Part VI: Summary of the risk management plan

This is a summary of the 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 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 RMP.

I. The medicine and what it is used for

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

II. 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.

II.A 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

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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 Part VI-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	• Clinical significance of gadolinium retention in the brain • Clinical significance of gadolinium accumulation in organs and tissues other than brain tissues • Safety of use in pregnancy and lactation • Safety use in Children

NSF: Nephrogenic Systemic Fibrosis

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	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 GBCAs. Therefore, it is considered an important identified risk for Primovist.
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-based 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 **Additional risk minimisation measures** • None

Gd: Gadolinium; GBCA: Gadolinium Based Contrast Agent; NSF: Nephrogenic Systemic Fibrosis; SmPC: Summary of Product Characteristics

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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	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 GBCAs) than with some other GBCAs. 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 5.2. • 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	**Additional pharmacovigilance activities:** • ODYSSEY study (ongoing)

GBCA: Gadolinium Based Contrast Agent; NSF: Nephrogenic Systemic Fibrosis; 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 MRI contrast agents, including Primovist. No risk factors for this phenomenon other than frequent and/or repeated use of gadolinium-based contrast agents have been identified. Source of evidence: animal studies, scientific literature, and 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

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

	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 5.2. • 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	**Additional pharmacovigilance activities:** • ODYSSEY study (ongoing)

ICSR: Individual Case Safety Report; MRI: Magnetic Resonance Imaging; NSF: Nephrogenic Systemic Fibrosis; SmPC: Summary of Product Characteristics

Table Part VI-5: 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 5.2. • 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	**Additional pharmacovigilance activities:** • ODYSSEY study (ongoing)

SmPC: Summary of Product Characteristic

Table Part VI-6: 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 5.2 • 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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Table Part VI-6: Missing information: Clinical significance of gadolinium accumulation in the organs and tissues other than brain tissues

	Additional risk minimisation measures • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • ODYSSEY study (ongoing)

SmPC: Summary of Product Characteristic

Table Part VI-7: Missing information: Safety of use in pregnancy and lactation

Risk minimisation measures	**Routine risk minimisation measures** • SmPC Sections: 4.1, 4.2, 4.6, and 5.3. • Prescription-only medicine **Additional risk minimisation measures** • None

SmPC: Summary of Product Characteristic

Table Part VI-8: Missing information: Safety of use in children

Risk minimisation measures	**Routine risk minimisation measures** • SmPC Sections: 4.2 and 5.1. • Prescription-only medicine **Additional risk minimisation measures** • None

SmPC: Summary of Product Characteristic

II.C Post-authorisation development plan

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

None.

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, continue to be explored with the following ongoing study.

Clinical study ODYSSEY: (Bayer Study No. 20405; Clinical Trials.gov Identifier: NCT04373564) with long-term follow-up in collaboration with other MAHs to evaluate potential long-term effects on motor and cognitive function in patients who receive multiple doses of GBCAs.

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.