PART VI
Summary of Activities in the Risk Management Plan by Product

Active substance(s) (INN or common name):	Gadobutrol

Medicinal products to which this RMP refers:	2

Name of Marketing Authorisation Holder or Applicant:	Bayer AG

Data lock point for this module	30 APR 2019

Version number of RMP when this module was last updated	6.1

1. Summary of Risk Management Plan for Gadovist and Gadograf (Gadobutrol)

This is a summary of the RMP for Gadovist and Gadograf (gadobutrol) The RMP details the important risks of Gadovist/Gadograf, how these risks can be minimised, and how more information will be obtained about these risks and uncertainties (missing information).

Gadovist's and Gadograf's summary of product characteristics (SmPC) and their package leaflets give essential information to healthcare professionals and patients on how Gadovist and Gadograf should be used.

This summary of the RMP for Gadovist and Gadograf should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of the RMP for Gadovist and Gadobutrol.

2. The Medicine and what it is used for

Gadovist/Gadograf is used for diagnostic purposes only. Gadovist/Gadograf is indicated in adults and children of all ages (including term neonates) for:

- 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).

Gadovist/Gadograf can also be used for MR imaging of pathologies of the whole body. It facilitates visualisation of abnormal structures or lesions and helps in the differentiation between healthy and pathological tissue.

Gadovist and Gadograf contain gadobutrol as the active substance and it is given by intravenous administration only.

3. Risks Associated with the Medicine and Activities to Minimise or further Characterise the Risks

Important risks of Gadovist and Gadograf, together with measures to minimise such risks, and the proposed studies for learning more about these risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging

- The authorised pack size—the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status—the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Benefit Risk Evaluation Report/Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Gadovist/Gadograf is not yet available, it is listed under "missing information" below.

3.1 List of Important Risks and Missing Information

Important risks of Gadovist and Gadograf are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Gadovist/Gadograf. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 3-1: Summary of safety concerns

Important identified risks	• Nephrogenic systemic fibrosis (NSF)
Important potential risks	• Adverse clinical effects of accumulation and retention of gadolinium in the brain • Adverse clinical effects of accumulation and retention of gadolinium in organs and tissues other than brain tissues
Missing information	• Safety of use in pregnancy and lactation • Safety in children • Clinical significance of gadolinium retention in the brain • Clinical significance of gadolinium accumulation in organs and tissues other than brain tissues

3.2 Summary of Important Risks

Important Identified Risk: Nephrogenic systemic fibrosis (NSF)	
Evidence for linking the risk to the medicine	Non-clinical studies, clinical trials, post-marketing experience, scientific literature
Risk factors and risk groups	Patients with acute or chronic severe renal impairment, acute renal insufficiency of any severity due to hepato-renal syndrome, or in the peri-operative liver transplantation period receiving Gd-based contrast agents are assumed to be at increased risk for NSF. High and/or repeated doses of GdCAs in these at-risk populations have been suggested to be a possible risk factor for development of NSF. Regulatory authorities including both FDA and EMA have classified the marketed GdCAs into risk groups based on complex stability of the gadolinium-chelates. Gadobutrol (and the other macrocyclic agents) are in the lowest risk class.

Risk minimisation measures	Routine risk minimisation measures
	<u>Text in Gadovist SmPC:</u>
	• Strong warnings in Section 4.4 about the risk of NSF in patients with
	  ◦ acute or chronic severe renal impairment (GFR < 30 mL/min/1.73m^2) or
	  ◦ acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.
	• Listed in Section 4.8 Undesirable Effects.
	• Section 4.4 Special warnings and precautions for use: Impaired renal function-Prior to administration of gadobutrol, it is recommended that all patients are screened for renal dysfunction by obtaining laboratory tests.
	Haemodialysis shortly after gadobutrol administration may be useful at removing gadobutrol from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.
	<u>Text in Gadovist SmPC</u>
	• Section 6.6
	The peel-off tracking label on the vials/bottles should be stuck onto the patient record to enable accurate recording of the gadolinium contrast agent used. The dose used should also be recorded. If electronic patient records are used, the name of the product, the batch number, and the dose should be entered into the patient's record.
	Prescription only medicine

Additional risk minimisation measures	None

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Important Identified Risk: Nephrogenic systemic fibrosis (NSF)	
Additional pharmacovigilance activities	Study of Long-Term Gd Retention in Bone and Skin (ALS-Gd 64/001) Follow-up of potential cases using a topic-specific questionnaire Expedited reporting of new cases Annual NSF reports to FDA and EMA

Important Potential Risk: Adverse clinical effects of accumulation and retention of gadolinium in the brain	
Evidence for linking the risk to the medicine	It has been demonstrated that all GdCAs enter the brain, mostly likely via the choroid plexus and the cerebrospinal fluid (CSF). However, no evidence has been presented to date that any adverse health effects are related to these traces of gadolinium in the brain.
Risk factors and risk groups	Patients who tend to have higher concentrations of Gd in the brain include those who have multiple doses of primarily linear GdCAs, those who have high doses of GdCAs, and those who have repeated or closely spaced GdCA-enhanced MRIs.
Risk minimisation measures	Routine risk minimisation measures Text in Gadovist SmPC: • Posology: The lowest dose that provides sufficient enhancement for diagnostic purposes should be used. The dose should be calculated based on the patient's body weight, and should not exceed the recommended dose per kilogram of body weight detailed in this section. • Section 4.1 Therapeutic indications: gadobutrol should be used only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI). Prescription only medicine
Additional risk minimisation measures	None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Follow-up of reported cases using a topic-specific questionnaire in order to evaluate potential clinical consequences Additional stated activities**:** Non-clinical studies in rats Non-clinical studies in mice and non-human primates (planned) Clinical study with long term follow-up (planned)

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Important Potential Risk: Adverse clinical effects of accumulation and retention of gadolinium in organs and tissues other than brain tissues	
Evidence for linking the risk to the medicine	Non-clinical and clinical studies have demonstrated that traces of gadolinium may remain in parts of the body including the bones, brain, skin and other organs for extended periods of time after injection. Gadolinium levels have been detected in laboratory testing of blood, urine, hair, fingernails, etc. NSF has been linked to gadolinium deposition in the skin of renally impaired patients. There is no confirmation of adverse health effects attributable to the traces of Gd in the body in patients with normal renal function.
Risk factors and risk groups	Patients with primarily severe (eGFR < 30 mL/min/1.73, m^2) renal impairment are considered to be at increased risk for NSF. No other specific risk factors or risk groups are specifically known, as no other risks have been identified. Patients who receive high and/or repeated dosing of GdCAs, especially when closely spaced, would be considered to be at higher risk for accumulation of higher concentrations of gadolinium in the body; however, no adverse health effects have been confirmed in such patients. Macrocyclic agents deposit less gadolinium; however, all amounts are small and no harmful effects have been confirmed to be associated with any agent in patients with normal renal function. Reports of persistent symptoms and elevated gadolinium levels in laboratory tests have been received concerning patients with normal renal function who received GdCAs, including gadobutrol. A causal relationship has not been established.
Risk minimisation measures	Routine risk minimisation measures <u>Text in Gadovist SmPC:</u> • Information in Section 4.2 that gadobutrol elimination may be delayed in patients with severely impaired renal function. • Text regarding NSF in Section 4.4 • Section 4.1 Therapeutic indications: Gadobutrol should be used only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI). • Posology: The lowest dose that provides sufficient enhancement for diagnostic purposes should be used. The dose should be calculated based on the patient's body weight, and should not exceed the recommended dose per kilogram of body weight detailed in this section. Prescription only medicine
Additional risk minimisation measures	None

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Important Potential Risk: Adverse clinical effects of accumulation and retention of gadolinium in organs and tissues other than brain tissues	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Follow-up of reported cases using a topic-specific questionnaire in order to evaluate potential clinical consequences of Gd accumulation in the body. Additional stated activities: Non-clinical studies in rats to evaluate long-term effects on motor and cognitive function. Planned non-clinical studies in mice. Planned non-clinical studies in non-human primates. Planned clinical trial with long-term follow-up.

Missing information: Safety of use during pregnancy and lactation	
Evidence for linking the risk to the medicine	Non-clinical studies demonstrate that gadolinium crosses the placenta in small amounts An article by Ray *et al.* suggested that patients who receive contrast enhanced MRIs at any stage of pregnancy had a higher incidence of abortions, stillbirths and adverse foetal and childhood outcomes
Risk factors and risk groups	None have been identified
Risk minimisation measures	Routine risk minimisation measures Text in Gadovist SmPC: • Information in Section 4.6.1 regarding use in pregnancy • Section 4.1 Therapeutic indications: Gadobutrol should be used only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI). Prescription only medicine
Additional risk minimisation measures	None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Follow-up of cases to obtain pregnancy outcomes • Non-clinical studies in mice-planned

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Missing information: Safety in children	
Evidence for linking the risk to the medicine	The safety and efficacy of gadobutrol has been established in clinical trials of children of all ages, including term neonates. Gadobutrol has been shown to cross the placenta in small amounts and the potential risks to the foetus are unknown.
Risk factors and risk groups	Children who were exposed to gadolinium-containing contrast media in utero. Very young children with immature renal function. Children who require ongoing monitoring with MRI.
Risk minimisation measures	Prescription only medicine
Additional risk minimisation measures	None
Additional pharmacovigilance activities	Non-clinical studies in mice and monkeys planned

Missing information: Clinical significance of gadolinium retention in the brain	
Evidence for linking the risk to the medicine	It has been demonstrated that all GdCAs enter the brain, mostly likely via the choroid plexus and the cerebrospinal fluid (CSF). However, no evidence has been presented to date that any adverse health effects are related to these traces of gadolinium in the brain.
Risk factors and risk groups	Patients who tend to have higher concentrations of Gd in the brain include those who have multiple doses of primarily linear GdCAs, those who have high doses of GdCAs, and those who have repeated or closely spaced GdCA-enhanced MRIs.
Risk minimisation measures	Routine risk minimisation measures Text in Gadovist SmPC: • Posology: The lowest dose that provides sufficient enhancement for diagnostic purposes should be used. The dose should be calculated based on the patient's body weight, and should not exceed the recommended dose per kilogram of body weight detailed in this section. • Section 4.1 Therapeutic indications: gadobutrol should be used only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI). Prescription only medicine

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Missing information: Clinical significance of gadolinium retention in the brain	
Additional risk minimisation measures	None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Follow-up of reported cases using a topic-specific questionnaire in order to evaluate potential clinical consequences Additional stated activities**:** Non-clinical studies in rats Non-clinical studies in mice and non-human primates (planned) Clinical study with long term follow-up (planned)

Missing information: Clinical significance of gadolinium accumulation in organs and tissues other than brain tissues	
Evidence for linking the risk to the medicine	Non-clinical and clinical studies have demonstrated that traces of gadolinium may remain in parts of the body including the bones, brain, skin and other organs for extended periods of time after injection. Gadolinium levels have been detected in laboratory testing of blood, urine, hair, fingernails, etc. NSF has been linked to gadolinium deposition in the skin of renally impaired patients. There is no confirmation of adverse health effects attributable to the traces of Gd in the body in patients with normal renal function.
Risk factors and risk groups	Patients with primarily severe (eGFR < 30 mL/min/1.73, m^2) renal impairment are considered to be at increased risk for NSF. No other specific risk factors or risk groups are specifically known, as no other risks have been identified. Patients who receive high and/or repeated dosing of GdCAs, especially when closely spaced, would be considered to be at higher risk for accumulation of higher concentrations of gadolinium in the body; however, no adverse health effects have been confirmed in such patients. Macrocyclic agents deposit less gadolinium; however, all amounts are small and no harmful effects have been confirmed to be associated with any agent in patients with normal renal function. Reports of persistent symptoms and elevated gadolinium levels in laboratory tests have been received concerning patients with normal renal function who received GdCAs, including gadobutrol. A causal relationship has not been established.
Risk minimisation measures	Routine risk minimisation measures <u>Text in Gadovist SmPC:</u> • Information in Section 4.2 that gadobutrol elimination may be delayed in patients with severely impaired renal function. • Text regarding NSF in Section 4.4 • Section 4.1 Therapeutic indications: Gadobutrol should be used only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI).

Missing information: Clinical significance of gadolinium accumulation in organs and tissues other than brain tissues	
	• Posology: The lowest dose that provides sufficient enhancement for diagnostic purposes should be used. The dose should be calculated based on the patient's body weight, and should not exceed the recommended dose per kilogram of body weight detailed in this section. Prescription only medicine
Additional risk minimisation measures	None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Follow-up of reported cases using a topic-specific questionnaire in order to evaluate potential clinical consequences of Gd accumulation in the body. Additional stated activities: Non-clinical studies in rats to evaluate long-term effects on motor and cognitive function. Planned non-clinical studies in mice. Planned non-clinical studies in non-human primates. Planned clinical trial with long-term follow-up.

3.3 Post-authorisation Development Plan

3.3.1 Studies which are conditions of the Marketing Authorisation for Gadobutrol

The following study is a condition of the marketing authorisation or a specific obligation for the originator product Gadovist.

Study short name*:* Study of long-term Gd-retention in bone and skin (Study No.: ALS-Gd64/001).

Purpose of the study: To explore the potential for the long-term retention of Gd in the bones of patients with moderate or severe renal impairment or stable renal function who have received a single or multiple dose of a GdCA.

Table 3-2: Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Study Status	**Summary of objectives**	**Safety concerns/efficacy issue addressed**	**Milestones**	**Due dates**
Interventional study of long-term gadolinium retention in bone and skin (Study	To explore the potential for the long-term retention of gadolinium in the bones of patients	NSF, gadolinium accumulation in organs and tissues other than brain tissues, clinical	Ongoing FPFV 06 MAY 2013	Final report estimated: Q4/2019 (delays have been experienced due

Table 3-2: Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Study Status	Summary of objectives	Safety concerns/efficacy issue addressed	Milestones	Due dates
No.: ALS Gd 64/001) (CHMP follow-up measure EMA/HA/A-31/1097/FUM001) Ongoing	with moderate or severe renal impairment or stable renal function who have received a single dose of a GdCA or multiple doses of the same GdCA.	significance of gadolinium accumulation in organs and tissues other than brain tissues		to slow enrolment)

3.3.2 Other Studies in the Post-authorisation Development Plan

As part of the post-authorisation development plan, the potential risk of gadolinium accumulation and retention in the brain and body, and its unknown clinical significance, continues to be explored with a series of ongoing and planned activities:

- Ongoing studies in rats to evaluate long-term effects of gadolinium retention on cognitive and motor function
- Planned non-clinical studies in mice
- Planned non-clinical studies in non-human primates
- Clinical trial protocol under development with plan for long-term follow-up