Summary of the Risk Management Plan for Gadovist®

Active substance: Gadobutrol

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Based on the EU-RMP v8.2 for Gadovist®/Gadograf®

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Summary of activities in the risk management plan

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Gadovist® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Gadovist® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Bayer (Schweiz) AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Gadovist®.

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.

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

I. 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 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 MRI 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.

II. 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.

II.A 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 Part VI-1: Summary of safety concerns

Important identified risks	• Nephrogenic systemic fibrosis
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

II.B Summary of important risks

Table Part VI-2: Important Identified Risk: Nephrogenic systemic fibrosis (NSF)

Evidence for linking the risk to the medicine	Nephrogenic systemic fibrosis is a rare fibrosing disorder of possible multi-factorial aetiology that occurs primarily in patients with severe renal impairment. It is an identified risk for all GdCAs based on non-clinical studies, published literature and post-marketing experience. Bayer conducted an extensive non-clinical program in rats, in which NSF-like skin disorders were reproduced only in rats given the highest doses of the least stable GdCA (Omniscan). Bayer also conducted clinical studies with gadobutrol and other GdCAs to evaluate the magnitude of risk for this disorder in patients with impaired renal function, and no NSF reports arising from these studies were received for gadobutrol. Risk minimisation measures were promptly initiated and included labelling changes (e.g., recommendation that all patients are screened for renal dysfunction, limitations on repeated use, and ensuring recording of product name and dose administered), educational programs and an interactive information website. As a result, NSF has virtually ceased to exist. The cumulative data from all sources suggest that the risk of developing NSF after receiving macrocyclic GdCAs such as gadobutrol is very low. Nevertheless, the severity of the event and its routine risk minimisation messages in the label with clinical recommendations justify its continued inclusion as an important identified risk.
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 Food and Drug Administration (FDA) and European Medicines Agency (EMA) have classified the marketed GdCAs into risk groups based on the 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 SmPC:</u> • Section 4.1 mentions that gadobutrol should only be used when the diagnostic information is essential, and not available with unenhanced magnetic resonance imaging (MRI). • The lowest sufficient dose is recommended in Section 4.2, and for renally impaired patients, the dose should not exceed 0.1 mmol/kg BW, more than one dose should not be used during a scan, and injections should not be repeated unless the interval is at least seven days. • Strong warnings in Section 4.4 about patient populations at risk, recommendation to confirm renal function with laboratory testing; recommendation that prompt dialysis might be helpful in patients already on dialysis. • Listed in Section 4.8.

Table Part VI-2: Important Identified Risk: Nephrogenic systemic fibrosis (NSF)

	• Section 4.9 mentions that gadobutrol can be removed with dialysis (with no evidence that it is suitable for NSF prevention) • Section 6.6: the peel-off label enables accurate tracking of the GdCA used and dose in patient's medical records or entering such information electronically. Prescription only medicine **Additional risk minimisation measures:** None

BW: Body Weight, Gd: Gadolinium, GdCA: Gadolinium-containing Contrast Agent; EMA: European Medicines Agency; FDA: Food and Drug Administration; Kg: Kilogram, mmol: Millimole, MRI: Magnetic Resonance Imaging; NSF: Nephrogenic Systemic Fibrosis; SmPC: Summary of Product Characteristics

Table Part VI-3: Important Potential Risk: Adverse clinical effects of accumulation and retention of gadolinium in the brain

Evidence for linking the risk to the medicine	Non-clinical and clinical studies have shown that small amounts of gadolinium/GdCAs may be detectable in the brain, especially after multiple, high-dose or closely spaced CE-MRI procedures, and in particular with multi-purpose linear agents. Gadolinium has been measured in the brain on autopsy and necropsy in both humans and animals. To date, no adverse health effects have been confirmed to be related to this finding. Source of evidence: animal studies, scientific literature and individual case safety reports.
Risk factors and risk groups	No risk groups or risk factors have been identified with certainty. Patients who receive repeated and/or high dose contrast-enhanced MRIs would be most at risk. The phenomenon has been reported in children and adults. It might be assumed that patients with CNS diseases/a disrupted blood-brain barrier might be at an increased risk for entry of gadolinium into the brain, as that is the mechanism by which the efficacy of GdCAs in CNS indications is achieved. However, all GdCAs enter the brain *via* the cerebrospinal fluid (CSF). Non-clinical studies suggest that while the amounts detected for both classes of agents are small, more gadolinium retention occurs with the linear agents as opposed to the macrocyclic agents. Patients with renal insufficiency have a delayed excretion of GdCAs and therefore may be at increased risk for a longer period of exposure; however, the increased signal intensity has been observed in patients with and without renal impairment.
Risk minimisation measures	**Routine risk minimisation measures:** Text in SmPC: • Section 4.1 mentions that gadobutrol should be used only when diagnostic information is essential and not available with unenhanced MRI. • The lowest sufficient dose is recommended in Section 4.2. • Section 6.6: the peel-off label enables accurate tracking of the GdCA used and dose in patient's medical records or entering such information electronically.

Table Part VI-3: Important Potential Risk: Adverse clinical effects of accumulation and retention of gadolinium in the brain

	Prescription only medicine
	Additional risk minimisation measures:
	DHCPL (completed)
Additional pharmacovigilance activities	**Additional pharmacovigilance activities[a]:**
	Non-clinical studies in non-human primates (ongoing)
	Clinical study (ongoing)

[a] See section II.C of this summary for an overview of the post-authorisation development plan.
CE-MRI: Contrast-Enhanced Magnetic Resonance Imaging, CNS: Central Nervous System; CSF: Cerebrospinal Fluid, DHCPL: Dear Health Care Professional Letter, GdCA: Gadolinium-containing Contrast Agent, MRI: Magnetic Resonance Imaging; SmPC: Summary of Product Characteristics

Table Part VI-4: 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	There have been reports of unexpectedly prolonged retention of gadolinium in organs and tissues other than the brain (for example, in bones) after repeated use of GdCAs, including gadobutrol. No risk factors for this phenomenon other than frequent, repeated use of GdCAs have been identified. Gadolinium has been definitively measured in various organs by scientific methods including ICP-MS; however, it has not been confirmed that any adverse health effects have resulted 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. Sources of evidence: animal studies, scientific literature, and individual case safety reports (ICSRs).
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 (which may be associated with accumulation and retention of gadolinium in the skin). Linear agents are thought to pose a higher risk for NSF than macrocyclic agents. The amount of gadolinium retained is higher with linear agents than with macrocyclic agents. The highest amounts are seen with the linear non-ionic agents Omniscan and OptiMARK. Macrocyclic agents including gadobutrol have the lowest concentrations of gadolinium. No risk groups or risk factors for bone or other organ retention have been identified with certainty. 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

Table Part VI-4: Important Potential Risk: Adverse clinical effects of accumulation and retention of gadolinium in organs and tissues other than brain tissues

	health effects have been confirmed in such patients. Bayer continues to evaluate this topic to verify if certain patient populations are more susceptible to effects of gadolinium accumulation and retention in various body organs.
Risk minimisation measures	**Routine risk minimisation measures:** Text in SmPC: • Section 4.1 mentions that gadobutrol should be used only when diagnostic information is essential and not available with unenhanced MRI. • Information in Section 4.2 that gadobutrol elimination may be delayed in patients with severely impaired renal function. The lowest sufficient dose is recommended. • Text regarding NSF in Section 4.4 • Section 6.6: the peel-off label enables accurate tracking of the GdCA used and dose in patient's medical records or entering such information electronically. Prescription only medicine **Additional risk minimisation measures:** DHCPL (completed)
Additional pharmacovigilance activities	**Additional pharmacovigilance activities[a]:** Non-clinical studies in non-human primates (ongoing) Clinical study with long-term follow-up (ongoing)

[a] See section II.C of this summary for an overview of the post-authorisation development plan.
DHCPL: Dear Health Care Professional Letter, eGFR: Estimated Glomerular Filtration Rate; GdCA: Gadolinium containing Contrast Agent, ICP-MS: Inductively Coupled Plasma Mass Spectrometry; ICSR: Individual Case Safety Report; mL: Millilitre; min: Minutes, MRI: Magnetic Resonance Imaging; m^2: Square Meter; NSF: Nephrogenic Systemic Fibrosis, SmPC: Summary of Product Characteristics, <: Less Than

Table Part VI-5: Missing information: Safety of use during pregnancy and lactation

Risk minimisation measures	**Routine risk minimisation measures:** Text in SmPC: • Section 4.1 mentions that gadobutrol should be used only when diagnostic information is essential and not available with unenhanced MRI. • The lowest sufficient dose is recommended in Section 4.2. • Section 4.6 mentions there are no data in pregnant women, and animal studies have shown reproductive toxicity at repeated high doses (also included in Section 5.3). Gadobutrol should not be used during pregnancy unless required by the patient's clinical condition. For lactation, no effects on the infant are anticipated (small excretion in milk and poor gut absorption) and continuing or discontinuing of breast feeding for a period of 24 hours after

Table Part VI-5: Missing information: Safety of use during pregnancy and lactation

	administration should be at the discretion of the doctor and lactating mother. Prescription only medicine **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: None

MRI: Magnetic Resonance Imaging; SmPC: Summary of Product Characteristics

Table Part VI-6: Missing information: Safety in children

Risk minimisation measures	**Routine risk minimisation measures:** Text in SmPC: • Section 4.2 and Section 4.4 mention that due to immature renal function in neonates up to four weeks of age and infants up to one-year of age, gadobutrol should only be used in these patients after careful consideration. In Section 4.2, it is stated that the dose should not exceed 0.1 mmol/kg BW. More than one dose should not be used during a scan, and due to lack of information on repeated administration, injections should not be repeated unless the interval is at least seven days. • Section 6.6: The peel-off label enables accurate tracking of the GdCA used and dose in patient's medical records or entering such information electronically. Prescription only medicine **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**[a]: Non-clinical studies in non-human primates (ongoing)

[a] See section II.C of this summary for an overview of the post-authorisation development plan.
BW: Body Weight, GdCA: Gadolinium containing Contrast Agent; kg: Kilogram; mmol: Millimole, SmPC: Summary of Product Characteristics

Table Part VI-7: Missing information: Clinical significance of gadolinium retention in the brain

Risk minimisation measures	**Routine risk minimisation measures:** Text in SmPC: • Section 4.1 mentions that gadobutrol should be used only when diagnostic information is essential and not available with unenhanced MRI • The lowest sufficient dose is recommended in Section 4.2 • Section 6.6: the peel-off label enables accurate tracking of the GdCA used and dose in patient's medical records or entering such information electronically. Prescription only medicine

Table Part VI-7: Missing information: Clinical significance of gadolinium retention in the brain

	Additional risk minimisation measures:
	DHCPL (completed)
Additional pharmacovigilance activities	**Additional pharmacovigilance activities[a]:**
	Non-clinical studies in non-human primates (ongoing)
	Clinical study with long term follow-up (ongoing)

[a] See section II.C of this summary for an overview of the post-authorisation development plan.
GdCA: Gadolinium containing Contrast Agent; MRI: Magnetic Resonance Imaging; SmPC: Summary of Product Characteristics; DHCPL: Dear Health Care Professional Letter

Table Part VI-8: Missing information: Clinical significance of gadolinium accumulation in organs and tissues other than brain tissues

Risk minimisation measures	**Routine risk minimisation measures:**
	Text in SmPC:
	• Section 4.1 mentions that gadobutrol should be used only when diagnostic information is essential and not available with unenhanced MRI
	• Information in Section 4.2 that gadobutrol elimination may be delayed in patients with severely impaired renal function. The lowest sufficient dose is recommended.
	• Text regarding NSF in Section 4.4
	• Section 6.6: The peel-off label enables accurate tracking of the GdCA used and dose in patient's medical records, or entering such information electronically
	Prescription only medicine
	Additional risk minimisation measures:
	DHCPL (completed)
Additional pharmacovigilance activities	**Additional pharmacovigilance activities[a]:**
	Non-clinical studies in non-human primates (ongoing)
	Clinical study with long-term follow-up (ongoing)

[a] See section II.C of this summary for an overview of the post-authorisation development plan.
DHCPL: Dear Health Care Professional Letter, GdCA: Gadolinium containing Contrast Agent; MRI: Magnetic Resonance Imaging; NSF: Nephrogenic Systemic Fibrosis; SmPC: Summary of Product Characteristics

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Gadovist/Gadograf.

II.C.2 Other studies in 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 activities. Some of these studies also address the concerns of safety of use in children:

- Non-clinical studies in non-human primates ("Juvenile toxicity study in monkey") (ongoing). Objective: Detect potential effects due to Gadolinium exposure following repeated intravenous administration of Omniscan or MultiHance or Gadovist to juvenile monkeys. Final report expected by 2023.
- Clinical study (ODYSSEY, Study No. 20405, NCT 04373564) with long-term follow-up, in collaboration with other marketing authorisation holders (MAHs), to evaluate potential long-term effects on motor and cognitive function, in patients who receive multiple doses of GdCAs. First patient first visit: 24 MAR 2021. Last patient last visit: 31 DEC 2028 (anticipated). Patients will be monitored over a period of five-years. The length of the study is estimated to be nine-years.