PRIMOVIST®
(Gadoxetate disodium)
EU Risk Management Plan

Part VI–Summary of Activities in the Risk Management Plan by Product

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Active substance(s) (INN or common name):	Gadoxetate disodium

Medicinal products to which this RMP refers:	1

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	3.1

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Summary of Risk Management Plan for Primovist (Gadoxetate disodium)

This is a summary of the Risk Management Plan (RMP) for Primovist. The RMP details important risks associated with Primovist, how these risks can be minimised, and how more information will be obtained about Primovist's risks and uncertainties (missing information).

Primovist's Summary of Product Characteristics (SmPC) and its package leaflet gives essential information to healthcare professionals and patients on how Primovist should be used.

Important new concerns or changes to the current ones will be included in updates of the Primovist's RMP.

1. The medicine and what it is used for

Primovist is authorised for diagnostic use. Primovist is a gadolinium-containing contrast agent for T1-weighted magnetic resonance imaging (MRI) of the liver (see SmPC for the full indication). It contains gadoxetate disodium (gadoxetic acid, Gd-EOB-DTPA) as the active substance and is given by the intravenous route of administration as a solution for injection.

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

Important risks of Primovist, together with measures to minimise such risks and the proposed studies for learning more about Primovist's 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 minimise its risks.

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

In addition to these measures, information about adverse reactions is collected continuously and is regularly analysed, including PBRER/PSUR 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 Primovist is not yet available, it is listed under "missing information" below.

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2.1 List of Important Risks and Missing Information

Important risks of Primovist 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 Primovist. 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 2-1: 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 • Clinical significance of gadolinium retention in the brain • Clinical significance of gadolinium accumulation in organs and tissues other than brain tissues

2.2 Summary of Important Risks

Important identified risk: Nephrogenic systemic fibrosis (NSF)	
Evidence for linking the risk to the medicine	No case of NSF has been documented so far for Primovist from any source. However, non-clinical studies post-marketing experience and the scientific literature provide evidence that NSF can occur with other GdCAs. Therefore, it is considered an important identified risk for Primovist (see also Annex 7).
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 perioperative liver transplantation period receiving Gd-containing contrast agents are assumed to be increased risk for NSF.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Sections: 4.1, 4.2, 4.4, 4.8, and 4.9. • SmPC Section 6.6: Peel-off (“sticky”) label for accurate tracking of the contrast agent used and dose in patient’s medical records, or entering such information electronically. • Prescription-only medicine

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Important identified risk: Nephrogenic systemic fibrosis (NSF)	
Additional risk minimisation measures	None
Additional pharmacovigilance activities	“Bone Study” (PASS: Study of the potential long-term retention of gadolinium in bone and skin)

Important potential risk: Adverse clinical effects of accumulation and retention of gadolinium in the brain	
Evidence for linking the risk to the medicine	Studies have shown that small amounts of gadolinium may remain in the brain, especially after multiple, high-dose, or closely spaced imaging procedures. Evidence suggests that less gadolinium may be left in the brain with Primovist, because of its low dose (one-quarter that of other GdCAs) than with some other GdCAs. To date, no adverse health effects have been confirmed to be related to this finding. Source of evidence: animal studies and scientific literature.
Risk factors and risk groups	No risk groups or risk factors have been identified with certainty. Potential risk groups are: patients who receive repeated and/or high-dose contrast-enhanced MRIs, especially closely spaced procedures. Patients with renal insufficiency may be at increased risk (although the increased signal intensity has been observed in patients with and without renal impairment). Non-clinical studies have shown that the multi-purpose linear agents deposit more gadolinium than either macrocyclic agents or Primovist, although all amounts are small. No adverse health effects associated with accumulation and retention of gadolinium in the brain have been confirmed with any agent.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Sections: 4.1, 4.2, 4.4, and 4.9. • SmPC Section 6.6: Peel-off (“sticky”) label for accurate tracking of the contrast agent used and dose in patient’s medical records, or entering such information electronically. • DHCPL • Prescription-only medicine
Additional risk minimisation measures	None
Additional pharmacovigilance activities	None

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	There have been reports of unexpectedly prolonged retention of

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Important potential risk: Adverse clinical effects of accumulation and retention of gadolinium in organs and tissues other than brain tissues	
to the medicine	gadolinium in organs and tissues other than the brain (for example, in bones) after repeated use of MRI contrast agents, including Primovist. No risk factors for this phenomenon other than frequent and/or repeated use of gadolinium-containing contrast agents have been identified. Source of evidence: animal studies, scientific literature, ICSRs.
Risk factors and risk groups	No risk groups or risk factors for bone or other organ accumulation and retention have been identified with certainty. Patients with severe renal impairment or acute kidney injury are considered to be at increased risk for NSF (which may be associated with accumulation of gadolinium in the skin). Linear agents are thought to pose a higher risk for NSF than macrocyclic agents. Patients requiring multiple MRIs may be at increased risk.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Sections: 4.1, 4.2, 4.4, and 4.9. • SmPC Section 6.6: Peel-off (“sticky”) label for accurate tracking of the contrast agent used and dose in patient’s medical records, or entering such information electronically. • Prescription-only medicine
Additional risk minimisation measures	None
Additional pharmacovigilance activities	“Bone Study” (PASS: Study of the long-term gadolinium retention in bone and skin)

Missing information: Safety of use in pregnancy and lactation	
Risk minimisation measures	• SmPC Sections: 4.1, 4.2, 4.6, and 5.3. • Prescription-only medicine
Additional risk minimisation measures	None
Additional pharmacovigilance activities	None

Missing information: Clinical significance of accumulation and retention of gadolinium in the brain	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Sections: 4.1, 4.2, 4.4 and 4.9. • SmPC Section 6.6: Peel-off (“sticky”) label for accurate tracking of the contrast agent used and dose in patient’s medical records, or entering such information electronically.

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Missing information: Clinical significance of accumulation and retention of gadolinium in the brain	
	• Prescription-only medicine
Additional risk minimisation measures	None
Additional pharmacovigilance activities	None

Missing information: Clinical significance of gadolinium accumulation in the organs and tissues other than brain tissues	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Sections: 4.1, 4.2, 4.4, and 4.9. • SmPC Section 6.6: Peel-off (“sticky”) label for accurate tracking of the contrast agent used and dose in patient’s medical records, or entering such information electronically. • Prescription-only medicine
Additional risk minimisation measures	None
Additional pharmacovigilance activities	“Bone Study” (PASS: Study of the long-term gadolinium retention in bone and skin)

2.3 Post-authorisation Development Plan

2.3.1 Studies which are conditions of the Marketing Authorisation

The following study is a condition of the marketing authorisation or a specific obligation for Primovist:

Study short name: “Bone Study” (Study of long-term Gd-retention in bone and skin).

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.

An Interim Analysis (IA) was conducted on all subjects enrolled in the single dose subgroups for gadobutrol, gadoteric acid, gadodiamide, and gadopentetic acid, as well as on all subjects of the control group (naïve subjects) and was submitted to the EMA in NOV 2018.

The estimated study timelines are described in Table 2-2. The study recruitment is currently on hold.

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Table 2-2: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Category 1-Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Interventional study of long-term gadolinium retention in bone and skin ("Bone Study", Study No.: ALS Gd 64/001) (CHMP follow-up measure EMA/HA/A-31/1097/FUM001) Ongoing	To explore the potential for the long-term retention of gadolinium in the bones of patients 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.	Nephrogenic systemic fibrosis (NSF), Adverse clinical effects of accumulation and retention of gadolinium in organs and tissues other than brain tissues, and Clinical significance of gadolinium accumulation in organs and tissues other than brain tissues	LPLV Final report Submission Final study report	Expected by DEC 2018 Expected by JUN 2019 Expected by Q4/2019

2.3.2 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, continue to be explored with a series of ongoing and planned stated 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