Gadograf should not be used during pregnancy unless clearly necessary.

The passage of Gadograf into breast milk has not been investigated in humans so far.
Small amounts of gadobutrol enter milk in animals (less than 0.01% of the dose administered). Breast feeding should be discontinued for at least 24 hours after the administration of gadobutrol.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Adverse reactions are “rare (≥1/10,000 to <1/1,000)” to “uncommon (≥1/1,000 to <1/100)”.

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

	Adverse reactions from clinical trial data (experience in more than 2900 patients)		**Additional adverse reactions from postmarketing spontaneous reporting**
System Organ Class	**Uncommon** (≥1/1,000 to <1/100)	**Rare** (≥1/10,000 to <1/1,000)	**Rare** (≥1/10,000 to <1/1,000)
Cardiac disorders			Cardiac arrest, Tachycardia
Nervous system disorders	Headache, Dizziness, Paresthesia, Dysgeusia	Parosmia	Loss of consciousness, Convulsion
Eye disorders			Conjunctivitis, Eyelid oedema

	Adverse reactions from clinical trial data (experience in more than 2900 patients)		Additional adverse reactions from postmarketing spontaneous reporting
System Organ Class	**Uncommon** (≥1/1,000 to <1/100)	**Rare** (≥1/10,000 to <1/1,000)	**Rare** (≥1/10,000 to <1/1,000)
Respiratory, thoracic and mediastinal disorders		Dyspnoea	Respiratory arrest, Bronchospasm, Cyanosis, Oropharyngeal swelling, Cough, Sneezing
Gastrointestinal disorders	Nausea	Vomiting	
Skin and subcutaneous tissue disorders		Urticaria, Rash	Face edema, Hyperhidrosis, Pruritus, Erythema
Vascular disorders	Vasodilatation	Hypotension	Circulatory collapse, Flushing
General disorders and administration site conditions	Injection site pain, Injection site reaction		Feeling hot, Malaise
Immune system disorders		Anaphylactoid reaction	Anaphylactoid shock

Additional safety information:
Short-lasting mild to moderate feelings of coldness, warmth or pain at the injection site have been uncommonly observed in association with the venous puncture or contrast medium injection.

On paravascular injection Gadograf may cause tissue pain lasting up to several minutes.

Hypersensitivity reactions (e.g. urticaria, rash, vasodilitation) have been uncommonly reported and were mostly of mild to moderate intensity. In rare cases anaphylactoid reactions ranging to shock may occur. Delayed anaphylactoid reactions (after hours to days) have been observed rarely (see section 4.4).
Patients with an allergic disposition suffer more frequently than others from hypersensitivity reactions.

4.9 Overdose

The maximum daily single dose tested in humans is 1.5 mmol gadobutrol/kg body weight.
No signs of intoxication from an overdose have so far been observed during clinical use.

Due to potential effects of Gadograf on cardiac repolarization in cases of overdose, disturbances of cardiac rhythm may be possible. Cardiovascular monitoring (including ECG) and control of renal function is recommended as a measure of precaution.

In case of an overdose, Gadograf can be removed from the body by extracorporeal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC – Code: V08C A09
Paramagnetic contrast media
The contrast-enhancing effect is mediated by gadobutrol, the nonionic complex consisting of gadolinium(III) and the macrocyclic ligand dihydroxy-hydroxymethylpropyl-tetraazacyclododecane-triacetic acid (butrol).

In clinical doses, gadobutrol leads to shortening of the relaxation times of protons in tissue water. At 0.47 T (20 MHz), pH 7 and 40°C the paramagnetic effect (relaxivity), as determined from the effect on spin-lattice relaxation time (T1) - is about 3.6 l $mmol^{-1}$ sec^{-1} and the spin-spin relaxation time (T2) is about 4 l $mmol^{-1}$ sec^{-1}. Within the range 0.47 to 2.0 Tesla, the relaxivity displays only slight dependency on the strength of the magnetic field.

Gadobutrol does not cross an intact blood-brain barrier and therefore does not accumulate in healthy brain tissue or in lesions featuring an intact blood-brain barrier. With high local tissue concentrations of gadobutrol the T2 effect results in a lessening of signal intensity.

In a pivotal phase III liver study average sensitivity in combined pre and postcontrast MRI for Gadograf-treated patients was 79% and specificity was 81% for lesion detection and classification of suspected malignant liver lesions (patientbased analysis).

In a pivotal phase III kidney study average sensitivity was 91% (patient-based analysis) and 85% (lesion-based analysis) for classification of malignant and benign renal lesions. Average specificity in a patient-based analysis was 52% and in a lesion-based analysis 82%.

The increase of sensitivity from precontrast to combined pre and postcontrast MRI for Gadograf-treated patients was 33% in the liver study (patient-based analysis) and 18% in the kidney study (patient-based analysis as well as lesion-based analysis). The increase in specificity from precontrast to combined pre and postcontrast MRI was 9% in the liver study (patient based analysis) while there was no increase in specificity in the kidney study (patient-based analysis as well as lesion-based analysis).
All results are average results obtained in blinded reader studies.

5.2 Pharmacokinetic properties

After intravenous administration, gadobutrol is rapidly distributed in the extra cellular space. Plasma protein binding is negligible.
The pharmacokinetics of gadobutrol in humans are dose proportional. Up to 0.4 mmol gadobutrol/kg body weight, the plasma level declines after an early distribution phase with a mean terminal half-life of 1.8 hours (1.3 – 2.1 hours), identical to the renal elimination rate. At a dose of 0.1 mmol gadobutrol/kg BW, an average of 0.59 mmol gadobutrol/l plasma was measured 2 minutes after the injection and 0.3 mmol gadobutrol/l plasma 60 minutes post injection. Within two hours more than 50% and within 12 hours more than 90% (or 92%) of the given dose is eliminated via the urine. At a dose of 0.1 mmol gadobutrol/kg BW, an average of 100.3 ± 2.6% of the dose was excreted within 72 h after administration. In healthy persons renal clearance of gadobutrol is 1.1 to 1.7 ml min^{-1} kg^{-1} and thus comparable to the renal clearance of inulin, pointing to the fact that gadobutrol is eliminated primarily by glomerular filtration. Less than 0.1% of the dose is eliminated via the faeces. No metabolites are detected in plasma or urine.

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.
Repeated dosing in reproduction toxicological studies caused a retardation of embryonal development in rats and an increase in embryolethality in monkeys and in rabbits at maternally toxic dose levels (8 to 17 times

the diagnostic dose) only. It is not known whether these effects can also be induced by a single administration.

Cardiovascular effects seen in animals (dogs) at exposure levels similar (0.25 mmol/kg) and higher (1.25 mmol/kg), respectively, to maximum clinical exposure levels were a dose dependent transient increase in blood pressure (5% and 10%, above saline control) and myocardial contractility (5% and 16%, above saline control).
Cardiovascular safety pharmacology studies as well as clinical phase I studies gave indication for a potential of Gadograf to block cardiac potassium channels and an effect on cardiac repolarization when administered in doses 3 to 8fold higher than normally administered to patients. Therefore, the possibility that Gadograf may cause torsade de pointes arrhythmias in an individual patient can not be excluded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcobutrol sodium
Trometamol
Hydrochloric acid
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Shelf life of the medicinal product as packaged for sale:
3 years

Shelf life after first opening of the container:
Any solution for injection not used in one examination must be discarded. Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless opening has taken place in controlled and validated aseptic conditions.

The following applies to the use of the infusion bottle containing 65 ml:
After opening of the infusion bottle under aseptic conditions Gadograf remains stable for at least 8 hours at room temperature.

6.4 Special precautions for storage

No special precautions for storage.
Special precautions for storage of sterile product which has been opened are described in section 6.3.

6.5 Nature and contents of container

1 vial (type II glass) with a stopper (chlorobutyl elastomer) and a pure aluminium with internal and external lacquer flanged cap containing 7.5 ml, 15 ml or 30 ml solution for injection.

1 infusion bottle (type II glass) with a stopper (chlorobutyl elastomer) and a pure aluminium with internal and external lacquer flanged cap containing 65 ml solution for injection.

Pack sizes of:
1 and 10 vials
1 and 10 bottles

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicinal product should be visually inspected before use.
Gadograf should not be used in case of severe discoloration, the occurrence of particulate matter or a defective container.
Gadograf should not be drawn up into the syringe from the vial until immediately before use. Contrast medium not used in one examination must be discarded.

In addition, the following applies to use of the infusion bottle containing 65 ml:
The contrast medium must be administered by means of an automatic injector. The tube from the injector to the patient (patient's tube) must be changed after every examination.
Any contrast medium solution left over in the bottle, the connecting tubes and all disposable parts of the injector system must be discarded within 8 hours. Any additional instructions from the respective equipment manufacturer must also be strictly adhered to.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: [To be completed nationally]
Date of last renewal: 24.01.2005

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

[To be completed nationally]

1. NAME OF THE MEDICINAL PRODUCT

Gadograf 1.0 mmol/ml solution for injection in prefilled syringes

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 604.72 mg gadobutrol (equivalent to 1.0 mmol gadobutrol containing 157.25 mg gadolinium).

For a full list of excipients, see section 6.1.

Physico-chemical properties:
Osmolality at 37°C: 1603 mOsm/kg H_2O
Viscosity at 37°C: 4.96 mPa·s

3. PHARMACEUTICAL FORM

Solution for injection in prefilled syringe
Clear, colourless to pale yellow liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Contrast enhancement in cranial and spinal magnetic resonance imaging (MRI).
Contrast enhanced MRI of liver or kidneys in patients with high suspicion or evidence of having focal lesions to classify these lesions as benign or malignant.
Contrast enhancement in magnetic resonance angiography (CE-MRA).

4.2 Posology and method of administration

Gadograf should only be administered by physicians experienced in the field of clinical MRI practice.

- General information

The dose required is administered intravenously as a bolus injection. Contrast-enhanced MRI can commence immediately afterwards (shortly after the injection depending on the pulse sequences used and the protocol for the examination).
Optimal opacification is observed during arterial first pass for CE-MRA and within a period of about 15 minutes after injection of Gadograf for CNS indications (time depending on type of lesion/tissue). Tissue enhancement generally lasts up to 45 minutes after injection of Gadograf.

T1 -weighted scanning sequences are particularly suitable for contrast-enhanced examinations.

Intravascular administration of contrast media should, if possible, be done with the patient lying down. After the administration, the patient should be kept under observation for at least half an hour, since experience shows that the majority of undesirable effects occur within this time.

- Dosage
- Adults

CNS indications:
The recommended dose for adults is 0.1 mmol per kilogram body weight (mmol/kg BW). This is equivalent to 0.1 ml/kg BW of the 1.0 M solution.
If a strong clinical suspicion of a lesion persists despite an unremarkable MRI or when more accurate information might influence therapy of the patient, a further injection of up to 0.2 mmol/kg BW within 30 minutes of the first injection may be performed.

CE-MRI of liver and kidneys:
The recommended dose for adults is 0.1 mmol per kilogram body weight (mmol/kg BW). This is equivalent to 0.1 ml/kg BW of the 1.0 M solution.

CE-MRA:
Imaging of 1 field of view (FOV): 7.5 ml for body weight below 75 kg; 10 ml for body weight of 75 kg and higher (corresponding to 0.1-0.15 mmol/kg BW).
Imaging of >1 field of view (FOV): 15 ml for body weight below 75 kg; 20 ml for body weight of 75 kg and higher (corresponding to 0.2-0.3 mmol/kg BW).

- Paediatric patients

Gadograf is not recommended for use in population below age 18 due to a lack of data on efficacy and safety.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Gadograf should not be used in patients with uncorrected hypokalemia. In patients with severe cardiovascular disease Gadograf should only be administered after careful risk benefit assessment because only limited data are available so far.

Gadograf should be used with special care in patients
- with known congenital long QT syndrome or a family history of congenital long QT syndrome
- with known previous arrhythmias after taking medicinal products that prolong cardiac repolarisation
- who are currently taking a medicinal product that is known to prolong cardiac repolarisation e.g. a Class III antiarrhythmic (e.g. amiodarone, sotalol).

The possibility that Gadograf may cause torsade de pointes arrhythmias in an individual patient cannot be excluded (see section 5.3 Preclinical safety data).

Since contrast medium elimination is delayed in patients with severely impaired renal function, the benefits must be weighed very carefully against the risks in such cases. In particularly severe cases, it is advisable to remove Gadograf from the body by extracorporeal haemodialysis: For removal of the agent from the body, at least 3 dialysis sessions within 5 days of the injection should be performed.

No impairment of renal functions has been observed during clinical trials performed on a limited number of patients. Data are too limited to exclude the possibility of renal toxicity or aggravation of renal impairment.

The usual safety requirements for magnetic resonance imaging, especially the exclusion of ferromagnetic materials, also apply when using Gadograf.

Hypersensitivity reactions, as have been reported for other contrast media containing gadolinium, have also been observed after administration of Gadograf. To be able to react immediately to an emergency, medicinal products and equipment (e.g. endotracheal tube and respirator) should be within hand reach.

In patients with an allergic disposition the decision to use Gadograf must be made after particularly careful evaluation of the risk-benefit ratio. In rare cases delayed anaphylactoid reactions (after hours to days) have been observed.

Like with other gadolinium containing contrast agents special precaution is necessary in patients with a low threshold for seizures.

While injecting Gadograf into veins with a small lumen there is the possibility of adverse effects such as reddening and swelling.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Pregnancy and lactation

There are no adequate data from the use of gadobutrol in pregnant women. In animal studies repeated dosing of gadobutrol only at maternally toxic dose levels (8 to 17 times the diagnostic dose) caused retardation of the embryonal development and embryolethality but no teratogenicity. The potential risk of single administration for humans is unknown.

Gadograf should not be used during pregnancy unless clearly necessary.

The passage of Gadograf into breast milk has not been investigated in humans so far.
Small amounts of gadobutrol enter milk in animals (less than 0.01% of the dose administered). Breast feeding should be discontinued for at least 24 hours after the administration of gadobutrol.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Adverse reactions are “rare (≥1/10,000 to <1/1,000)” to “uncommon (≥1/1,000 to <1/100)”.

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

	Adverse reactions from clinical trial data (experience in more than 2900 patients)		**Additional adverse reactions from postmarketing spontaneous reporting**
System Organ Class	**Uncommon** (≥1/1,000 to <1/100)	**Rare** (≥1/10,000 to <1/1,000)	**Rare** (≥1/10,000 to <1/1,000)
Cardiac disorders			Cardiac arrest, Tachycardia
Nervous system disorders	Headache, Dizziness, Paresthesia, Dysgeusia	Parosmia	Loss of consciousness, Convulsion
Eye disorders			Conjunctivitis, Eyelid oedema

	Adverse reactions from clinical trial data (experience in more than 2900 patients)		Additional adverse reactions from postmarketing spontaneous reporting
System Organ Class	**Uncommon** (≥1/1,000 to <1/100)	**Rare** (≥1/10,000 to <1/1,000)	**Rare** (≥1/10,000 to <1/1,000)
Respiratory, thoracic and mediastinal disorders		Dyspnoea	Respiratory arrest, Bronchospasm, Cyanosis, Oropharyngeal swelling, Cough, Sneezing
Gastrointestinal disorders	Nausea	Vomiting	
Skin and subcutaneous tissue disorders		Urticaria, Rash	Face edema, Hyperhidrosis, Pruritus, Erythema
Vascular disorders	Vasodilatation	Hypotension	Circulatory collapse, Flushing
General disorders and administration site conditions	Injection site pain, Injection site reaction		Feeling hot, Malaise
Immune system disorders		Anaphylactoid reaction	Anaphylactoid shock

Additional safety information:
Short-lasting mild to moderate feelings of coldness, warmth or pain at the injection site have been uncommonly observed in association with the venous puncture or contrast medium injection.

On paravascular injection Gadograf may cause tissue pain lasting up to several minutes.

Hypersensitivity reactions (e.g. urticaria, rash, vasodilitation) have been uncommonly reported and were mostly of mild to moderate intensity. In rare cases anaphylactoid reactions ranging to shock may occur. Delayed anaphylactoid reactions (after hours to days) have been observed rarely (see section 4.4).
Patients with an allergic disposition suffer more frequently than others from hypersensitivity reactions.

4.9 Overdose

The maximum daily single dose tested in humans is 1.5 mmol gadobutrol/kg body weight.
No signs of intoxication from an overdose have so far been observed during clinical use.

Due to potential effects of Gadograf on cardiac repolarization in cases of overdose, disturbances of cardiac rhythm may be possible. Cardiovascular monitoring (including ECG) and control of renal function is recommended as a measure of precaution.

In case of an overdose, Gadograf can be removed from the body by extracorporeal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC – Code: V08C A09
Paramagnetic contrast media
The contrast-enhancing effect is mediated by gadobutrol, the nonionic complex consisting of gadolinium(III) and the macrocyclic ligand dihydroxy-hydroxymethylpropyl-tetraazacyclododecane-triacetic acid (butrol).

In clinical doses, gadobutrol leads to shortening of the relaxation times of protons in tissue water. At 0.47 T (20 MHz), pH 7 and 40°C the paramagnetic effect (relaxivity), as determined from the effect on spin-lattice relaxation time (T1) - is about 3.6 l $mmol^{-1}$ sec^{-1} and the spin-spin relaxation time (T2) is about 4 l $mmol^{-1}$ sec^{-1}. Within the range 0.47 to 2.0 Tesla, the relaxivity displays only slight dependency on the strength of the magnetic field.

Gadobutrol does not cross an intact blood-brain barrier and therefore does not accumulate in healthy brain tissue or in lesions featuring an intact blood-brain barrier. With high local tissue concentrations of gadobutrol the T2 effect results in a lessening of signal intensity.

In a pivotal phase III liver study average sensitivity in combined pre and postcontrast MRI for Gadograf-treated patients was 79% and specificity was 81% for lesion detection and classification of suspected malignant liver lesions (patientbased analysis).

In a pivotal phase III kidney study average sensitivity was 91% (patient-based analysis) and 85% (lesion-based analysis) for classification of malignant and benign renal lesions. Average specificity in a patient-based analysis was 52% and in a lesion-based analysis 82%.

The increase of sensitivity from precontrast to combined pre and postcontrast MRI for Gadograf-treated patients was 33% in the liver study (patient-based analysis) and 18% in the kidney study (patient-based analysis as well as lesion-based analysis). The increase in specificity from precontrast to combined pre and postcontrast MRI was 9% in the liver study (patient based analysis) while there was no increase in specificity in the kidney study (patient-based analysis as well as lesion-based analysis).
All results are average results obtained in blinded reader studies.

5.2 Pharmacokinetic properties

After intravenous administration, gadobutrol is rapidly distributed in the extra cellular space. Plasma protein binding is negligible.
The pharmacokinetics of gadobutrol in humans are dose proportional. Up to 0.4 mmol gadobutrol/kg body weight, the plasma level declines after an early distribution phase with a mean terminal half-life of 1.8 hours (1.3 – 2.1 hours), identical to the renal elimination rate. At a dose of 0.1 mmol gadobutrol/kg BW, an average of 0.59 mmol gadobutrol/l plasma was measured 2 minutes after the injection and 0.3 mmol gadobutrol/l plasma 60 minutes post injection. Within two hours more than 50% and within 12 hours more than 90% (or 92%) of the given dose is eliminated via the urine. At a dose of 0.1 mmol gadobutrol/kg BW, an average of 100.3 ± 2.6% of the dose was excreted within 72 h after administration. In healthy persons renal clearance of gadobutrol is 1.1 to 1.7 ml min^{-1} kg^{-1} and thus comparable to the renal clearance of inulin, pointing to the fact that gadobutrol is eliminated primarily by glomerular filtration. Less than 0.1% of the dose is eliminated via the faeces. No metabolites are detected in plasma or urine.

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.
Repeated dosing in reproduction toxicological studies caused a retardation of embryonal development in rats and an increase in embryolethality in monkeys and in rabbits at maternally toxic dose levels (8 to 17 times

the diagnostic dose) only. It is not known whether these effects can also be induced by a single administration.

Cardiovascular effects seen in animals (dogs) at exposure levels similar (0.25 mmol/kg) and higher (1.25 mmol/kg), respectively, to maximum clinical exposure levels were a dose dependent transient increase in blood pressure (5% and 10%, above saline control) and myocardial contractility (5% and 16%, above saline control).
Cardiovascular safety pharmacology studies as well as clinical phase I studies gave indication for a potential of Gadograf to block cardiac potassium channels and an effect on cardiac repolarization when administered in doses 3 to 8fold higher than normally administered to patients. Therefore, the possibility that Gadograf may cause torsade de pointes arrhythmias in an individual patient can not be excluded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcobutrol sodium
Trometamol
Hydrochloric acid
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Shelf life of the medicinal product as packaged for sale:
3 years

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

One 10-ml prefilled syringe (type I glass) with a plunger stopper (chlorobutyl elastomer) and a tip cap (chlorobutyl elastomer) contains 5 ml, 7.5 ml, 10 ml solution for injection.

One 17-ml prefilled syringe (type I glass) with a plunger stopper (chlorobutyl elastomer) and a tip cap (chlorobutyl elastomer) contains 15 ml solution for injection.

One 20-ml prefilled syringe (type I glass) with a plunger stopper (chlorobutyl elastomer) and a tip cap (chlorobutyl elastomer) contains 20 ml solution for injection.

Pack sizes of:
1 and 5 prefilled syringes

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicinal product should be visually inspected before use.

Gadograf should not be used in case of severe discoloration, the occurrence of particulate matter or a defective container.
Gadograf should not be prepared until immediately before use. Gadograf not used in one examination must be discarded.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: [To be completed nationally]
Date of last renewal: 24.01.2005

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}
[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Carton / Outer package

1. NAME OF THE MEDICINAL PRODUCT

Gadograf 1.0 mmol/ml solution for injection
Gadobutrol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 604.72 mg gadobutrol (equivalent to 1.0 mmol gadobutrol containing 157.25 mg gadolinium).

3. LIST OF EXCIPIENTS

Excipients: Calcobutrol sodium, Trometamol, Hydrochloric acid, Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 x 7.5 ml
1 x 15 ml
1 x 30 ml
1 x 65 ml
10 x 7.5 ml
10 x 15 ml
10 x 30 ml
10 x 65 ml

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

[7.5 ml / 15 ml / 30 ml:]
After first opening use immediately within 24 h (stored 2 – 8 °C).
[65 ml:]
After first opening use immediately within 24 h (stored 2 – 8 °C) or within 8 h (stored at r.t.)

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Carton / Outer Package

1. NAME OF THE MEDICINAL PRODUCT

Gadograf 1.0 mmol/ml solution for injection in prefilled syringes
Gadobutrol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 604.72 mg gadobutrol (equivalent to 1.0 mmol gadobutrol containing 157.25 mg gadolinium).

3. LIST OF EXCIPIENTS

Excipients: Calcobutrol sodium, Trometamol, Hydrochloric acid, Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in prefilled syringe

1 x 5 ml
1 x 7.5 ml
1 x 10 ml
1 x 15 ml
1 x 20 ml
5 x 5 ml
5 x 7.5 ml
5 x 10 ml
5 x 15 ml
5 x 20 ml

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

7.5 ml Vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Gadograf 1.0 mmol/ml solution for injection
Gadobutrol
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP {MM/YYYY}
After first opening use immediately within 24 h (stored 2 – 8 °C).

4. BATCH NUMBER

Lot {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

7.5 ml

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Prefilled syringes (5 ml, 7.5 ml, 10 ml)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Gadograf 1.0 mmol/ml solution for injection in prefilled syringes
Gadobutrol
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml
7.5 ml
10 ml

6. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Gadograf 1.0 mmol/ml, solution for injection

Gadobutrol

Read all of this leaflet carefully before you are given this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or the person giving you Gadograf (the radiologist) or the hospital/MRI-centre personnel.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or radiologist.

In this leaflet:

1. WHAT GADOGRAF IS AND WHAT IT IS USED FOR

Gadograf is a contrast medium for magnetic resonance imaging (MRI) of the brain, spine, vessels, liver and kidneys.
MRI is a form of medical diagnostic imaging that uses the behaviour of water molecules in normal and abnormal tissues. This is done by a complex system of magnets and radiowaves. Computers record the activity and translate that into images.

It is provided as a solution for intravenous injection. This medicine is for diagnostic use only.

2. BEFORE YOU ARE GIVEN GADOGRAF

Do not use GADOGRAF
- if you are allergic (hypersensitive) to gadobutrol or any of the other ingredients of Gadograf (see “What Gadograf contains”)

Take special care with GADOGRAF
- if you suffer or have suffered from allergy (e.g. hay fever, hives) or asthma
- if you had a previous reaction to contrast media
- if you have a very poor kidney function
- if you have a serious disease of the heart and blood vessels
- if you suffer from low potassium levels
- if you, or someone in your family, has ever had problems with the electrical rhythm of the heart (long QT syndrome)
- if you have had changes to the rhythm or rate of your heartbeat after taking medicines
- you suffer from brain conditions with seizures or from other diseases of the nervous system

Before you receive Gadograf, tell your doctor if any of these applies to you. Your doctor will decide whether the intended examination is possible or not.

- Allergy-like reactions may occur after use of Gadograf. Severe reactions are possible. Delayed reactions have been observed (after hours or days) (see section 4 “Possible Side Effects”).
- Tell your doctor if you have a heart pacemaker or if there are any implants or clips containing iron in your body.

- If you are younger than 18, use of Gadograf is not recommended.

Using other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. These include especially medicines that change the rhythm or rate of your heartbeat.

Pregnancy and breast-feeding
Tell your doctor if you are pregnant or could be pregnant, since Gadograf should not be used during pregnancy unless it is considered absolutely necessary.
Tell your doctor if you are breast-feeding or intending to breast-feed. Breast-feeding should be stopped for at least 24 hours following Gadograf administration.

Important information about some of the ingredients of GADOGRAF
This medicinal product contains less than 1 mmol sodium (23 mg) per dose (based on the average amount given to a 70 kg person), i.e. essentially 'sodium-free'.

3. HOW TO USE GADOGRAF

Gadograf is injected by a doctor via a small needle into a vein. Gadograf will be administered immediately before your MRI examination.
After the injection you will be observed for at least 30 minutes.
The actual dosage of Gadograf that is right for you will depend on your body weight and on the region of examination:
A single injection of 0.1 millilitre Gadograf per kg body weight is generally sufficient (this means for a person weighing 70 kg the dose would be 7 millilitres). A total amount of 0.3 millilitre Gadograf per kg body weight may be administered at maximum.
Further information regarding the administration and handling of Gadograf is given at the end of the leaflet.

If you receive more GADOGRAF than you should have received:
Overdosing is unlikely. If it does happen, the doctor will treat any symptoms that follow. In some cases he will check whether your heart and kidneys work properly.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Gadograf can cause side effects, although not everybody gets them.

Below we list possible side effects by how likely they are, using the following categories:

Uncommon: between 1 and 10 in every 1000 patients are likely to get these.
Rare: between 1 and 10 in every 10,000 patients are likely to get these.

Side effects which have been observed in clinical trials before the approval of Gadograf:

Uncommon	Rare
Headache Dizziness Numbness and tingling Problems with sense of taste Nausea (feeling sick) Widening of blood vessels Injection site pain Injection site reaction	Problems with sense of smell Breathing difficulties Vomiting Hives (nettle-type rash) Skin rash Low blood pressure Allergy-like reaction

Short-lasting mild to moderate feelings of coldness, warmth or pain at the injection site have been uncommonly observed during or after the injection of Gadograf.

Gadograf may cause local pain lasting up to several minutes if it is injected beside the vein.

Additional side effects which have been reported after the approval of Gadograf:

Rare
Cardiac arrest, Fast heart beat Loss of consciousness, Convulsion Conjunctivitis, Swelling (edema) of the eyelid Breathing difficulties (bronchospasm, swelling of the throat), Breathing arrest, Blueness of the lips, Cough, Sneezing Swelling (edema) of the face, Excessive sweating, Itching, Redness of the skin Fainting, Flushing Feeling hot, Generally feeling unwell Severe allergy-like reaction (shock)

As with other gadolinium containing contrast media**,** in rare cases **allergy-like reactions** (hypersensitivity and anaphylaxis) may occur, including severe reactions (shock) that may need immediate medical intervention. Mild swelling of the face, lips, tongue or throat, coughing, itching, runny nose, sneezing and hives (nettle-type rash) may be the first signs that a severe reaction is happening.
Tell the MRI department staff immediately if you experience any of these signs or have difficulty in breathing.
Delayed allergy-like reactions, hours to several days after the administration of Gadograf, have been observed in rare cases. If this should happen to you, tell your doctor or radiologist.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or radiologist.

5. HOW TO STORE GADOGRAF

This medicine does not require any special storage conditions.

Keep out of the reach and sight of children.

Do not use Gadograf after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of the month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What GADOGRAF contains

- The active substance is gadobutrol 604.72 mg corresponding to 1 mmol/ml
- The other ingredients are calcobutrol sodium, trometamol, hydrochloric acid and water for injections

1 vial with 7.5 ml of the solution contains 4535 mg gadobutrol.
1 vial with 15 ml of the solution contains 9070 mg gadobutrol.
1 vial with 30 ml of the solution contains 18141 mg gadobutrol.

1 infusion bottle with 65 ml of the solution contains 39307 mg gadobutrol.

What GADOGRAF looks like and contents of the pack

Gadograf is a clear, colourless to pale yellow solution. The contents of the packs are:

1 or 10 injection vials with 7.5, 15 or 30 ml solution for injection
1 or 10 infusion bottles with 65 ml solution for injection (in 100-ml infusion bottle)

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

[To be completed nationally]

Manufacturer:

Schering AG
Müllerstrasse 178
D - 133 42 Berlin, Germany
Telephone: +49 30 468-1111

This medicinal product is authorised in the Member States of the EEA under the following names:

Germany	Gadograf
Spain	Gadograf

This leaflet was last approved in {MM/YYYY}. [To be completed nationally]

The following information is intended for medical or healthcare professionals only:

- Before injection

This medicinal product is a clear, colourless to pale yellow solution. It should be visually inspected before use.
Gadograf should not be used in case of severe discoloration, the occurrence of particulate matter or a defective container.

- Handling

Vials
Gadograf should not be drawn up into the syringe from the vial until immediately before use. Contrast medium not used in one examination must be discarded.

Large volume containers
In addition, the following applies to use of the infusion bottle containing 65 ml:
The contrast medium must be administered by means of an automatic injector. The tube from the injector to the patient (patient's tube) must be changed after every examination.
Any contrast medium solution left over in the bottle, the connecting tubes and all disposable parts of the injector system must be discarded within 8 hours. Any additional instructions from the respective equipment manufacturer must also be strictly adhered to.

Any solution not used in one examination is to be discarded in accordance with local requirements.

Further information regarding the use of Gadograf is given in section 3 of the leaflet.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Gadograf 1.0 mmol/ml, solution for injection, prefilled syringe

Gadobutrol

Read all of this leaflet carefully before you are given this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or the person giving you Gadograf (the radiologist) or the hospital/MRI-centre personnel.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or radiologist.

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1. WHAT GADOGRAF IS AND WHAT IT IS USED FOR

Gadograf is a contrast medium for magnetic resonance imaging (MRI) of the brain, spine, vessels, liver and kidneys.
MRI is a form of medical diagnostic imaging that uses the behaviour of water molecules in normal and abnormal tissues. This is done by a complex system of magnets and radiowaves. Computers record the activity and translate that into images.

It is provided as a solution for intravenous injection. This medicine is for diagnostic use only.

2. BEFORE YOU ARE GIVEN GADOGRAF

Do not use GADOGRAF
- if you are allergic (hypersensitive) to gadobutrol or any of the other ingredients of Gadograf (see “What Gadograf contains”).

Take special care with GADOGRAF
- if you suffer or have suffered from allergy (e.g. hay fever, hives) or asthma
- if you had a previous reaction to contrast media
- if you have a very poor kidney function
- if you have a serious disease of the heart and blood vessels
- if you suffer from low potassium levels
- if you, or someone in your family, has ever had problems with the electrical rhythm of the heart (long QT syndrome)
- if you have had changes to the rhythm or rate of your heartbeat after taking medicines
- you suffer from brain conditions with seizures or from other diseases of the nervous system

Before you receive Gadograf, tell your doctor if any of these applies to you. Your doctor will decide whether the intended examination is possible or not.

- Allergy-like reactions may occur after use of Gadograf. Severe reactions are possible. Delayed reactions have been observed (after hours or days) (see section 4 “Possible Side Effects”).

- Tell your doctor if you have a heart pacemaker or if there are any implants or clips containing iron in your body.

If you are younger than 18, use of Gadograf is not recommended

Using other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. These include especially medicines that change the rhythm or rate of your heartbeat.

Pregnancy and breast-feeding
Tell your doctor if you are pregnant or could be pregnant, since Gadograf should not be used during pregnancy unless it is considered absolutely necessary.
Tell your doctor if you are breast-feeding or intending to breast-feed. Breast-feeding should be stopped for at least 24 hours following Gadograf administration.

Important information about some of the ingredients of GADOGRAF
This medicinal product contains less than 1 mmol sodium (23 mg) per dose (based on the average amount given to a 70 kg person), i.e. essentially 'sodium-free'.

3. HOW TO USE GADOGRAF

Gadograf is injected by a doctor via a small needle into a vein. Gadograf will be administered immediately before your MRI examination.
After the injection you will be observed for at least 30 minutes.
The actual dosage of Gadograf that is right for you will depend on your body weight and on the region of examination:
A single injection of 0.1 millilitre Gadograf per kg body weight is generally sufficient (this means for a person weighing 70 kg the dose would be 7 millilitres). A total amount of 0.3 millilitres Gadograf per kg body weight may be administered at maximum.
Further information regarding the administration and handling of Gadograf is given at the end of the leaflet.

If you receive more GADOGRAF than you should have received:
Overdosing is unlikely. If it does happen, the doctor will treat any symptoms that follow. In some cases he will check whether your heart and kidneys work properly.

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Like all medicines, Gadograf can cause side effects, although not everybody gets them.

Below we list possible side effects by how likely they are, using the following categories:

Uncommon: between 1 and 10 in every 1000 patients are likely to get these.
Rare: between 1 and 10 in every 10,000 patients are likely to get these.

Side effects which have been observed in clinical trials before the approval of Gadograf:

Uncommon	Rare
Headache Dizziness Numbness and tingling Problems with sense of taste Nausea (feeling sick) Widening of blood vessels Injection site pain Injection site reaction	Problems with sense of smell Breathing difficulties Vomiting Hives (nettle-type rash) Skin rash Low blood pressure Allergy-like reaction

Short-lasting mild to moderate feelings of coldness, warmth or pain at the injection site have been uncommonly observed during or after the injection of Gadograf.

Gadograf may cause local pain lasting up to several minutes if it is injected beside the vein.

Additional side effects which have been reported after the approval of Gadograf:

Rare
Cardiac arrest, Fast heart beat Loss of consciousness, Convulsion Conjunctivitis, Swelling (edema) of the eyelid Breathing difficulties (bronchospasm, swelling of the throat), Breathing arrest, Blueness of the lips, Cough, Sneezing Swelling (edema) of the face, Excessive sweating, Itching, Redness of the skin Fainting, Flushing Feeling hot, Generally feeling unwell Severe allergy-like reaction (shock)

As with other gadolinium containing contrast media**,** in rare cases **allergy-like reactions** (hypersensitivity and anaphylaxis) may occur, including severe reactions (shock) that may need immediate medical intervention. Mild swelling of the face, lips, tongue or throat, coughing, itching, runny nose, sneezing and hives (nettle-type rash) may be the first signs that a severe reaction is happening.
Tell the MRI department staff immediately if you experience any of these signs or have difficulty in breathing.
Delayed allergy-like reactions, hours to several days after the administration of Gadograf, have been observed in rare cases. If this should happen to you, tell your doctor or radiologist.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or radiologist.

5. HOW TO STORE GADOGRAF

This medicine does not require any special storage conditions.
Keep out of the reach and sight of children.

Do not use Gadograf after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of the month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What GADOGRAF contains

- The active substance is gadobutrol 604.72 mg corresponding to 1 mmol/ml
- The other ingredients are calcobutrol sodium, trometamol, hydrochloric acid and water for injections

1 prefilled syringe with 5.0 ml of the solution contains 3023 mg gadobutrol.
1 prefilled syringe with 7.5 ml of the solution contains 4535 mg gadobutrol.
1 prefilled syringe with 10 ml of the solution contains 6047 mg gadobutrol.
1 prefilled syringe with 15 ml of the solution contains 9070 mg gadobutrol.
1 prefilled syringe with 20 ml of the solution contains 12094 mg gadobutrol.

What GADOGRAF looks like and contents of the pack

Gadograf is a clear, colourless to pale yellow solution. The contents of the packs are:

1 or 5 prefilled syringes with 5, 7.5, 10 ml solution for injection (in 10-ml prefilled syringe)
1 or 5 prefilled syringes with 15 ml solution for injection (in 17-ml prefilled syringe)
1 or 5 prefilled syringes with 20 ml solution for injection

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

[To be completed nationally]

Manufacturer:

Schering AG
Müllerstrasse 178
D - 133 42 Berlin, Germany
Telephone: +49 30 468-1111

This medicinal product is authorised in the Member States of the EEA under the following names:

Germany	Gadograf
Spain	Gadograf

This leaflet was last approved in {MM/YYYY}.

The following information is intended for medical or healthcare professionals only:

- Before injection

This medicinal product is a clear, colourless to pale yellow solution. It should be visually inspected before use.
Gadograf should not be used in case of severe discoloration, the occurrence of particulate matter or a defective container.

- Handling

Gadograf should not be prepared until immediately before use. Gadograf not used in one examination must be discarded.

Any solution not used in one examination is to be discarded in accordance with local requirements.

Further information regarding the use of Gadograf is given in section 3 of the leaflet.