Summary of the Risk Management Plan for

ELUCIREM 0.5 mmol/mL, solution for injection
VUEWAY 0.5 mmol/mL, solution for injection

(Gadopiclenol)

Marketing Authorisation Holder:	Guerbet AG
RMP version number:	V 0.3
Data lock point for this RMP:	18.11.2021

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 ELUCIREM 0.5 mmol/mL, solution for injection / VUEWAY 0.5 mmol/mL, solution for injection 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 ELUCIREM 0.5 mmol/mL, solution for injection / VUEWAY 0.5 mmol/mL, solution for injection in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Guerbet AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of ELUCIREM 0.5 mmol/mL, solution for injection / VUEWAY 0.5 mmol/mL, solution for injection.

This is a summary of the risk management plan (RMP) for ELUCIREM 0.5 mmol/mL, solution for injection / VUEWAY 0.5 mmol/mL, solution for injection. The RMP details important risks of the product, how these risks can be minimised, and how more information will be obtained about the risks and uncertainties (missing information) of ELUCIREM 0.5 mmol/mL, solution for injection / VUEWAY 0.5 mmol/mL, solution for injection.

The summary of product characteristics (SmPC) and the package leaflet (PL) of ELUCIREM 0.5 mmol/mL, solution for injection / VUEWAY 0.5 mmol/mL, solution for injection give essential information to healthcare professionals and patients on how the product should be used.

This summary of the RMP for ELUCIREM 0.5 mmol/mL, solution for injection / VUEWAY 0.5 mmol/mL, solution for injection 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 ELUCIREM 0.5 mmol/mL, solution for injection / VUEWAY 0.5 mmol/mL, solution for injection.

I. The medicine and what it is used for

ELUCIREM 0.5 mmol/mL, solution for injection / VUEWAY 0.5 mmol/mL, solution for injection is authorised for in adults and children aged 2 years and older for contrast-enhanced magnetic resonance imaging (MRI) to improve detection and visualization of pathologies with disruption of the blood-brain-barrier (BBB) and/or abnormal vascularity of:

- the brain, spine, and associated tissues of the central nervous system (CNS);
- the liver, kidney, pancreas, breast, lung, prostate, and musculoskeletal system.

It should be used only when diagnostic information is essential and not available with unenhanced MRI

(see SmPC for the full indication).

It contains gadopiclenol as the active substance and it is given intravenously.

Further information about the evaluation of ELUCIREM 0.5 mmol/mL, solution for injection / VUEWAY 0.5 mmol/mL, solution for injection benefits can be found in ELUCIREM 0.5 mmol/mL, solution for injection / VUEWAY 0.5 mmol/mL, solution for injection EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpages : link to the ELUCIREM EPAR summary landing page and link to the VUEWAY EPAR summary landing page.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of ELUCIREM 0.5 mmol/mL / VUEWAY 0.5 mmol/mL, 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 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 ELUCIREM 0.5 mmol/mL, solution for injection / VUEWAY 0.5 mmol/mL, solution for injection is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of ELUCIREM 0.5 mmol/mL, solution for injection / VUEWAY 0.5 mmol/mL, solution for injection 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 ELUCIREM 0.5 mmol/mL / VUEWAY 0.5 mmol/mL, solution for injection. 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 1 - List of important risks and missing information

List of important risks and missing information	
Important identified risks	• Nephrogenic Systemic Fibrosis (NSF).
Important potential risks	• Adverse clinical effects of accumulation and retention of gadolinium in organs and tissues other than brain tissues. • Adverse clinical effects of accumulation and retention of gadolinium in the brain.
Missing information	• Safety in pregnancy and lactation. • Clinical significance of gadolinium accumulation and retention in other organs and tissues than brain tissues. • Clinical significance of gadolinium accumulation and retention in the brain.

II.B Summary of important risks

Important identified risks

Table 2 - Important identified risks: Nephrogenic Systemic Fibrosis (NSF)

Nephrogenic Systemic Fibrosis (NSF)	
Evidence for linking the risk to the medicine	Scientific literature; other GBCA products. NSF is a disease exclusively reported in patients with renal failure who were administered GBCAs. Non-clinical data: No evidence of biochemical toxicity or pathological abnormalities of the skin was observed, and similar to other macrocyclic GBCAs, gadoterate and gadobutrol, tissue retention of Gd was found to be low (except in the liver) in renally impaired rats treated with gadopiclenol.
Risk factors and risk groups	The risk factors for NSF can be divided into patient-related factors and those related to the molecular structure and stability of the GBCA used. Based on current evidences, cumulative analyses of NSF reports have shown that severe kidney dysfunction (eGFR < 30 mL/min/1.73 m^2) is the main patient-related risk factor. The degree of renal insufficiency is also important, with a much greater incidence of NSF in patients with category G5 of CKD (established renal failure; eGFR < 15 mL/min/1.73 m^2 or on dialysis) compared with category G4 of CKD (severe decrease in eGFR, with or without other evidence of kidney damage; eGFR ~ 15-29 mL/min/1.73 m^2). Acute kidney injury is also considered a risk factor for NSF. Furthermore, a proinflammatory state in a patient with impaired renal function has been reported as a risk factor. Despite initial concerns, severe liver disease has been deleted from the list of risk factors for NSF, as long as the patient has a normal renal function. Because of renal immaturity in fetuses, neonates, and infants, this population (and consequently pregnant women because of the risk to the fetus) is considered potentially at risk. Higher doses and multiple administrations of GBCAs, especially within a short period of time, have been reported as risk factors for the development of NSF . To be noted, gadopiclenol is administered at half-dose of gadolinium compared to the Gd dose usually administered with other GBCAs.
Risk minimisation measures	<u>Routine risk minimisation measures</u>: SmPC section 4.1. SmPC section 4.2. SmPC section 4.4.

Nephrogenic Systemic Fibrosis (NSF)	
	SmPC section 4.8. SmPC section 4.9. Peel-off label (SmPC section 6.6). Other routine risk minimisation measures beyond the Product Information: Prescription only medicine. Additional risk minimisation measures: None.
Pharmacovigilance activities	Routine pharmacovigilance activities with signal detection and adverse reactions reporting including: Adverse event follow-up report form for collection of additional information. Additional pharmacovigilance activities: None.

Important potential risks

Table 3 - Important potential risks: Adverse clinical effects of accumulation and retention of gadolinium in organs and tissues other than brain tissues

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	Scientific literature; other GBCA products; non-clinical data.
Risk factors and risk groups	Renal insufficiency (decreased elimination). Neonates (immature Blood Brain Barrier (BBB) and renal function). Patients with risk of BBB disruption: elderly patients, brain radiotherapy. Patients susceptible of receiving multiple injections of GBCAs for their disease diagnosis and monitoring.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.1. SmPC section 4.2. Peel-off label (SmPC section 6.6). Other routine risk minimisation measures beyond the Product Information: Prescription only medicine.

	Additional risk minimisation measures: None.
Pharmacovigilance activities	Routine pharmacovigilance activities with signal detection and adverse reactions reporting including: Specific GBCA long-term effects follow-up report form. Additional pharmacovigilance activities: None.

Table 4 - 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 the brain	
Evidence for linking the risk to the medicine	Scientific literature; other GBCA products; non-clinical data.
Risk factors and risk groups	Renal insufficiency (decreased elimination). Neonates (immature BBB and renal function). Patients with risk of BBB disruption: elderly patients, brain radiotherapy. Patients susceptible of receiving multiple injections of GBCAs for their disease diagnosis and monitoring
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.1. SmPC section 4.2. Peel-off label (SmPC section 6.6). Other routine risk minimisation measures beyond the Product Information: Prescription only medicine. Additional risk minimisation measures: None.
Pharmacovigilance activities	Routine pharmacovigilance activities with signal detection and adverse reactions reporting including: Specific GBCA long-term effects follow-up report form. Additional pharmacovigilance activities: Post-authorisation safety study GMRA-105 (ODYSSEY): Prospective evaluation of potential effects of repeated gadolinium-containing contrast agent administrations of the same GBCA on motor and cognitive functions in neurologically normal adults in comparison to a non-GBCA exposed control group.

Missing information

Table 5 - Missing information: Safety in pregnancy and lactation

Safety in pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.1. SmPC section 4.2. SmPC section 4.6. Peel-off label (SmPC section 6.6). Other routine risk minimisation measures beyond the Product Information: Prescription only medicine. Additional risk minimisation measures: None.
Pharmacovigilance activities	Routine pharmacovigilance activities with signal detection and adverse reactions reporting including: Pregnancy forms and follow-up forms. Additional pharmacovigilance activities: None.

Table 6 - Missing information: Clinical significance of gadolinium accumulation and retention in other organs and tissues than brain tissues

Clinical significance of gadolinium accumulation and retention in other organs and tissues than brain tissues	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.1. SmPC section 4.2. Peel-off label (SmPC section 6.6). Other routine risk minimisation measures beyond the Product Information: Prescription only medicine. Additional risk minimisation measures: None.
Pharmacovigilance activities	Routine pharmacovigilance activities with signal detection and adverse reactions reporting including: Specific GBCA long-term effects follow-up report form.

	Additional pharmacovigilance activities: - Preclinical studies in mice investigating the occurrence of small fiber neuropathy after single or repeated administration. - Preclinical study in rats investigating early (W1, M1) and long-term (M5) gadolinium retention after a single half-dose of gadopiclenol vs full-dose of already marketed macrocyclic GBCAs. - Preclinical study in rats investigating speciation of Gd retained after repeated injections of a half-dose of gadopiclenol vs gadobutrol.

Table 7 - Missing information: Clinical significance of gadolinium accumulation and retention in the brain

Clinical significance of gadolinium accumulation and retention in the brain	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.1. SmPC section 4.2. Peel-off label (SmPC section 6.6). Other routine risk minimisation measures beyond the Product Information: Prescription only medicine. Additional risk minimisation measures: None.
Pharmacovigilance activities	Routine pharmacovigilance activities with signal detection and adverse reactions reporting including: Specific GBCA long-term effects follow-up report form. Additional pharmacovigilance activities: - Preclinical studies in mice investigating the occurrence of small fiber neuropathy after single or repeated administration. - Preclinical study in rats investigating early (W1, M1) and long-term (M5) gadolinium retention after a single half-dose of gadopiclenol vs full-dose of already marketed macrocyclic GBCAs. - Preclinical study in rats investigating speciation of Gd retained after repeated injections of a half-dose of gadopiclenol vs gadobutrol. - Post-authorisation safety study GMRA-105 (ODYSSEY): Prospective evaluation of potential effects of repeated gadolinium-containing contrast agent administrations of the

	same GBCA on motor and cognitive functions in neurologically normal adults in comparison to a non-GBCA exposed control group.

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 ELUCIREM 0.5 mmol/mL, solution for injection / VUEWAY 0.5 mmol/mL, solution for injection.

II.C.2 Other studies in post-authorisation development plan

The MAH has planned a post-authorisation safety study for additional pharmacovigilance activities, in order to evaluate the long-term effects of gadopiclenol through participation in the ongoing ODYSSEY clinical study.
An amended protocol including gadopiclenol will be submitted to the EMA. The implementation at the level of sites will come later and will depend on the revision of the operational plans and submission to the Ethics Committees and Competent Authorities, and on the approval of the protocol amendment in each European country participating to the ODYSSEY clinical study.