EU Risk Management Plan for

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

(Gadopiclenol)

RMP version to be assessed as part of this application:	
RMP version number:	V 0.3
Data lock point for this RMP:	18.11.2021
Date of final sign off:	
Rationale for submitting an updated RMP:	Response to the request of supplementary information as outlined in the Response to the request of supplementary information as outlined in the CHMP List of Outstanding Issues (Procedure EMEA/H/C/005626/0000)
Summary of significant changes in this RMP:	1. Updated Section III.2 according to the guidance of the RMP in the EU 2. Replacement of targeted follow-up questionnaire in cases of potential persistent symptoms

Other RMP versions under evaluation:	
RMP version number:	NA
Submitted on:	NA
Procedure number:	NA

Details of the currently approved RMP:	
Version number:	NA
Approved with procedure:	NA

Date of approval (opinion date):	NA

QPPV names:	Eric LANCELOT	Letizia VITALI
QPPV signatures:	PPD	PPD
Dates: 19 April 2023		

Table of Contents

Part I: Product(s) Overview 7

Part II: Safety specification 9

Part II: Module SI - Epidemiology of the indication(s) and target population(s) 9

Part II: Module SII - Non-clinical part of the safety specification 12

Part II: Module SIII - Clinical trial exposure 17

Part II: Module SIV - Populations not studied in clinical trials 26

SIV.1 Exclusion criteria in clinical studies within the development programme 26

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes 27

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes 27

Part II: Module SV - Post-authorisation experience 27

SV.1 Post-authorisation exposure 27

Part II: Module SVI - Additional EU requirements for the safety specification 28

Part II: Module SVII - Identified and potential risks 28

SVII.1 Identification of safety concerns in the initial RMP submission 28

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP 28

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP 32

SVII.2 New safety concerns and reclassification with a submission of an updated RMP 35

SVII.3 Details of important identified risks, important potential risks, and missing information 35

SVII.3.1 Presentation of important identified risks and important potential risks 35

SVII.3.2 Presentation of the missing information 42

Part II: Module SVIII - Summary of the safety concerns 45

Part III: Pharmacovigilance Plan (including post-authorisation safety studies) 46

III.1 Routine pharmacovigilance activities 46

III.2 Additional pharmacovigilance activities 46

III.3 Summary table of additional pharmacovigilance activities 48

Part IV: Plans for post-authorisation efficacy studies 51

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities) 51

V.1 Routine Risk Minimisation Measures 51

V.2 Additional Risk Minimisation Measures 57

V.3 Summary of risk minimisation measures 57

Part VI: Summary of the risk management plan 61

I. The medicine and what it is used for 61

II. Risks associated with the medicine and activities to minimise or further characterise the risks 62

II.A List of important risks and missing information 62

II.B Summary of important risks 63

II.C Post-authorisation development plan 69

Part VII: Annexes 70

Annex 1 EudraVigilance Interface 71

Annex 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme 71

Annex 3 Protocols for proposed, on-going and completed studies in the pharmacovigilance plan 74

Annex 4 Specific adverse drug reaction follow-up forms 79

Annex 5 Protocols for proposed and on-going studies in RMP part IV 104

Annex 6 Details of proposed additional risk minimisation activities (if applicable) 104

Annex 7 Other supporting data (including referenced material) 105

Annex 8 Summary of changes to the risk management plan over time 108

Abbreviations & Acronyms

ADR	Adverse Drug Reaction
AE	Adverse Event
AMP	Auxiliary Medicinal Product
ATC Code	Anatomical Therapeutic Chemical Classification System Code
AUC	Area Under the Curve
BBB	Blood-Brain Barrier
CA	Contrast Agent
CD	Concomitant Disease
CKD	Chronic Kidney Disease
C_{max}	Maximum Concentration
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
DCN	Deep Cerebellar Nuclei
DN	Dentate Nucleus
ECG	Electrocardiogram
EEA	European Economic Area
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EU	European Union
FIRES	Febrile Infection-Related Epilepsy Syndrome
GBCA	Gadolinium-Based Contrast Agent
Gd	Gadolinium
GD	Gestation Day
GP	Globus Pallidus
GVP	Good Pharmacovigilance Practices
IH	Immediate Hypersensitivity
IMP	Investigational Medicinal Product
INN	International Non-proprietary Name
IA	Intraarterial

IV	Intravenous
LOQ	Limit Of Quantification
MAH	Marketing Authorisation Holder
MH	Medical History
MNPCE	Micronucleated Polychromatic Erythrocyte
MR	Magnetic Resonance
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
NA	Not Applicable
NSF	Nephrogenic Systemic Fibrosis
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
PK	Pharmacokinetics
PL	Package Leaflet
PSUR	Periodic Safety Update Report
PTZ	Pentylenetetrazol
QPPV	Qualified Person Responsible for Pharmacovigilance
RMP	Risk Management Plan
SEC	Size-Exclusion Chromatography
SFN	Small Fiber Neuropathy
SI	Signal Intensity
SmPC	Summary of Product Characteristics

Part I: Product(s) Overview

Table 1– Product Overview

Active substance(s) **(INN or common name)**	Gadopiclenol
Pharmacotherapeutic group(s) **(ATC Code)**	Paramagnetic contrast media (V08CA) Gadopiclenol (V08CA012)
Marketing Authorisation Applicant	Guerbet Bracco
Number of medicinal products to which this RMP refers	2
Invented name(s) in the European Economic Area (EEA)	**ELUCIREM 0.5 MMOL/ML (gadopiclenol)** **VUEWAY 0.5 MMOL/ML (gadopiclenol)**
Marketing authorisation procedure	Centralised
Brief description of the product	*Chemical class*: Gadopiclenol is a gadolinium chelate of 2,2′,2″-(3,6,9-triaza-1(2,6)-pyridinacyclodecaphane-3,6,9-triyl) tris(5-((2,3-dihydroxypropyl)amino)-5-oxopentanoic acid) (registry number 933983-75-6). Its molecular weight is 970.11 g/mol, when calculated without the 2 water molecules that coordinate in solution. This is a non-ionic macrocyclic Gadolinium (Gd) based-Contrast Agent (GBCA).
	Summary of mode of action: Gadopiclenol is a paramagnetic contrast agent for Magnetic Resonance Imaging (MRI) to be used by intravenous (IV) route. The contrast enhancing effect is mediated by the Gd atom contained in the pyclen-based macrocyclic structure. The contrast agent relaxes the hydrogen atoms of the water molecules that it encounters, and this relaxation enhancement generates image contrast on T_1- or T_2-weighted images. The extent to which a contrast agent can affect the relaxation rate of tissue water is termed relaxivity (r_1 or r_2). Gadopiclenol presents a high relaxivity in water due to the chemical structure of its macrocylic ligand. The pyclen-based macrocyclic structure is highly stable in terms of Gd dissociation and exhibits high relaxivity due to improved water access to the Gd ion. Indeed, two water molecules complete the nine

	coordination links of Gd^{3+}, in addition to the 7 links established with other atoms of the macrocyclic ligand: the four nitrogens and the three oxygens of the carboxylate functions.
	Important information about its composition: None
Hyperlink to the Product Information	Not applicable
Indication(s) in the EEA	*Current*: This medicinal product is for diagnostic use only. Gadopiclenol is indicated 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.
	Proposed:
Dosage in the EEA	*Current*: The recommended dose of gadopiclenol is 0.05 mmol/kg body weight equivalent to 0.1 ml/kg body weight for all indications.
	Proposed:
Pharmaceutical form(s) and strength(s)	*Current*: Solution for injection to be administered IV as a bolus injection, available in vials or pre-filled syringes. Each mL of solution for injection contains 485.1 mg of gadopiclenol (equivalent to 0.5 mmol of gadopiclenol).

	Proposed:
Is the product/will the product be subject to additional monitoring in the EU?	Yes [1] Reason: new active substance

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Gadopiclenol is a non-ionic macrocyclic GBCA used for enhancing the contrast of body organs and tissues on magnetic resonance (MR) images. It is intended to be used in adults and children aged 2 years and older for contrast enhanced MRI to improve detection, visualization and characterization of lesions in the central nervous system (brain, spine and surrounding tissues), and in the body (head and neck, thorax including breast, abdomen including liver and kidneys, pelvis including prostate, and musculo-skeletal system).

Other marketed non-ionic macrocyclic GBCAs are gadobutrol, which has been authorised since 2011, and gadoteridol, already authorised since 1992. Gadoteric acid is an ionic macrocyclic GBCA, authorised since 1989. Further authorised GBCAs are the linear ionic agents gadoxetic acid and gadobenic acid indicated for MRI of the liver, and the linear ionic agent gadopentetic acid for intra-articular use (G3).

Table 2 and Table 3 give an overview of the exposure to GBCAs authorised to date, by indication, gender and age in the 5 most populated European countries for the first half of 2020. It is to be noted that the overall sex distribution is almost 1:1 with a ratio of 51.4 % men to 48.6 % women. Furthermore, the most frequent indications are MRI of the central nervous system, head and neck (33.4 %), followed by MRI of the heart including magnetic resonance angiography (MRA) (24.9 %) and of the abdomen including liver and kidney (14.6 %). The main age groups are 50-64 years (33.6 %), followed by 30-49 years (24.0 %) and 64-74 years (21.5 %). Obvious sex-specific differences are the examination of the chest, breast and mediastinum, where 5.5 times more women are affected, MRI of the limbs and joints (1.6 times more men), and MRI of the heart including MRA (1.38 times more men).

Table 2 - Exposure by indication and gender in Top 5 European countries during the first semester of 2020 in the context of contrast-enhanced MRI (Source DRG - Clarivate - EU5 Imaging Market Guide - AMR database H1–2020 - (France + Germany + Italy + Spain + UK))

Indications (examples)	**Males**	**Females**	**All**
Overall	**1.983.857**	**1.875.075**	**3.858.932**
Central Nervous System, Head and Neck	673.880	614.222	**1.288.102**
Chest, Breast and Mediastinum	46.406	252.998	**299.404**

[1] according to the latest EMA list of medicines under additional monitoring, dated 25.04.2013 (updated on 22.07.2022)

Heart and MRA	556.715	438.334	**995.049**
Abdomen including Liver and Kidney	266.238	262.182	**528.421**
Pelvis including Prostate	161.121	129.779	**290.900**
Limbs and Joints	279.496	177.560	**457.056**

Table 3 - Exposure by indication and age group in Top 5 European countries during the first semester of 2020 in the context of contrast-enhanced MRI (Source DRG - Clarivate - EU5 Imaging Market Guide - AMR database H1–2020 - (France + Germany + Italy + Spain + UK))

Indications (examples)	**Classes of age (years)**							
	0-12 years	***13-17 years***	***18-29 years***	***30-49 years***	***50-64 years***	***65-74 years***	***75+ years***	***All ages***
Overall	**20.594**	**47.767**	**267.212**	**929.257**	**1.301.816**	**832.436**	**459.871**	**3.858.932**
Central Nervous System, Head and Neck	10.950	21.977	104.265	368.941	416.318	249.227	116.425	1.288.102
Chest, Breast and Mediastinum	7.989	8.180	9.256	91.729	109.920	59.303	16.626	303.004
Heart and MRA	0	1.590	36.358	155.516	331.323	273.420	162.488	960.696
Abdomen including Liver and Kidney	1.654	9.654	47.514	145.597	190.843	114.521	52.991	562.774
Pelvis including Prostate	0	1.297	13.666	37.069	83.105	76.757	79.006	290.900
Limbs and Joints	0	5.069	56.159	130.405	170.306	59.208	32.314	453.456

Part II: Module SII - Non-clinical part of the safety specification

Table 4 - Key Safety findings from non-clinical studies (2.4 Non-clinical overview)

Key Safety findings (from non-clinical studies)	Relevance to human usage
Safety pharmacology	
Renal function The effects of gadopiclenol on renal function (urine output, serum/urine electrolyte balance, serum and urinary biochemistry and glomerular filtration rate) were evaluated in rats after an oral saline overload given 15 minutes post-dosing. Regardless of the dose level, gadopiclenol did not induce any change in the serum sodium, potassium, chloride or creatinine levels nor in the serum osmolality. Gadopiclenol at doses of 1.25 and 2.5 mmol/kg induced some decrease in urine volume up to 6 hours post-dosing (-23% to 33% compared to controls), without any dose relationship and without any change in urine concentrations of sodium, potassium, chloride and creatinine. At 5 mmol/kg, gadopiclenol induced a decrease in sodium (-19%) and chloride (-18%) urinary concentrations. Regardless of the dose level, an increase in urine osmolality was observed (+23% to +35%, compared to controls). The modifications in the aforementioned serum and urine concentrations resulted in no change in the glomerular filtration rate and in no relevant changes in the excretion fractions of sodium, potassium and chloride up to 5 mmol/kg. The free water clearance was decreased in a dose related manner (-26% to -73%, compared to controls), statistically significant at 2.5 and 5 mmol/kg. No change in urinary pH was observed, irrespective of the dose level.	*Safety margin* Under the experimental conditions used to assess the effects of gadopiclenol on renal function and based on the effects on urine osmolality and the free water clearance, a NOAEL can be established at 1.25 mmol/kg, given intravenously as a 2-minute infusion (i.e. 4 times the intended human dose). *Clinical data* Gadopiclenol is excreted almost exclusively by the kidney which can therefore be a target organ for toxicity. Routine monitoring of kidney function was performed during the clinical trials with renal function parameters measured at least 24 hours after exposure, including blood creatinine, eGFR, Blood Urea Nitrogen (BUN), and cystatin C (if the measurement was performed at 24 hours) for early detection of potential acute kidney injury. Further details on adverse reactions related to renal disorders are described in section SVII.1.1.
Proconvulsant effect No effect on the main central and peripheral nervous system functions was attributable to gadopiclenol but a minor proconvulsant effect (decrease in the time of onset of Pentylenetetrazol (PTZ)-induced seizures) was	*Safety margin*: Based on in vivo studies, the NOAEL of gadopiclenol on the time of occurrence of PTZ-induced seizures is 2.5 mmol/kg (i.e. 8 times the intended human dose).

Key Safety findings (from non-clinical studies)	**Relevance to human usage**
observed in PTZ-treated rats only at the highest dose tested (5 mmol/kg).	*Clinical data:* During the clinical development, 2 patients experienced seizures after administration of gadopiclenol. Nevertheless, none were assessed as related to gadopiclenol. Both patients had pre-existing Central Nervous System (CNS) lesions with history of seizures. In addition, 2 children experienced epilepsy, both non-related to gadopiclenol, 1 occurring in a patient with worsening of neurodegenerative disease and the second with concomitant disease of Febrile Infection-Related Epilepsy Syndrome (FIRES) (2.5 Clinical overview). Proconlvulsant effect is a known class effect observed with GBCAs.
Toxicity	
Single-dose toxicity Regarding single-dose toxicity, gadopiclenol, when given as a single IV injection in mice, rats or dogs, was well tolerated up to high dose levels, providing a sufficient safety margin. No or only minor and reversible effects were observed. Transient swelling of face and/or limbs in rodents or optic nerve in dogs (reversible in a few hours) was only observed at the highest injected doses. Minimal to mild tubular cell vacuolation was observed in the kidneys, with a dose-related incidence and severity. This is a classical finding with both GBCA and iodinated contrast agents and is known to have no functional consequence.	Single-dose toxicity studies are considered as the most relevant studies for human risk assessment of gadopiclenol as it will be given as a single dose in Humans. Safety margins* are between 19 to 25 and confirms the very high tolerance profile of gadopiclenol after single administration.
Repeat-dose toxicity In repeat-dose toxicity studies performed in rats (dosing up to 10 mmol/kg/day) and dogs (dosing up to 4 mmol/kg/day), gadopiclenol was well tolerated in both species even at high dose levels up to 28 days. The NOAEL in the repeat-dose toxicity study was considered 2.5 mmol/kg and 2 mmol/kg in rats and dogs, respectively.	Safety margins* of repeated-dose toxicity studies are between 9 to 15 -fold the intended human dose. Nevertheless the experimental conditions of the repeated-dose studies represent very drastic conditions in terms of exposure (dose levels and duration) compared to the conditions use.

Key Safety findings (from non-clinical studies)	**Relevance to human usage**
Compared to single-dose toxicity, histological changes were exacerbated, particularly in rats, but without associated clinical pathological changes. Some additional treatment related adverse effects were seen (in rats only), on body weight, food consumption, clinical signs (including swelling of the face and/or limbs), clinical pathology parameters and histology. However, these changes were always partially or totally reversible. No additional changes due to repeat-dosing were seen in dogs.	So the relevance of these studies for Humans is limited as gadopiclenol is administered as a single dose in clinical practice.
Juvenile Toxicity The safety toxicological profile and tissue Gd presence of gadopiclenol was similar in juvenile and adult rats. Its tolerance was excellent whatever the age. Similar microscopic findings (reversible tubular kidney vacuolations) to adult rats were observed. No new toxicity (except a reversible non-adverse effect on iron balance after repeated administrations) or target organ was evidenced in juvenile animals. The NOAEL in juvenile rats was considered 2.5 mmol/kg/day, i.e. the maximum tested dose.	*Safety margin* The juvenile toxicity study performed in rats did not highlight any specific concerns for pediatric patients compared to adults.
Local intolerance Study in rabbits: The local tolerance of gadopiclenol appears acceptable following a single administration in rats (IV route), dogs (IV route) and rabbits (IV, IA routes) or following repeated IV injections in rats and dogs. However, signs of intolerance/irritations were observed following a single perivenous and repeated IV administrations in rabbits. Therefore, caution is required during the administration to clinical study subjects to avoid any extravasation.	*Clinical data* Injection site reactions of various types happened in some subjects after IV injection of gadopiclenol, including pain, oedema, coldness, warmth, haematoma and erythema. In studies testing different doses, these AEs were more frequent at higher doses (2.7.4 Summary of clinical safety). No confirmed case of extravasation of gadopiclenol was reported during the clinical development and no serious reaction at injection site was reported (2.7.4 Summary of clinical safety).
Nephrogenic Systemic Fibrosis (NSF) Several supportive (non-GLP) non-clinical studies (most studies done in renally-impared adult rats) have been conducted with the aim to contribute to a better	*Clinical data* No NSF-like events related to the administration of gadopiclenol have been observed in clinical studies, including in at-

Key Safety findings (from non-clinical studies)	**Relevance to human usage**
understanding of the potential risk of NSF after gadopiclenol administration. Gadopiclenol showed a low potential for NSF induction with no histopatological skin lesions and no signs of *in vivo* dissociation., confirming the high stability of this new GBCA, similarly to that of other macrocyclic agents. On the contrary the non-ionic and linear GBCA, gadodiamide (Omniscan®), was generally poorly tolerated.	risk patients with mild to severe renal function impairment (2.7.4 Summary of clinical safety). Although the underlying pathophysiologic mechanisms of NSF are not fully understood, a large body of evidence suggests that such a condition results in Humans from a chemical transformation of the GBCA molecules leading to Gd release and accumulation in the body. The linear GBCAs of the high-risk group are more prone to release Gd than the macrocyclic GBCAs of the low risk group, and more likely to induce NSF. Gadopiclenol is a Gd-complex based on a pyclen macrocyclic structure, offering a good chemical stability, suggesting a low risk for inducing NSF and a high r1 relaxivity that enables to use half of the standard dose to get the same MR efficacy. However, since NSF is a risk associated to all GBCAs, it is considered as an important identified risk for gadopiclenol (see section SVII.3.1)
Gadolinium Deposition, Speciation and Safety in Brain and Other Organs Repeated administrations of gadopiclenol to healthy rats (non-GLP studies) are not assiociated with T1 signal hyperintensity in the DCN. Long-term Gd exposure is lower after gadopiclenol and Gadavist/Gadovist® (another macrocyclic GBCA) as compared to the linear agent Omniscan®. Gadolinium exposure after gadopiclenol is similar to that achieved with Gadavist/Gadovist® in brain when admistered as the same dose. However, a massive Gd washout (-74 to -98%) was observed over a 1-year recovery period (except in femur) and was similar to Gadavist/Gadovist®. In termes of speciation and Gd spatial distribution in brain and kidneys, gadopiclenol behaves like Gadavist/Gadovist®, as expected for a macrocyclic contrast agent. Gadolinium presence in tissues had not an impact on renal function and was not associated with abnormalities in tissues.	*Clinical data* T1 hypersignals observed with other GBCAs, mostly after multiple administrations of linear GBCAs, on unhanced-MR images of rat DCN have also been observed in patients with normal renal function . They have been associated with Gd deposition in the Dentate Nucleus (DN) . In addition, Gd deposits have been found in other organs and tissues (liver, bone, skin, etc) with all types of GBCAs, the clinical significance of which is not yet known. Adverse clinical effects of accumulation and retention of gadolinium in brain and other organs and tissues are considered as important potential risks and the clinical significance as missing information. (see section SVII.1.2). The clinical study GDX-44-005 confirmed that gadopiclenol is eliminated predominantly by

Key Safety findings (from non-clinical studies)	Relevance to human usage
	renal clearance. No gadopiclenol was detected in any of the plasma and urine follow-up samples available at 1, 3 and 6 months, indicating that all amounts of gadopiclenol were eliminated after single IV injection, in healthy volunteers and in patients with renal impairment of any stage (GDX-44-005 study report).

** safety margins are calculated based on the ratios between the NOAELs in animals and the intended human dose of 0.05 mmol/kg, using either the ratios of gender averaged means of Area Under the Curve (AUC) (from toxicokinetics in toxicology studies)*

Part II: Module SIII - Clinical trial exposure

This RMP presents the pooled data from the eight clinical studies completed with gadopiclenol as listed in

Table 5. In these studies, a total of 1097 subjects were included and exposed to at least one Investigational Medicinal Product (IMP) or Auxiliary Medicinal Product (AMP), including 1047 subjects who were exposed to at least one dose of gadopiclenol (95.4%), 535 to the comparator gadobutrol, 256 to the comparator gadobenate dimeglumine (54.9%), 66 exposed to the placebo (sodium chloride) and 48 to moxifloxacin (positive control used in the cardiac safety study).

Table 5 gives an overview of the distribution of subjects by clinical trial, study products and indications. The objectives of all the studies are described in Annex 2.

Table 5: Distribution of Subjects by Study and IMP/AMP – All Subjects Exposed to IMP/AMP (N= 1097).

	Gadopiclenol All doses (N=1047)	Gadobenate dimeglumine (N=256)	Gadobutrol (N=535)	Placebo (N=66)	Moxifloxacin (N=48)	Total (N=1097)
All subjects	1047 (100%)	256 (100%)	535 (100%)	66 (100%)	48 (100%)	1097 (100%)
Safety and PK	124 (11.8%)			66 (100%)	48 (100%)	142 (12.9%)
GDX-44-003 - part 1	36 (29.0%)			18 (27.3%)		54 (38.0%)
GDX-44-005	40 (32.3%)					40 (28.2%)
GDX-44-006	48 (38.7%)			48 (72.7%)	48 (100%)	48 (33.8%)
CNS studies	515 (49.2%)	256 (100%)	245 (45.8%)			534 (48.7%)
GDX-44-003 - part 2	12 (2.3%)					12 (2.2%)
GDX-44-004	256 (49.7%)	256 (100%)				272 (50.9%)
GDX-44-010	247 (48.0%)		245 (100%)			250 (46.8%)
Body studies	328 (31.3%)		290 (54.2%)			341 (31.1%)
GDX-44-008	40 (12.2%)					40 (11.7%)
GDX-44-011	288 (87.8%)		290 (100%)			301 (88.3%)
Pediatric studies	80 (7.6%)					80 (7.3%)
GDX-44-007	80 (100%)					80 (100%)

	Gadopiclenol All doses (N=1047)	Gadobenate dimeglumine (N=256)	Gadobutrol (N=535)	Placebo (N=66)	Moxifloxacin (N=48)	Total (N=1097)

Because of cross-over studies, the sum of numbers of patients in each column is different from the overall number of patients reported in the Total column.
Source: 5.3.5.3 Reports Of Analyses Of Data From More Than One Study

The tested doses of gadopiclenol ranged from 0.025 mmol/kg to 0.3 mmol/kg in the safety and pharmacokinetic studies, and from 0.025 mmol/kg to 0.2 mmol/kg in the CNS studies. For the body study, only 0.5 mmol/kg and 0.1 mmol/kg were tested (see Table 6). Most of the subjects were exposed to only one dose of gadopiclenol, except for the subjects of the GDX-44-006 study who received two doses of gadopiclenol: 0.1 and 0.3 mmol/kg. Overall, in these pooled studies, the majority of the subjects received the recommended dose of 0.05 mmol/kg (67.6%).

Table 6: Distribution of Subjects by Study and Dose of Gadopiclenol (mmol/kg) – All Subjects Exposed to Gadopiclenol (N= 1047).

	Gadopiclenol 0.025 (N=62)	Gadopiclenol 0.05 (N=708)	Gadopiclenol 0.075 (N=9)	Gadopiclenol 0.1 (N=197)	Gadopiclenol 0.2 (N=65)	Gadopiclenol 0.3 (N=54)	Gadopiclenol All doses (N=1047)
All subjects	62 (100%)	708 (100%)	9 (100%)	197 (100%)	65 (100%)	54 (100%)	1047 (100%)
Safety and PK	6 (9.7%)	6 (0.8%)	6 (66.7%)	94 (47.7%)	6 (9.2%)	54 (100%)	124 (11.8%)
GDX-44-003 - part 1	6 (100%)	6 (100%)	6 (100%)	6 (6.4%)	6 (100%)	6 (11.1%)	36 (29.0%)
GDX-44-005				40 (42.6%)			40 (32.3%)
GDX-44-006				48 (51.1%)		48 (88.9%)	48 (38.7%)
CNS studies	56 (90.3%)	324 (45.8%)	3 (33.3%)	73 (37.1%)	59 (90.8%)		515 (49.2%)
GDX-44-003 - part 2		3 (0.9%)	3 (100%)	3 (4.1%)	3 (5.1%)		12 (2.3%)
GDX-44-004	56 (100%)	74 (22.8%)		70 (95.9%)	56 (94.9%)		256 (49.7%)
GDX-44-010		247 (76.2%)					247 (48.0%)
Body studies		298 (42.1%)		30 (15.2%)			328 (31.3%)
GDX-44-008		10 (3.4%)		30 (100%)			40 (12.2%)
GDX-44-011		288 (96.6%)					288 (87.8%)
Pediatric studies		80 (11.3%)					80 (7.6%)
GDX-44-007		80 (100%)					80 (100%)

Because of cross-over studies, the sum of numbers of patients in each column is different from the overall number of patients reported in the "All doses" column.
Source: 5.3.5.3 Reports Of Analyses Of Data From More Than One Study

Table 7 shows that 10 % of the subjects included in the development program and exposed to at least one IMP/AMP during the clinical trials were healthy volunteers while the rest were patients (n=987). Eighty children who were between 2 and 17 years of age were included in a study dedicated to assess the efficacy and safety of gadopiclenol in pediatric patients, and represent 8.1% of the total number of subjects exposed to at least one IMP/AMP during the clinical trials.

Table 7: Distribution of Subjects by Population, Age class and Indication for each IMP/AMP – All Subjects Exposed to IMP/AMP (N= 1097).

	Gadopiclenol All doses (N=1047)	Gadobenate dimeglumine (N=256)	Gadobutrol (N=535)	Placebo (N=66)	Moxifloxacin (N=48)	Total (N=1097)
All subjects	1047 (100%)	256 (100%)	535 (100%)	66 (100%)	48 (100%)	1097 (100%)
Healthy volunteers	92 (8.8%)			66 (100%)	48 (100%)	110 (10.0%)
Patients	955 (91.2%)	256 (100%)	535 (100%)			987 (90.0%)
Adults	875 (91.6%)	256 (100%)	535 (100%)			907 (91.9%)
CNS	515 (58.9%)	256 (100%)	245 (45.8%)			534 (58.9%)
Body	328 (37.5%)		290 (54.2%)			341 (37.6%)
Safety and PK	32 (3.7%)					32 (3.5%)
Pediatric	80 (8.4%)					80 (8.1%)
CNS	60 (75.0%)					60 (75.0%)
Body	20 (25.0%)					20 (25.0%)

Because of cross-over studies, the sum of numbers of patients in each column is different from the overall number of patients reported in the Total column.
CNS (Central Nervous System) studies are GDX-44-003 part2, GDX-44-004, GDX-44-007 and GDX-44-010.
Body study are GDX-44-008, GDX-44-007 and GDX-44-011.
Safety and PK studies are GDX-44-003 part1,GDX-44-005 and GDX-44-006.
*%: (n row / N Patients) for Adults; %: (n row / N Adults)*100 for Body, CNS and Safety PK; %: (n row / N column) *100 for all others.*
Source: 5.3.5.3 Reports Of Analyses Of Data From More Than One Study

Among the global study population, slightly more women than male were included and received at least one dose of gadopiclenol (54.0%) (see Table 8).
The mean age of subjects was lower in those exposed to the placebo (37.4 years) and moxifloxacin (40.5 years), compared to the mean age of subjects exposed to contrast agents, i.e. gadopiclenol (50.8 years), gadobenate dimeglumine (54.0 years), and gadobutrol (57.1 years), which were mainly administered to patients with CNS or body lesions (see Table 8). Most of the subjects (66.6%) who received gadopiclenol were adults between 18 and 64 years of age, whereas 19.9% were elderlies between 65 and 74 years of age, and 5.9% were more than 75 years of age.

For most of the subjects who received the dose of 0.05 mmol/kg of gadopiclenol, the mean age was about 51.2 years (see Table 8).

Table 8 also shows the distribution of subjects by race and IMP/AMP administered: the majority of the included subjects (82.9%) were white subjects; 9.4% were Asian, 4.7% American Indian or Alaska native, 2.7% Black or African American, 0.3% Native Hawaiian or Other Pacific Islander, and 0.3% from another race (see Table 8).

Table 8: Demographic Characteristics by IMP/AMP – All Subjects Exposed to IMP/AMP (N= 1097).

	Gadopiclenol All doses (N=1047)	Gadobenate dimeglumine (N=256)	Gadobutrol (N=535)	Placebo (N=66)	Moxifloxacin (N=48)	Total (N=1097)
Sex						
n	1047	256	535	66	48	1097
Female	565 (54.0%)	151 (59.0%)	304 (56.8%)	32 (48.5%)	24 (50.0%)	597 (54.4%)
Male	482 (46.0%)	105 (41.0%)	231 (43.2%)	34 (51.5%)	24 (50.0%)	500 (45.6%)
Age (years)						
n	1047	256	535	66	48	1097
Mean (SD)	50.8 (18.4)	54.0 (13.4)	57.1 (13.2)	37.4 (11.9)	40.5 (11.6)	50.6 (18.4)
Median	55.0	55.0	58.0	35.5	39.0	54.0
Min. ; Max.	2 ; 88	19 ; 88	18 ; 86	19 ; 59	19 ; 59	2 ; 88
Age in classes						
n	1047	256	535	66	48	1097
>=2 and <7 years	26 (2.5%)	0	0	0	0	26 (2.4%)
>=7 and <12 years	23 (2.2%)	0	0	0	0	23 (2.1%)
>=12 and <18 years	31 (3.0%)	0	0	0	0	31 (2.8%)
>=18 and <65 years	697 (66.6%)	198 (77.3%)	352 (65.8%)	66 (100%)	48 (100%)	741 (67.5%)
>=65 and <75 years	208 (19.9%)	45 (17.6%)	136 (25.4%)	0	0	212 (19.3%)

	Gadopiclenol All doses (N=1047)	Gadobenate dimeglumine (N=256)	Gadobutrol (N=535)	Placebo (N=66)	Moxifloxacin (N=48)	Total (N=1097)
>=75 years	62 (5.9%)	13 (5.1%)	47 (8.8%)	0	0	64 (5.8%)

Because of cross-over studies, sum of numbers of patients in each column is different from the overall number of patients reported in the Total column
Source: 5.3.5.3 Reports Of Analyses Of Data From More Than One Study

	Gadopiclenol All doses (N=1047)	Gadobenate dimeglumine (N=256)	Gadobutrol (N=535)	Placebo (N=66)	Moxifloxacin (N=48)	Total (N=1097)
Race (multiple choices)						
n	999	256	535	48	48	1031
White	828 (82.9%)	218 (85.2%)	410 (76.6%)	47 (97.9%)	47 (97.9%)	855 (82.9%)
Asian	95 (9.5%)	28 (10.9%)	66 (12.3%)	1 (2.1%)	1 (2.1%)	97 (9.4%)
Black or African American	25 (2.5%)	9 (3.5%)	10 (1.9%)	0	0	28 (2.7%)
Native Hawaiian Or Other Pacific Islander	3 (0.3%)	1 (0.4%)	2 (0.4%)	0	0	3 (0.3%)
American Indian or Alaska native	48 (4.8%)	1 (0.4%)	46 (8.6%)	0	0	48 (4.7%)
Other	3 (0.3%)	0	3 (0.6%)	0	0	3 (0.3%)
Not collected	48	0	0	18	0	66
Height (cm)						
n	1047	256	535	66	48	1097
Mean (SD)	164.93 (14.49)	165.13 (10.69)	166.80 (9.62)	173.45 (8.72)	173.54 (8.53)	165.04 (14.32)
Median	165.00	164.00	166.00	172.00	172.00	165.00
Min. ; Max.	88.0 ; 197.0	138.0 ; 193.0	143.0 ; 197.0	154.0 ; 191.0	154.0 ; 190.0	88.0 ; 197.0
Weight (kg)						
n	1046	256	534	66	48	1096
Mean (SD)	73.49 (20.21)	75.80 (17.90)	76.54 (18.73)	73.85 (10.32)	75.04 (10.28)	73.56 (20.09)
Median	73.00	74.00	74.00	72.70	73.50	73.00
Min. ; Max.	10.4 ; 194.0	44.0 ; 194.0	36.0 ; 162.0	56.0 ; 97.0	56.0 ; 97.0	10.4 ; 194.0
Missing data	1	0	1	0	0	1

	Gadopiclenol All doses (N=1047)	Gadobenate dimeglumine (N=256)	Gadobutrol (N=535)	Placebo (N=66)	Moxifloxacin (N=48)	Total (N=1097)

Because of cross-over studies, the sum of numbers of patients in each column is different from the overall number of patients reported in the Total column.
Source: 5.3.5.3 Reports Of Analyses Of Data From More Than One Study

Table 9: Demographic Characteristics by Dose of Gadopiclenol – All Subjects Exposed to Gadopiclenol (N= 1047).

	Gadopiclenol 0.025 (N=62)	Gadopiclenol 0.05 (N=708)	Gadopiclenol 0.075 (N=9)	Gadopiclenol 0.1 (N=197)	Gadopiclenol 0.2 (N=65)	Gadopiclenol 0.3 (N=54)	Gadopiclenol All doses (N=1047)
Sex							
n	62	708	9	197	65	54	1047
Female	36 (58.1%)	393 (55.5%)	5 (55.6%)	87 (44.2%)	41 (63.1%)	27 (50.0%)	565 (54.0%)
Male	26 (41.9%)	315 (44.5%)	4 (44.4%)	110 (55.8%)	24 (36.9%)	27 (50.0%)	482 (46.0%)
Age (years)							
n	62	708	9	197	65	54	1047
Mean (SD)	52.0 (13.6)	51.2 (19.9)	35.3 (13.4)	50.8 (15.1)	49.9 (15.0)	39.7 (11.5)	50.8 (18.4)
Median	55.0	55.0	28.0	54.0	53.0	38.5	55.0
Min. ; Max.	22 ; 74	2 ; 88	23 ; 57	18 ; 81	18 ; 79	19 ; 59	2 ; 88
Age in classes							
n	62	708	9	197	65	54	1047
>=2 and <7 years	0	26 (3.7%)	0	0	0	0	26 (2.5%)
>=7 and <12 years	0	23 (3.2%)	0	0	0	0	23 (2.2%)
>=12 and <18 years	0	31 (4.4%)	0	0	0	0	31 (3.0%)
>=18 and <65 years	48 (77.4%)	424 (59.9%)	9 (100%)	154 (78.2%)	56 (86.2%)	54 (100%)	697 (66.6%)
>=65 and <75 years	14 (22.6%)	149 (21.0%)	0	38 (19.3%)	7 (10.8%)	0	208 (19.9%)
>=75 years	0	55 (7.8%)	0	5 (2.5%)	2 (3.1%)	0	62 (5.9%)

Because of cross-over studies, the sum of numbers of patients in each column is different from the overall number of patients reported in the "All doses" column.
Source: 5.3.5.3 Reports Of Analyses Of Data From More Than One Study

Table 10 shows the distribution of the subjects who received at least one IMP/AMP and who had specific risk factors, either renal impairment, hepatic insufficiency, cardiac diseases, history of convulsions or history of hypersensitivity. Near 7% of the subjects had moderate or severe renal impairment and at least 11.6% had a history of hypersensitivity, 8.6% a history of seizures, 6% a hepatic insufficiency and 9.6% cardiac diseases (see Table 10). Patients with risk factors were evenly distributed in each dose group (see Table 10).

Table 10: Risk Factors by IMP/AMP – All Subjects Exposed to IMP/AMP (N= 1097).

	Gadopiclenol All doses (N=1047)	Gadobenate dimeglumine (N=256)	Gadobutrol (N=535)	Placebo (N=66)	Moxifloxacin (N=48)	Total (N=1097)
Renal Insufficiency						
n	1047	256	535	66	48	1097
Patients with no or mild renal impairment	974 (93.0%)	251 (98.0%)	492 (92.0%)	66 (100%)	48 (100%)	1021 (93.1%)
Patients with moderate renal impairment	57 (5.4%)	5 (2.0%)	43 (8.0%)	0	0	60 (5.5%)
Patients with severe renal impairment	16 (1.5%)	0	0	0	0	16 (1.5%)
Hepatic Insufficiency						
n	1047	256	535	66	48	1097
Patients without hepatic diseases	980 (93.6%)	252 (98.4%)	507 (94.8%)	66 (100%)	48 (100%)	1030 (93.9%)
Patients with hepatic diseases	67 (6.4%)	4 (1.6%)	28 (5.2%)	0	0	67 (6.1%)
Cardiac Diseases						
n	1047	256	535	66	48	1097
Patients without coronary heart disease of any type and rhythm disorders	947 (90.4%)	232 (90.6%)	477 (89.2%)	66 (100%)	48 (100%)	997 (90.9%)
Patients with coronary heart disease of any type and rhythm disorders	100 (9.6%)	24 (9.4%)	58 (10.8%)	0	0	100 (9.1%)
Hypersensitivity						
n	1047	256	535	66	48	1097
Patients without allergic diseases	927 (88.5%)	232 (90.6%)	451 (84.3%)	62 (93.9%)	46 (95.8%)	970 (88.4%)
Patients with allergic diseases	120 (11.5%)	24 (9.4%)	84 (15.7%)	4 (6.1%)	2 (4.2%)	127 (11.6%)
Medical history of convulsions						
n	1047	256	535	66	48	1097

	Gadopiclenol All doses (N=1047)	Gadobenate dimeglumine (N=256)	Gadobutrol (N=535)	Placebo (N=66)	Moxifloxacin (N=48)	Total (N=1097)
Patients without history of convulsions	955 (91.2%)	220 (85.9%)	501 (93.6%)	66 (100%)	48 (100%)	1003 (91.4%)
Patients with history of convulsions	92 (8.8%)	36 (14.1%)	34 (6.4%)	0	0	94 (8.6%)

Because of cross-over studies, the sum of numbers of patients in each column is different from the overall number of patients reported in the Total column.
Renal Insufficiency: Patients with no or mild renal impairment (eGFR >= 60 ml/min/1.73m2); Patients with moderate renal impairment (30 <= eGFR <60 ml/min/1.73m2); Patients with severe renal impairment (eGFR < 30 ml/min/1.73m2 + dialyzed patients).
For eGFR central values where used ; if missing, local data were considered.
Hepatic Insufficiency: Only liver insufficiency in Concomitant Disease (CD) (definition based on MedDRA v23.1 preferred term).
Cardiac Diseases: Coronary heart disease of any type and rhythm disorders in CD and Medical History (MH) (definition based on MedDRA v23.1 preferred term).
Hypersensitivity: Allergic disease in CD and MH (definition based on MedDRA v23.1 preferred term).
Medical history of convulsions: Medical history of convulsions in CD and MH (definition based on MedDRA v23.1 preferred term).
Source: 5.3.5.3 Reports Of Analyses Of Data From More Than One Study

Table 11: Risk Factors by Dose of Gadopiclenol – All Subjects Exposed to Gadopiclenol (N= 1047).

	Gadopiclenol 0.025 (N=62)	Gadopiclenol 0.05 (N=708)	Gadopiclenol 0.075 (N=9)	Gadopiclenol 0.1 (N=197)	Gadopiclenol 0.2 (N=65)	Gadopiclenol 0.3 (N=54)	Gadopiclenol All doses (N=1047)
Renal Insufficiency							
n	62	708	9	197	65	54	1047
Patients with no or mild renal impairment	61 (98.4%)	662 (93.5%)	9 (100%)	172 (87.3%)	64 (98.5%)	54 (100%)	974 (93.0%)
Patients with moderate renal impairment	1 (1.6%)	46 (6.5%)	0	9 (4.6%)	1 (1.5%)	0	57 (5.4%)
Patients with severe renal impairment	0	0	0	16 (8.1%)	0	0	16 (1.5%)
Hepatic Insufficiency							
n	62	708	9	197	65	54	1047
Patients without hepatic diseases	62 (100%)	668 (94.4%)	9 (100%)	173 (87.8%)	62 (95.4%)	54 (100%)	980 (93.6%)
Patients with hepatic diseases	0	40 (5.6%)	0	24 (12.2%)	3 (4.6%)	0	67 (6.4%)
Cardiac Diseases							
n	62	708	9	197	65	54	1047

	Gadopiclenol 0.025 (N=62)	Gadopiclenol 0.05 (N=708)	Gadopiclenol 0.075 (N=9)	Gadopiclenol 0.1 (N=197)	Gadopiclenol 0.2 (N=65)	Gadopiclenol 0.3 (N=54)	Gadopiclenol All doses (N=1047)
Patients without coronary heart disease of any type and rhythm disorders	58 (93.5%)	636 (89.8%)	9 (100%)	181 (91.9%)	57 (87.7%)	54 (100%)	947 (90.4%)
Patients with coronary heart disease of any type and rhythm disorders	4 (6.5%)	72 (10.2%)	0	16 (8.1%)	8 (12.3%)	0	100 (9.6%)
Hypersensitivity							
n	62	708	9	197	65	54	1047
Patients without allergic diseases	53 (85.5%)	612 (86.4%)	9 (100%)	186 (94.4%)	61 (93.8%)	52 (96.3%)	927 (88.5%)
Patients with allergic diseases	9 (14.5%)	96 (13.6%)	0	11 (5.6%)	4 (6.2%)	2 (3.7%)	120 (11.5%)
Medical history of convulsions							
n	62	708	9	197	65	54	1047
Patients without history of convulsions	55 (88.7%)	642 (90.7%)	9 (100%)	191 (97.0%)	52 (80.0%)	54 (100%)	955 (91.2%)
Patients with history of convulsions	7 (11.3%)	66 (9.3%)	0	6 (3.0%)	13 (20.0%)	0	92 (8.8%)

Because of cross-over studies, the sum of numbers of patients in each column is different from the overall number of patients reported in the "All doses" column.
Renal Insufficiency: Patients with no or mild renal impairment (eGFR >= 60 ml/min/1.73m2); Patients with moderate renal impairment (30 <= eGFR <60 ml/min/1.73m2); Patients with severe renal impairment (eGFR < 30 ml/min/1.73m2 + dialyzed patients).
For eGFR central values where used ; if missing, local data were considered.
Hepatic Insufficiency: Only liver insufficiency in CD (definition based on MedDRA v23.1 preferred term).
Cardiac Diseases: Coronary heart disease of any type and rythm disorders in CD and MH (definition based on MedDRA v23.1 preferred term).
Hypersensitivity: Allergic disease in CD and MH (definition based on MedDRA v23.1 preferred term).
Medical history of convulsions: Medical history of convulsions in CD and MH (definition based on MedDRA v23.1 preferred term).
Source: 5.3.5.3 Reports Of Analyses Of Data From More Than One Study

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in clinical studies within the development programme

Table 12 - Exclusion criteria in clinical studies within the development programme

Criterion	Reason for exclusion	Included as missing information?	Rationale for not including as missing information
Hypersensitivity towards one or more components of the study drug	Increased risk of potential life-threatening hypersensitivity reaction.	No	Included as contraindication in the product information.
Paediatric patients (0-2 y)	Sensitive population with immature renal function. Planned dedicated study in the very young population (0-2 years of age).	No	Indication proposed in adults and children aged 2 years and older.
Pregnant and lactating women	Exposure of pregnant women in current practice must be avoided except when the benefit outweighs the risks to the foetus and to the pregnant woman.	Yes	Warning included in the product information.
Patients with severe renal impairment (as class-effect for GBCAs)	Increased risk of NSF.	No	No NSF was observed in the study GDX-44-005 on the 16 patients with severe renal impairment, including 8 patients under haemodialysis. Warning about risk associated to renal impairment included in the product information.
Known class III/IV congestive heart failure according to the New York Heart Association classification	Severe conditions excluded to reduce the risk of adverse events caused by severe underlying conditions and concomitant drugs.	No	No serious cardiac Adverse Drug Reactions (ADRs) related to gadopiclenol were observed in the development program.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions which would occur in less than 1 in 1000 subjects, adverse reactions with a very long latency, or those caused by prolonged or repeated exposure.

No serious reactions of hypersensitivity were observed during clinical development. Life-threatening anaphylactic reactions occur with GBCAs but are exceedingly rare (0.001% to 0.01%) .

Long-term follow-up was limited to a period of 6 months (study GDX-44-005). However, no gadopiclenol was detected in any of the plasma and urine follow-up samples available at 1, 3 and 6 months, indicating that all amounts of gadopiclenol were eliminated after gadopiclenol single IV injection, in healthy volunteers and in patients with renal impairment of any stage. In addition, eighty pediatric patients were followed up to 3 months after exposure to gadopiclenol.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 13 - Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Patients with history of hypersensitivity	Not excluded from the clinical development program, for exposure data (see Part II: Module SIII)
Population with relevant different ethnic origin	Not excluded from the clinical development program, for exposure data (see Part II: Module SIII)
Subpopulations carrying relevant genetic polymorphisms	Not excluded from the clinical development program. However, no exposure data is available

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable since the product has not been marketed yet.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

The potential for misuse for illegal purposes can be excluded as gadopiclenol does not show any pharmacodynamic effects on the CNS that could make it a recreational drug or substance facilitating assault.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reasons for not including an identified or potential risk in the list of safety concerns in the RMP:

Table 14 - Risks with minimal clinical impact on patients (in relation to the severity of the indication)

System Organ Class	***Frequency***	***Adverse drug reaction***	***Rationale***
Immune system disorders	Unknown (therapeutic class risk)	Mild to moderate hypersensitivity reactions (mainly skin, respiratory and vascular reactions, immediate or delayed)	Not life-threatening, no sequelae. Hypersensitivity is listed in section 4.4 and 4.8 of the SmPC.
Nervous system disorders	1.3% (14/1047) 0.2% (2/1047)	Headache Dysgeusia	Not life-threatening, no sequelae.
Gastrointestinal disorders	0.7% (7/1047) 0.4% (4/1047) 0.3% (3/1047) 0.2% (2/1047)	Nausea Diarrhoea Abdominal pain, including Abdominal pain upper Vomiting	Not life-threatening, no sequelae.
General disorders and administration site conditions	1.9% (20/1047) 0.6% (6/1047) 0.4% (4/1047)	Injection site pain Injection site coldness Fatigue	Not life-threatening, no sequelae.

System Organ Class	***Frequency***	***Adverse drug reaction***	***Rationale***
	0.3% (3/1047) 0.3% (3/1047) 0.3% (3/1047) 0.1% (1/1047) 0.1% (1/1047)	Injection site oedema Feeling hot Injection site warmth Injection site erythema Injection site haematoma	A precaution for use to avoid extravasation is listed in section 4.4 of the SmPC.

Table 15 - Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated

System Organ Class	***Frequency***	***Adverse drug reaction***	***Rationale***
None	NA	NA	NA

Table 16 - Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by users (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised)

System Organ Class	***Frequency***	***Adverse drug reaction***	***Rationale***
Immune system disorders	Unknown	Severe hypersensitivity reactions (anaphylactic, anaphylactoid reactions, Kounis Syndrome and hypersensitivity/anaphylactic reactions with cardiovascular events)	This is a therapeutic class risk of GBCAs. No severe anaphylactic reactions or shock have been reported for gadopiclenol. This risk may be life-threatening if not immediately treated but gadopiclenol is administered in hospital/radiology centers with adequate emergency units. It is listed in section 4.4 of the SmPC. A proactive monitoring through periodic reports and signal detection

System Organ Class	***Frequency***	***Adverse drug reaction***	***Rationale***
			process is proposed (SMQ) "Anaphylactic reaction" (narrow + broad).
Renal and urinary disorders	Unknown	Nephrotoxicity	This is a therapeutic class risk of GBCAs. The potential for GBCA nephrotoxicity was rather associated to administration of high doses of GBCAs, especially during angiography in patient with renal insufficiency or to achieve adequate imaging when GBCAs were substituted for iodine contrast. Gadopiclenol is intended to be used by IV route at the dose that provides sufficient enhancement for diagnostic purposes. Renal function was monitored through all clinical development. In the study GDX-44-005 performed in patients with mild to severe renal impairment, changes in serum creatinine and eGFR were < 15% for most of the subjects (GDX-44-005 study report). A total of 5 ADRs related to renal function disorders were reported with gadopiclenol during the clinical trials: 3 ADRs of "Blood creatinine increase" (one serious and 2 non-serious), none leading to clinical symptoms, in patients either with fluctuating

System Organ Class	***Frequency***	***Adverse drug reaction***	***Rationale***
			baseline or high risk of creatinine fluctuation and confounding factors (chronic kidney disease, hypertension, past chemotehrapy). One non-serious ADR of "Contrast-induced renal failure" was reported in a patient with hypertension, Chronic Kidney Disease (CKD), showing an eGFR decrease of 28% within one day after gadopiclenol administration. In addition, 1 non-serious ADR of "Increased Cystatin C" was reported but lacked of evidence to support the causal relationship (medical background of the patient and confounding factors) with gadopiclenol (2.7.4 Summary of clinical safety). A proactive monitoring through periodic reports and signal detection process is proposed. (SMQ "Acute renal failure" (narrow + broad) + SMQ "Chronic kidney disease" (narrow)
Nervous system disorders	Unknown	Seizures	Proconvulsant effect is a therapeutic class risk of GBCAs in patients with a lowered threshold for seizures. No cases of seizures related to gadopiclenol have been reported during the clinical development (2.5 Clinical overview). While there is no evidence suggesting that gadopiclenol

System Organ Class	***Frequency***	***Adverse drug reaction***	***Rationale***
			directly precipitates convulsion at the intended human dose, the possibility that it may decrease the convulsive threshold in susceptible patients cannot be ruled out. It is listed in section 4.4 of the SmPC. A proactive monitoring through periodic reports and signal detection process is proposed (SMQ "Convulsions" (narrow + broad)).
Injury, poisoning and procedural complications	No data available	Product administration error (double dose administered by mistake due to current practices with other GBCAs)	The use of the product is adequately described in the product information (see section 4.2 of the SmPC) and a grid provides the volume of gadopiclenol to be administered per patient body weight.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

The classification of a risk as "important" is based on information given in the Good pharmacovigilance practices (GVP) Module V Rev 2 G1. See also the document "Guidance on the format of the risk management plan (RMP) in the EU – in integrated format" Rev.2.0.1. for further details G2.

Table 17 - Important Identified Risks

Important Identified Risk	**Risk-benefit impact**
Nephrogenic Systemic Fibrosis (NSF)	Nephrogenic Systemic fibrosis is a delibitating and sometimes life-threatening disease. The association between NSF and exposure to GBCAs is widely accepted and the development of NSF is known to be related to the release of Gd3+ from the chelates, a phenomenon which depends on the chemical properties of different GBCAs. Almost all unconfounded cases of NSF have been reported after exposure to linear GBCAs.

	Gadopiclenol is a Gd-complex based on a pyclen macrocyclic structure, offering a good chemical stability, thus suggesting a low risk for inducing NSF and a high r1 relaxivity that enables to use half of the standard dose to get the same MR efficacy. No NSF cases have been reported for gadopiclenol during the clinical development.

Table 18 - Important Potential Risks

Important Potential Risks	**Risk-benefit impact**
Adverse clinical effects of accumulation and retention of gadolinium in organs and tissues other than brain tissues	This is a therapeutic class risk of GBCAs. This accumulation phenomenon has been mainly studied in skin and bone. The clinical significance remains unknown. The amount and the form of gadolinium (free or chelated) found in brain and in other organs and tissues differ between GBCAs and depend on their chemical stability. Based on the pharmacokinetic profile of gadopiclenol in Humans and on the results of non-clinical studies, gadopiclenol is expected to behave similarly to other macrocyclic agents. In addition, gadopiclenol is administered at half-dose of gadolinium compared to the Gd dose usually administered with other GBCAs. Nevertheless, long-term effects of gadolinium deposition should be monitored.
Adverse clinical effects of accumulation and retention of gadolinium in the brain	This is a class effect of GBCAs described in the literature. McDonald et al. have shown the presence of Gd-containing dark spots in the walls of cerebral vessels and in the neuronal interstitium of the DN of deceased patients who had previously received gadodiamide . Murata et al. have provided additional clinical evidence of Gd deposition in the brains of patients exposed to GBCAs and especially to linear ones . The amount and the form of gadolinium (free or chelated) found in brain differ between GBCAs and depend on their chemical stability. Based on the pharmacokinetic profile of gadopiclenol in Humans and on the results of non-clinical studies, gadopiclenol is expected to behave similarly to other macrocyclic agents. The clinical significance remains unknown.

Table 19 - Missing information

Missing information	**Risk-benefit impact**
Safety in pregnancy and lactation	Any adverse event that may affect the course of a pregnancy and/or the development of a foetus would be considered as serious. Exposure to a GBCA during pregnancy may be associated with a slightly higher rate of neonatal death although this risk is based only on a single large cohort study which had significant limitations and reported only very few cases of serious adverse events. In addition, the degree and the clinical significance of potential Gd deposition in the foetuses following *in utero* exposure remains unknown for all GBCAs and remains of special interest given the ongoing rapid development of brain and bone in foetal patients. As GBCAs may cross the placental barrier in low amounts, the long-term effects of exposure to gadopiclenol during pregnancy should be monitored. All GBCAs are excreted into breast milk in very small amounts and poor absorption from the gut is expected in the breast-fed child. Nevertheless, any adverse effect of gadopiclenol in breast-fed children will be monitored. Up to now, no health risks have been scientifically proven.
Clinical significance of accumulation and retention of gadolinium in organs and tissues other than brain tissues	Non-clinical and clinical studies have demonstrated that Gd may remain at very low concentrations in some parts of the body including the bones, brain, skin and other organs for extended periods of time after injection of GBCAs. Gadolinium presence has been detected in laboratory testing of blood, urine, hair, fingernails, etc. Effect on peripheral nerve fibers in mice and hyperalgesia in rats were observed with GBCas, including macrocyclic GBCAs but in a lesser extent than with linear ones. Nevertheless there is no confirmation of adverse health effects attributable to the traces of Gd in the body in patients with normal renal function.
Clinical significance of accumulation and retention of gadolinium in the brain	It has been demonstrated that all GBCAs enter the brain, most 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 trace amounts of Gd in the brain. No adverse neurological effects, such as cognitive or movement disorders, have been attributed to gadolinium deposition in the brain with any GBCA.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important Identified Risks

Table 20 – Important identified risk: Nephrogenic Systemic Fibrosis (NSF)

Nephrogenic Systemic Fibrosis (NSF)	
Potential mechanisms	The pathophysiology of NSF is mainly related to dissociation of the Gd3+ ion from the chelate molecule by transmetalation resulting in Gd retention within tissues and ultimately leading to an irreversible fibrotic reaction. Some of the hypotheses include the following: Gd3+ ion transmetallation with ferric iron, deposition of gadolinium phosphate, and ferric iron induced oxidative stress; macrophage phagocytosis of free Gd with subsequent stimulation of fibrocyte infiltration in the dermis; GBCAs acting as a stimulus to the immune response with downstream effects of activated dendritic cells and transforming growth factor beta synthesis; and GBCA activation of transglutaminases . Once inside the tissues, Gd stimulates a cascade of cytokine production which leads to inflammation and eventual fibrosis of the skin and visceral organs. Reduced GBCA clearance in patients with severe renal disease allows additional time for the dissociation to occur. The chelated forms GBCAs have a significant role. The disease has been mostly associated to the use of linear GBCAs and it appears that the gradual release of dissociated Gd is pivotal in the development of NSF and its delayed onset .
Evidence source(s) and strength of evidence	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 with gadopiclenol. Moreover, similar to what has been observed with 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 .

Characterisation of the risk	<u>Therapeutic class risk of GBCAs:</u> Nephrogenic Systemic Fibrosis is a rare but highly debilitating disorder that is characterized by an extensive thickening and hardening of the skin but may also involve other organs, such as the lungs, oesophagus, heart, and skeletal muscles. Initial symptoms typically include skin thickening and/or pruritus. Symptoms and signs may develop and progress rapidly, with some affected patients developing contractures and joint immobility. In some patients, the disease may be fatal. The diagnosis of NSF is determined by using the clinicopathological score developed by Girardi and colleagues, based on clinical signs and results of histologic analyses performed on biopsy specimen . <u>Preclinical data</u>: Studies on sensitized rat models of NSF (rats with impaired renal function) did not suggest a profibrotic risk associated with the use of gadopiclenol. The high kinetic stability of gadopiclenol suggests a low risk of inducing NSF. <u>Clinical data</u>: In the Phase I study performed in renally-impaired patients, including patients under hemodialysis, no suspected NSF or symptoms suspected to be related to NSF were reported in any cohort. As for all GBCAs, specific precautions for use should apply in patients with impaired renal function.
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/1.73m^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.
Preventability	Information of physicians using the product about the risk and recommending strict caution in patients with severe CKD and acute renal insufficiency of any severity. Although GBCAs are rapidly removed by hemodialysis, no studies have demonstrated that hemodialysis may prevent or mitigate the risk of NSF . Utilisation of peel-off tracking labels to record the frequency of use and the dose of gadolinium applied to each patient.
Impact on the risk-benefit balance of the product	Appropriate routine risk minimisation measures, as described in Part V, are included in the product information. Therefore, the overall risk-benefit balance of the product is considered only minimally affected. Peel-off tracking labels have been introduced for GBCAs to record the frequency of use and the actual dose of gadolinium injected. No further additional risk minimisation measures are considered necessary.
Public health impact	Expected to be low, as the cases due to macrocyclic GBCAs are too isolated to calculate a frequency from clinical studies.

Important Potential Risks

Table 21- Important potential risk: 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	
Potential mechanisms	It has been shown that that gadolinium may be either in a soluble, small-molecule form (e.g. as intact GBCA), in a soluble form bound to macromolecules, or in a non-soluble form . The last two forms are thought to be responsible for the retention of gadolinium in organs and tissues. The Gd^{3+} ion could, partly depending on the local environment (acidic pH), become detached from the ligand by transmetallation (exchange with other ions present in the local environment, such as Fe^{3+}, Cu^{2+}, or Zn^{2+} ions) and the Gd^{3+} ion could then precipitate locally as a salt (gadolinium hydroxide, gadolinium carbonate or gadolinium phosphate) or bind to other macromolecules, such as proteins, peptides or metalloenzymes . Long-term Gd retention in the body depends mainly on the chemical stability of the GBCAs, the applied doses and the frequency of the administrations, especially for linear GBCAs. Gadopiclenol is a macrocyclic GBCA with high kinetic stability. Furthermore, thanks to its high r1-relaxivity, gadopiclenol can be used at half of the standard dose to get the same efficacy as other non-specific GBCAs, thus enabling to administer a lower quantity of Gd to patients.
Evidence source(s) and strength of evidence	Scientific literature; other GBCA products; non-clinical data.
Characterisation of the risk	Beside NSF, no clinical consequences have been clearly associated to Gd accumulation in organs and tissues other than brain tissues (see the missing information in section SVII.3.2). Scientific literature: Non-clinical and clinical studies have demonstrated that trace amounts of Gd may be retained in various parts of the body including the bones, skin, peripheral nervous system and other organs such as the liver, spleen and kidneys for extended periods of time after injection of GBCAs, especially after repeated exposure to linear GBCAs . Gadolinium presence has been detected in laboratory testing of blood, urine, hair, fingernails, etc . Evidence of a deep compartment of Gd storage was demonstrated . The chelated forms GBCAs have a significant role, the accumulation and retention of gadolinium in organs and tissues other than brain tissues has been mostly associated to the use of linear GBCAs while gadopiclneol is a macrocyclic GBCA.

	Non-clinical data: Gadopiclenol was found in brain, kidneys, liver, muscle, bone and skin of rats after single and repeated administrations. However, the Gd concentrations decreased dramatically after a recovery period of 8 weeks. In addition, a massive Gd washout (-74 to -98%) was observed over a 1-year recovery period (except in femur) after 20 IV administrations of gadopiclenol, and was similar to gadobutrol, another macrocyclic GBCA, when administered at the same dose. The investigation of Gd spatial distribution in brain and kidneys, together with the use of speciation methods to analyze the chemical forms of Gd in the tissues, showed that gadopiclenol behaves like gadobutrol, i.e. that 100% of the gadolinium extracted from the tissues was present as intact GBCA molecules in the same area than the other macrocyclic comparator (2.4 Non-clinical overview). Clinical data: No gadopiclenol was detected in any of the plasma and urine follow-up samples available at 1, 3 and 6 months in healthy volunteers and in patients with renal impairment of any stage, confirming the total elimination of gadopiclenol after single IV injection (GDX-44-005 study report).
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.
Preventability	Using the lowest dose necessary for a diagnosis. Clinically well-indicated contrast-enhanced MRI with Gadopiclenol. As described for NSF, haemodialysis performed shortly after GBCA administration for patients who are already on dialysis. Utilisation of peel-off tracking labels to record the frequency of use and the dose of gadolinium applied to each patient.
Impact on the risk-benefit balance of the product	Appropriate routine risk minimisation measures, as described in Part V, are included in the product information. Therefore, the overall risk-benefit balance of the product is considered only minimally affected. Peel-off tracking labels have been introduced for GBCAs to record the frequency of use and the actual dose of gadolinium injected. No further additional risk minimisation measures are considered necessary.

Public health impact	The high kinetic stability of gadopiclenol and the absence of robust clinical data relating to Gd accumulation in organs and tissues other that brain, suggest that the potential public health impact of this safety concern is not quantifiable, to date.

Table 22- Important potential risk: Adverse clinical effects of accumulation and retention of gadolinium in the brain

Adverse clinical effects of accumulation and retention of gadolinium in brain	
Potential mechanisms	As proposed by Rasschaert et al. , one of the hypothesis is that there is an early access of Gd species to the cerebrospinal fluid, followed by passive diffusion into the brain parenchyma close to the cerebral ventricles. When accessing areas rich in endogenous metals or phosphorus, the less kinetically stable GBCAs would dissociate, and Gd would bind to endogenous macromolecules, and/or precipitate within the brain tissue. It is also proposed that Gd species enter the brain parenchyma along penetrating cortical arteries in periarterial pial-glial basement membranes and leave the brain along intramural periarterial drainage pathways. Lastly, Gd/GBCAs may access the brain parenchyma directly from the blood through the BBB in the walls of the capillaries. It is crucial to distinguish between the physiological distribution and drainage pathways for GBCAs and the possible dissociation of less kinetically stable GBCAs that lead to long-term Gd deposition in the brain.
Evidence source(s) and strength of evidence	Scientific literature; other GBCA products; non-clinical data.
Characterisation of the risk	There is no evidence to-date that gadolinium retention in brain leads to any disease or disorders in subjects with normal renal function (see Missing information section SVII.3.2). Scientific literature: Many publications described a concentration-dependent deposition of gadolinium in the brain both in adults and children, seen as high signal intensities (SI) in the globus pallidus and dentate nucleus on unenhanced T1-weighted images mostly after multiple administration of linear GBCAs. Postmortem or post-surgery human studies have validated gadolinium deposition in these T1-hyperintensity areas . Non-clinical data: As expected for a macrocyclic GBCA, Gd retention in brain is minimalized in the case of gadopiclenol compared with gadobenate dimeglumine (a linear GBCA), resulting in no T1 hypersignal in the DCN one month after rats received 20 IV injections of 0.6 mmol/kg bw (1.2 mL/kg bw) Gadopiclenol (0.6 mmol/kg corresponding to the

	clinical dose (0.1 mmol/kg) adjusted to the body surface area of the rat) . Another (non-GLP) study performed to evaluate the long-term Gd deposition in the whole body in rats showed that the total Gd exposure between M1 (1 month) and M12 (12 months) after the last administration with gadopiclenol was around 5 to 10-fold less important as compared to gadodiamide (a linear GBCA), and was similar to gadobutrol (a macrocyclic GBCA) in brain. Specific analytical techniques have been applied to characterize the Gd-containing chemical species present in brain samples. Such method of speciation and investigation of Gd spatial distribution showed that gadopiclenol behaves like gadobutrol, i.e. that 100% of the gadolinium extracted from the tissues was present as intact GBCA molecules in the same area than the other macrocyclic agent, gadobutrol (2.4 Non-clinical overview).
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.
Preventability	Using the lowest dose necessary for a diagnosis. Clinically well-indicated contrast-enhanced MRI with Gadopiclenol. As described for NSF, haemodialysis performed shortly after GBCA administration for patients who are already on dialysis. Utilisation of peel-off tracking labels to record the frequency of use and the dose of gadolinium applied to each patient.
Impact on the risk-benefit balance of the product	Appropriate routine risk minimisation measures, as described in Part V, are included in the product information. Therefore, the overall risk-benefit balance of the product is considered only minimally affected. Peel-off tracking labels have been introduced for GBCAs to record the frequency of use and the actual dose of gadolinium injected. No further additional risk minimisation measures are considered necessary.
Public health impact	The high kinetic stability of gadopiclenol and the absence of robust clinical data relating to Gd accumulation in brain, suggest that the potential public health impact of this safety concern is not quantifiable, to date.

SVII.3.2 Presentation of the missing information

Table 23 - Missing information: Safety in pregnancy and lactation

Safety in pregnancy and lactation	
Evidence source	Therapeutic class risk of GBCAs: The only cohort and longitudinal study available with a relatively large sample size evaluating the safety of GBCAs during pregnancy was a large observational study comparing the outcomes of pregnancies between women who underwent a contrast-enhanced MRI during the first trimester and women who did not undergo an MRI. The study showed a greater relative risk of stillbirth and neonatal death in the former group as compared to the latter. However, a main limitation of this study was the unavailability of MRI indications for the exposed cohort, which are potential confounders. Other limitations of the cohort analysis include no information on the GBCA administered (linear or macrocyclic GBCA), no trimester subset analysis, and a better control would have been a group of women who underwent non-enhanced MRI. To date, no other publication has confirmed this observation. In addition, the degree and clinical significance of potential Gd deposition in foetuses following *in utero* exposure remain unknown. Clinical data: There is no data on the use of gadopiclenol in pregnant women; only one subject became pregnant two days after gadopiclenol exposure during the clinical program and therapeutic pregnancy termination was performed in relation to hereditary congenital disease diagnosed in the foetus. There is no data on the use of gadopiclenol in breast-feeding women from the clinical development. Preclinical data: Gadopiclenol was not teratogenic in rats at a dose level ≤ 10 mmol/kg/day and in rabbits at a dose level ≤ 5 mmol/kg/day. In addition, gadopiclenol was not found to be genotoxic in the battery of tests performed. The NOAEL for maternal and developmental toxicity was 2.5 mmol/kg/day in rabbits. Placental transfer was evaluated by examination of total radioactivity distribution following a single IV administration of [^{153}Gd]-gadopiclenol to female rats on Day 18 of gestation at a target dose level of 0.6 mmol/kg. The results suggested little or no placental transfer to the pups. In comparison, the distribution of gadopiclenol in pregnant females was widespread, with the majority of maternal

	tissues presenting the highest Gd concentrations at 10 minutes post-dose. Studies in rats have shown negligible secretion of gadopiclenol in maternal milk. Blood pharmacokinetic parameters and renal clearance of gadopiclenol may be modified during pregnancy. Therefore the safety of gadopiclenol during the course of pregnancy and the long-term effects on pregnant women and foetuses should be monitored.
Population in need of further characterisation	Pregnant and breast-feeding women

Table 24 - Missing information: Clinical significance of gadolinium accumulation and retention in organs and tissues other than brain tissues

Clinical significance of gadolinium accumulation and retention in organs and tissues other than brain tissues	
Evidence source	Class effect: Non-clinical and clinical studies have demonstrated that trace amounts of Gd may be retained in various parts of the body including the bones, brain, skin and other organs such as the liver, spleen and kidneys for extended periods of time after injection. There is no confirmation of adverse health effects attributable to the trace amounts of Gd retained in the body in patients with normal renal function . Rarely patients have reported “gadolinium deposition disease“ with pain, tiredness, and skin, muscle or bone ailments for a long time, but these symptoms have not been directly linked to Gd deposition . No peer-reviewed data link adverse biological or neurological effects to gadolinium deposition . Murata et al. hypothesized that free gadolinium, which has an ion radius close to that of free calcium, could block the activity of some calcium dependent enzymes and block calcium channels, leading to problems with muscle contractions or nerve conduction . Many of these symptoms are analogous to NSF but are less severe . Recently, a publication suggested a potential link between small fiber neuropathy (SFN) and previous administration of a GBCA. In fact, the authors reported a significant decrease of intraepidermal nerve fiber density and significant increase of terminal axonal swellings in the footpads of mice after exposure to GBCAs. Furthermore, another publication recently suggested a link between repeated GBCA administrations and hyperalgesia. The authors investigated the effect of repeated intraperitoneal administrations of linear or macrocyclic

	GBCAs on Gd presence in the central and peripheral nervous system of young rats.
Population in need of further characterisation	Patients with severe (eGFR < 30 mL/min/1.73, m^2) renal impairment are considered to be at increased risk of gadolinium retention leading to NSF. Patients who receive high and/or repeated dosing of GBCAs, especially when closely spaced, would be considered to be at higher risk for Gd accumulation at high concentration in the body. However, no adverse health effects have been confirmed in such patients. The following high-risk patient populations can be considered: children, pregnant women, patients with inflammatory condition, renal insufficiency and/or patients who require multiple lifetime doses. Macrocyclic agents are less prone to induce Gd deposition. 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 Gd levels in laboratory tests have been received from patients with normal renal function who were exposed to GBCAs, including gadobutrol, a macrocylcic GBCA. A causal relationship has not been established.

Table 25 - Missing information: Clinical significance of gadolinium accumulation and retention in brain

Clinical significance of gadolinium accumulation and retention in the brain	
Evidence source	Class effect: Retention of gadolinium in Humans was found in dentate nucleus (DN) and globus pallidus (GP) leading to T1-weighted hyperintensities observed in unenhanced-MRI, especially after repeated administrations of linear GBCAs. It has been demonstrated that all GBCAs enter the brain, most likely via the choroid plexus and the CSF . No evidence has shown to date that any adverse health effects are related to the accumulation of these trace amounts of Gd in brain . In a recent animal study , behavioral analyses showed that locomotor abilities, anxiety level, and long-term or short-term memory were not different in mice injected with linear or macrocyclic GBCAs while there was evidence for brain gadolinium deposition in mice exposed to repeated administration of the linear GBCA. No motor or behavioral alterations were observed in mice.

Population in need of further characterisation	Patients who tend to have higher concentrations of Gd in brain include those who received multiple doses of primarily linear GBCAs, those who received high doses of GBCAs, and those who underwent repeated or closely spaced GBCA-enhanced MRIs. Patients with severe (eGFR < 30 mL/min/1.73, m^2) renal impairment are considered to be at increased risk of NSF. Patients who receive high and/or repeated dosing of GBCAs, especially when closely spaced, would be considered to be at higher risk for Gd accumulation at high concentration in the body. However, no adverse health effects have been confirmed in such patients. The following high-risk patient populations can be considered: children, pregnant women, patients with inflammatory condition, renal insufficiency and/or patients who require multiple lifetime doses.

Part II: Module SVIII - Summary of the safety concerns

Table 26 - Summary of safety concerns

Summary of safety concerns in	**Gadopiclenol**
Important identified risk	• NSF (Nephrogenic Systemic Fibrosis)
Important potential risk	• Adverse clinical effects of accumulation and retention of Gd in organs and tissues other than brain tissues. • Adverse clinical effects of accumulation and retention of Gd in the brain.
Missing information	• Safety in pregnancy and lactation • Clinical significance of Gd accumulation and retention in organs and tissues other than brain tissues. • Clinical significance of Gd accumulation and retention in the brain.

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific follow-up questionnaires (see Annex 4) for:

- NSF:

Upon receipt of a report of NSF, a specific questionnaire to better characterize the disease and to eliminate alternative explanations will be provided to the reporter in order to collect more information on the patient medical and surgical condition, the renal function of the patient, any risk factors, the suspected product and previous exposure to GBCAs.

- Clinical significance of gadolinium accumulation and retention in the brain and in other organs and tissues:

A standardised reporting form for ADRs lasting over 4 weeks will be provided to the reporters in order to gather information on GBCA long-term effects, the patient medical and surgical condition, the renal function of the patient, any risk factors, the suspected product and previous exposure to GBCAs.

- Safety in pregnancy:

Pregnancy forms and follow-up forms will be provided to the reporters in order to gather information about pregnancy and outcome.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are considered necessary for the important identified risk “NSF” and the missing information “Safety in pregnancy and lactation”.

For the important potential risks and missing information on gadolinium accumulation and retention in the brain and in other organs and tissues the following additional pharmacovigilance activities are being planned or conducted:

Preclinical studies

Following the work published by Radbruch et al. questioning the propensity of GBCAs to induce Small Fiber Neuropathy, a non-clinical (non-GPL) study was initiated internally and is currently ongoing (ER-21-00003, ER-21-00007). Briefly, mice receive a single IV administration of gadopiclenol. Behavior and histopathology of the small fibers are assessed following the administration. Depending on the results of this first study, other studies could be performed. A complementary study investigated the occurrence of small fiber neuropathy following repeated administrations was launched and is currently ongoing. The completion of these studies is expected in December 2023 and July 2024, respectively.

Additional studies are currently ongoing on Gd distribution and speciation in rats, after single or repeated IV administrations of gadopiclenol (ER-21-00015, ER-21-00011). Enrolment in these studies is projected to conclude in December 2023 and December 2024, respectively.

In addition, to evaluate the long-term effects in humans, the MAH plans to amend the current ongoing ODYSSEY clinical study (GMRA-105) to include gadopiclenol among the GBCAs under investigation.

PASS Study: Long-term impact of GBCA on motor and cognitive function following repeated Contrast-Enhanced MRI

Study short name and title:

ODYSSEY (GMRA-105) - 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

Rationale and study objectives:

To prospectively assess the potential effect of repeated exposure to either a linear or a macrocyclic GBCA on change from baseline to Year 5 in motor and cognitive function among neurologically normal adults in comparison to a matched non-GBCA exposed control group.

Study design:

This study is being conducted as a prospective, multinational, multicenter, longitudinal cohort study in two groups of participants exposed to GBCA (either macrocyclic or linear) and a matched control group of participants not exposed to any GBCA.

Study population:

Each GBCA-exposed participant should be likely to undergo at least 5 GBCA-enhanced MR examinations with the same GBCA throughout the 5-year study duration. This study will compare the results from the Control group of participants who have never been exposed to a GBCA to the results of each group (macrocyclic and linear) of GBCA-exposed participants.

Milestones:

Original Protocol finalisation: September 2019

Amended Protocol finalisation (including gadopiclenol): July 2023

Enrolment begun: March 2021

Enrolment to conclude: December 2028

Interim reports: Annual for FDA

Projected final report: Six months after completion

III.3 Summary table of additional pharmacovigilance activities

The MAH has planned categories 1-3 safety clinical studies included in the Pharmacovigilance Plan for products containing gadopiclenol as follows:

Study **Status**	**Summary of objectives**	**Safety concern(s) addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit risk)				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit risk)				
None				
Category 3 - Required additional pharmacovigilance activities (EMA)				
GMRA-105 **Title:** Prospective Evaluation of Potential Effects of Repeated Gadolinium-based Contrast Agent (GBCA) Administrations of the Same GBCA on Motor and Cognitive Functions in Neurologically Normal Adults in Comparison to a Non-GBCA Exposed Control Group - ODYSSEY **Planned**	To evaluate the potential effect on motor and cognitive function	Effects of gadolinium retention	Protocol amendment finalised	July 2023
			Interim Reports	Annual for EMA
			Final report	6 months after completion

Four non-clinical studies are currently ongoing in the context of Gd accumulation and retention in the body

Study Status	*Summary of objectives*	*Safety concerns addressed*	*Milestones*	*Due dates*
Investigation of Small Fiber Neuropathy (SFN) after single administration of gadolinium based-contrasts agents (GBCAs) in mice (ER-21-00003) *On going*	The aim of the study is to investigate a potential occurrence of small fiber neuropathy following single intravenous injection of gadopiclenol *versus* other GBCAs (at the human equivalent dose) in mice.	- Clinical effects of accumulation and retention of gadolinium in organs and tissues other than brain - Clinical effects of accumulation and retention of gadolinium in the brain	**In-life completion** **Determination of total Gd concentrations in the selected tissues** **Behavioral assessment** **Histopathology** **Final report**	June 2021 Dec 2021 Oct 2021 Expected July 2023 Expected Dec 2023
Investigation of Small Fiber Neuropathy (SFN) after repeated administrations of gadolinium based-contrasts agents (GBCAs) in mice (ER-21-00007) *On going*	The aim of the study is to investigate a potential occurrence of small fiber neuropathy following repeated intravenous injections of gadopiclenol *versus* other GBCAs (at the human equivalent dose) in mice.	- Clinical effects of accumulation and retention of gadolinium in organs and tissues other than brain - Clinical effects of accumulation and retention of gadolinium in the brain	**In-life completion** **Behavioral assessment** **Histopathology** **Determination of total Gd concentrations in the selected tissues** **Final report**	May 2022 Expected Dec 2022 Expected Dec 2023 Expected Dec 2023 Expected July 2024

Study Status	*Summary of objectives*	*Safety concerns addressed*	*Milestones*	*Due dates*
Early (W1, M1) and long-term (M5) gadolinium retention after a dose of 0.05 mmol/kg of gadopiclenol vs 0.1 mmol/kg dose of already marketed macrocyclic GBCAs in rat (ER-21-00015) *On going*	The main aim of the study is to provide information about Gd retention and wash-out after single administration of 0.05 mmol/kg of gadopiclenol, to better apprehend the behaviour of this GBCA at the human equivalent dose and to compare with the other marketed macrocyclic GBCAs.	- Clinical effects of accumulation and retention of gadolinium in organs and tissues other than brain - Clinical effects of accumulation and retention of gadolinium in the brain	**In-life completion** **Determination of Gd concentrations in the selected tissues** **Final report**	Aug 2021 Expected July 2023 Expected Dec 2023
Exhaustive speciation of Gd retained after repeated injections of 0.05 mmol/kg of gadopiclenol vs 0.1 mmol/kg of gadobutrol in rat (ER-21-00011) *On-going*	The main aim of this study is to document Gd retention until 12 months after repeated administrations by providing exhaustive speciation data of gadolinium to understand in which form(s) it is present in different organs.	- Clinical effects of accumulation and retention of gadolinium in organs and tissues other than brain - Clinical effects of accumulation and retention of gadolinium in the brain	**In-life completion** **Determination of Gd concentrations in the selected tissues** **Gd spatial distribution with LA-ICP-MS in selected tissues** **Speciation analysis in different organs** **Final report**	Mar 2022 Expected Dec 2023 Expected July 2024 Expected July 2024 Expected Dec 2024

Part IV: Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies are considered necessary.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Important identified risks

Table 27 - Important identified risks

Safety concern	Routine risk minimisation activities
Nephrogenic Systemic Fibrosis (NSF)	Routine risk minimisation activities recommending specific clinical measures to address the risk: *SmPC section 4.1 :* Recommendation for use of gadopiclenol 0.5 mmol/mL only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI). *SmPC section 4.2 and PL section 3:* Recommendation to use the lowest dose that provides sufficient enhancement for diagnostic purposes calculated based on the patient's body weight. A grid provides the volume of gadopiclenol 0.5 mmol/mL to be administered per body weight. Renal impairment: Recommendation to use gadopiclenol 0.5 mmol/mL in patients with severe renal impairment (GFR < 30 ml/min/1.73 m2) and in patients in the perioperative liver transplantation period only after careful risk/benefit assessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI. If it is necessary to use gadopiclenol 0.5 mmol/mL, the dose should not exceed 0.05 mmol/kg body weight. More than one dose should not be used during a scan. Gadopiclenol 0.5 mmol/mL

	injections should not be repeated unless the interval between injections is at least 7 days. *SmPC section 4.4 and PL section 3* Recommendation for screening renal function of patients, especially in elderly patients. Recommendation to use gadopiclenol 0.5 mmol/mL in at-risk patients with acute or chronic severe renal impairment and in patients undergoing liver transplantation after careful benefit/risk assessment. Information on the possibility to remove gadopiclenol 0.5 mmol/mL by haemodialysis in patients who are already undergoing haemodialysis. *SmPC section 4.8 and PL section 4* Information that cases of NSF have been reported with other gadolinium-containing contrast agents and that none of these events were observed with gadopiclenol 0.5 mmol/mL during the clinical trials. *SmPC section 4.9* Gadopiclenol 0.5 mmol/mL can be removed by haemodialysis. However, there is no evidence that haemodialysis is suitable for prevention of NSF. *Peel-off tracking labels (SmPC section 6.6)*: Use of peel-off tracking or corresponding documentation if electronic patient records are used, to enable a reliable identification of GBCA dose administered to the patient. Product labels (on vials and syringes) have a peel-off tracking label which can be stuck onto the patient file. This will ensure that the GBCA is reliably identifiable. If electronic patient records are used, the name of the product, the batch number and the dose should be entered into the patient record <u>Other routine risk minimisation measures beyond the Product Information:</u> Prescription only medicine

Important potential risks

Table 28 - Important potential risks

Safety concern	**Risk minimisation activities**
Adverse clinical effects of accumulation and retention of gadolinium in organs and tissues other than brain	<u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> *SmPC section 4.1:* Recommendation for use of gadopiclenol 0.5 mmol/mL only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI). *SmPC section 4.2 and PL section 3:* Recommendation to use the lowest dose that provides sufficient enhancement for diagnostic purposes calculated based on the patient's body weight. A grid provides volume of gadopiclenol 0.5 mmol/mL to be administered per body weight. *Peel-off tracking labels (SmPC section 6.6)*: Use of peel-off tracking or corresponding documentation if electronic patient records are used, to enable a reliable identification of GBCA dose administered to the patient. Product labels (on vials and syringes) have a peel-off tracking label which can be stuck onto the patient file. This will ensure that the GBCA is reliably identifiable. If electronic patient records are used, the name of the product, the batch number and the dose should be entered into the patient record. <u>Other routine risk minimisation measures beyond the Product Information:</u> Prescription only medicine
Adverse clinical effects of accumulation and retention of gadolinium in the brain	<u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> *SmPC section 4.1:* Recommendation for use of gadopiclenol 0.5 mmol/mL only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI).

	SmPC section 4.2 and PL section 3: Recommendation to use the lowest dose that provides sufficient enhancement for diagnostic purposes calculated based on the patient's body weight. A grid provides volume of gadopiclenol 0.5 mmol/mL to be administered per body weight. *Peel-off tracking labels (SmPC section 6.6)*: Use of peel-off tracking or corresponding documentation if electronic patient records are used, to enable a reliable identification of GBCA dose administered to the patient. Product labels (on vials and syringes) have a peel-off tracking label which can be stuck onto the patient file. This will ensure that the GBCA is reliably identifiable. If electronic patient records are used, the name of the product, the batch number and the dose should be entered into the patient record. <u>Other routine risk minimisation measures beyond the Product Information:</u> Prescription only medicine

Missing information

Table 29 - Missing information

Safety concern	**Routine risk minimisation activities**
Safety in pregnancy and lactation	Routine risk minimisation activities recommending specific clinical measures to address the risk: *SmPC section 4.1:* Recommendation for use of gadopiclenol 0.5 mmol/mL only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI). *SmPC section 4.2 and PL section 3:* Recommendation to use the lowest dose that provides sufficient enhancement for diagnostic purposes calculated based on the patient's body weight. A grid provides volume of gadopiclenol 0.5 mmol/mL to be administered per body weight. *SmPC section 4.6 and PL section 2:* *Pregnancy* Gadopiclenol 0.5 mmol/mL should not be used during pregnancy unless the clinical condition of the woman requires use of gadopiclenol 0.5 mmol/mL. *Breast-feeding* Recommendation on the decision for continuing or discontinuing breast feeding for a period of 24 hours after administration of gadopiclenol 0.5 mmol/mL, that should be at the discretion of the doctor and lactating mother. *Peel-off tracking labels (SmPC section 6.6)*: Use of peel-off tracking or corresponding documentation if electronic patient records are used, to enable a reliable identification of GBCA dose administered to the patient. Product labels (on vials and syringes) have a peel-off tracking label which can be stuck onto the patient file. This will ensure that the GBCA is reliably identifiable. If electronic patient records are used, the name of the product, the batch number and the dose should be entered into the patient record. Other routine risk minimisation measures beyond the Product Information: Prescription only medicine
Clinical significance of gadolinium accumulation and retention in other organs and tissues than brain tissues	Routine risk minimisation activities recommending specific clinical measures to address the risk: *SmPC section 4.1:*

	Recommendation for use of gadopiclenol 0.5 mmol/mL only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI). *SmPC section 4.2 and PL section 3:* Recommendation to use the lowest dose that provides sufficient enhancement for diagnostic purposes calculated based on the patient's body weight. A grid provides volume of gadopiclenol 0.5 mmol/mL to be administered per body weight. *Peel-off tracking labels (SmPC section 6.6)*: Use of peel-off tracking or corresponding documentation if electronic patient records are used, to enable a reliable identification of GBCA dose administered to the patient. Product labels (on vials and syringes) have a peel-off tracking label which can be stuck onto the patient file. This will ensure that the GBCA is reliably identifiable. If electronic patient records are used, the name of the product, the batch number and the dose should be entered into the patient record. <u>Other routine risk minimisation measures beyond the Product Information:</u> Prescription only medicine
Clinical significance of gadolinium accumulation and retention in the brain	<u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> *SmPC section 4.1:* Recommendation for use of gadopiclenol 0.5 mmol/mL only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI). *SmPC section 4.2 and PL section 3:* Recommendation to use the lowest dose that provides sufficient enhancement for diagnostic purposes calculated based on the patient's body weight. A grid provides volume of gadopiclenol 0.5 mmol/mL to be administered per body weight. *Peel-off tracking labels (SmPC section 6.6)*: Use of peel-off tracking or corresponding documentation if electronic patient records are used, to enable a reliable identification of GBCA dose administered to the patient. Product labels (on vials and syringes) have a peel-off tracking label which can be stuck onto the patient file. This will ensure that the GBCA is reliably identifiable. If electronic patient records are used,

	the name of the product, the batch number and the dose should be entered into the patient record. Other routine risk minimisation measures beyond the Product Information: Prescription only medicine

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of gadopiclenol.

V.3 Summary of risk minimisation measures

Table 30 - Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Nephrogenic Systemic Fibrosis (NSF)	Routine risk minimisation measures: SmPC section 4.1 SmPC section 4.2 SmPC section 4.4 SmPC section 4.8 SmPC section 4.9 Peel-off tracking labels Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities with signal detection and adverse reactions reporting including: Adverse event follow-up form for collection of additional information.
Important potential risks		
Adverse clinical effects of accumulation and retention of gadolinium in	Routine risk minimisation measures: SmPC section 4.1 SmPC section 4.2	Routine pharmacovigilance activities with signal detection and adverse reactions reporting including:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
organs and tissues other than brain tissues	Peel-off tracking labels Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: None	Adverse event follow-up form for adverse events lasting over 4 weeks. Additional pharmacovigilance activities: None.
Adverse clinical effects of accumulation and retention of gadolinium in the brain	Routine risk minimisation measures: SmPC section 4.1 SmPC section 4.2 Peel-off tracking labels Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities with signal detection and adverse reactions reporting including: Adverse event follow-up form for adverse events lasting over 4 weeks. Additional pharmacovigilance activities: ODYSSEY clinical study (post-authorisation safety study): 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		
Safety in pregnancy and lactation	Routine risk minimisation measures: SmPC section 4.1 SmPC section 4.2 SmPC section 4.6 Peel-off tracking labels Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities with signal detection and adverse reactions reporting including: Pregnancy forms and follow-up forms.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Clinical significance of gadolinium accumulation and retention in other organs and tissues than brain tissues	Routine risk minimisation measures: SmPC section 4.1 SmPC section 4.2 Peel-off tracking labels Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities with signal detection and adverse reactions reporting including: Adverse event follow-up form for adverse events lasting over 4 weeks. Additional pharmacovigilance activities: - Preclinical studies in mice investigating the occurence 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
Clinical significance of gadolinium accumulation and retention in the brain	Routine risk minimisation measures: SmPC section 4.1 SmPC section 4.2 Peel-off tracking labels Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities with signal detection and adverse reactions reporting including: Adverse event follow-up form for adverse events lasting over 4 weeks. Additional pharmacovigilance activities: - Preclinical studies in mice investigating the occurence 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.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		- Preclinical study in rats investigating speciation of Gd retained after repeated injections of a half-dose of gadopicenol vs gadobutrol. - ODYSSEY clinical study (post-authorisation safety study): 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.

Part VI: Summary of the risk management plan

Summary of risk management plan for
GADOPICLENOL 0.5 MMOL/ML

(Gadopiclenol)

This is a summary of the risk management plan (RMP) for GADOPICLENOL 0.5 MMOL/ML. 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 GADOPICLENOL 0.5 MMOL/ML.

The summary of product characteristics (SmPC) and the package leaflet (PL) of GADOPICLENOL 0.5 MMOL/ML give essential information to healthcare professionals and patients on how the product should be used.

This summary of the RMP for GADOPICLENOL 0.5 MMOL/ML 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 GADOPICLENOL 0.5 MMOL/ML.

I. The medicine and what it is used for

GADOPICLENOL 0.5 mmol/mL 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 GADOPICLENOL 0.5 mmol/mL's benefits can be found in GADOPICLENOL 0.5 mmol/mL's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage : link to the EPAR summary landing page.

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

Important risks of GADOPICLENOL 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 GADOPICLENOL 0.5 mmol/mL is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of GADOPICLENOL 0.5 mmol/mL 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 GADOPICLENOL 0.5 mmol/mL. 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 31 - 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

List of important risks and 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 the brain

II.B Summary of important risks

Important identified risks

Table 32 - 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 per 1.73m2) 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.

Nephrogenic Systemic Fibrosis (NSF)	
	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	Routine risk minimisation measures: SmPC section 4.1 SmPC section 4.2 SmPC section 4.4 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: An adverse event follow-up form for collection of additional information. Additional pharmacovigilance activities: none

Important potential risks

Table 33 - 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 34 - 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 35 - 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 36 - 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 37 - 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 occurence 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 gadopiclenol.

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 in July 2023. 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.

Part VII: Annexes

Table of contents

Annex 1 *EudraVigilance Interface* 71
Annex 2 *Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme* 71
Annex 3 *Protocols for proposed, on-going and completed studies in the pharmacovigilance plan* 74
Annex 4 *Specific adverse drug reaction follow-up forms* 79
Annex 5 *Protocols for proposed and on-going studies in RMP part IV* 104
Annex 6 *Details of proposed additional risk minimisation activities (if applicable)* 104
Annex 7 *Other supporting data (including referenced material)* 105
Annex 8 *Summary of changes to the risk management plan over time* 108

Annex 4 Specific adverse drug reaction follow-up forms

- NSF form is provided below:

CASES OF SUSPECTED NEPHROGENIC SYSTEMIC FIBROSIS (NSF) SPECIFIC PHARMACOVIGILANCE QUESTIONNAIRE

to be filled in by the reporter

Case ID:

Subject initials (first 2 letters): Name |____|; First name |____|

1-Patient demographics:

Date of birth: |__|__| /|__|__|/ |__|__|__|__|
or current age (at the time of this form completion): ____ Years

Gender: male: ☐ female ☐ Weight: |__|__|__| kg Height: |__|__|__| cm

2-Patient medical and surgical histories:

-Kidney disorder type:
……..…….

-Start date: |__|__| /|__|__|/ |__|__|__|__|

-GFR level / unit:
…….

-Creatininemia level / unit: ……..……

-Etiology of the renal disorder: ……..……

-Other histories:
……..……

……..……

……

……..…...…

-Any recent surgical procedure? Yes ☐ No ☐

If yes specify:……..……

……..……

-Any recent thrombotic event? Yes ☐ No ☐

If yes specify:

……..……

……

…

3-Symptoms reported: date of first symptom onset: |__|__| |__|__| |__|__|__|__|

- Skin…….……
.....
.....
.....

- Musculoskeletal:
……..……..……..
.....
.....

-Respiratory:
……...……

-Cardiovascular:
…….……..……

-Any other:
…….
…

……...
..

4-Biological work up

-Auto immune checkup? Yes ☐ No ☐

If yes specify the results:

……...…….…….…

……..

-Any Coagulation disorders? Yes ☐ No ☐

If yes: what type?
……...……..……..…

5-Biopsy results available? Yes ☐ No ☐

If yes procedure and results:
……..…….…….……

……..……..…
…
6-Suspected Guerbet product and previous administered Gadolinium Based Contrast Agents (GBCAs):

-Brand name / International Non-proprietary Name (INN):
|_____|

-Start date: |__|__| /|__|__|/ 20…. Stop date: |__|__| /|__|__|/ 20….

-Volume administered:

-Route of administration: |_____| (IV, IA, ….)

-Type of examination: |_____|

-Indication: |_____|

-Result: ……..……..……..…

-Brand name / INN: |_____|

-Start date: |__|__| /|__|__|/ 20…. Stop date: |__|__| /|__|__|/ 20….

-Volume administered:

-Route of administration: |_____| (IV, IA, ….)

-Type of examination: |_____|

-Indication: |_____|

-Result: ……..……

-Brand name / INN: |_____|

-Start date: |__|__| /|__|__|/ 20…. Stop date: |__|__| /|__|__|/ 20….

-Volume administered:

-Route of administration: |_____| (IV, IA, ….)

-Type of examination: |_____|

-Indication: |_____|

-Result: ……

-Brand name / INN: |_____|

-Start date: |__|__| /|__|__|/ 20…. Stop date: |__|__| /|__|__|/ 20….

-Volume administered:

-Route of administration: |_____| (IV, IA, ….)

-Type of examination: |_____|

-Indication: |_____|

-Result:

……

7-Concomitant drugs

-Other contrast medium? Yes ☐ No ☐

If yes specify, the following items: brand name, INN, start date, stop date, dosage, route of administration; indication, dechallenge/rechallenge

……

……

-Erythropoietine? Yes ☐ No ☐

If yes specify, the following items: brand name, INN, start date, stop date, dosage, route of administration; indication, dechallenge/rechallenge

……

……

-Anti hypertensive drugs? Yes ☐ No ☐

If yes specify, the following items: brand name, INN, start date, stop date, dosage, route of administration; indication, dechallenge/rechallenge

……

……

Any other (including dialysis, hemofiltration ...)? Yes ☐ No ☐ :

If yes specify, the following items: brand name, INN, start date, stop date, dosage, route of administration; indication, dechallenge/rechallenge

-……..……..……..……..……..……..…

-……..……..……..…..

-……..……..……..……

8-Any differential diagnosis evoked? Yes ☐ No ☐

If yes: please specify?
……..……..
…...
……...……
…

9-Any NSF / Nephrogenic Fibrosing Dermopathy (NFD) treatment? Yes ☐ No ☐

If yes: what type?
……..……..……

Outcome? ……...……..

10-Any other comment to be retained regarding that case:

……..……

……..……

Date: Title:

Signature:

Centers for Disease Control and Prevention Original Case Definition:

"Patients who have developed large areas of hardened skin with slightly raised plaques, papules, or confluent papules; with or without pigmentary alteration and/or with biopsies showing increased numbers of fibroblasts, alteration of the normal pattern of collagen bundles seen in the dermis, and increased dermal deposits of mucin".

For more information about NSF / NFD go to: http://www.icnfdr.org/.

- Long-term safety of gadolinium retention in the brain and in other organs and tissues form is provided here below:

TARGETED FOLLOW-UP QUESTIONNAIRE - POTENTIAL LONG-TERM SYMPTOMS ASSOCIATED WITH GADOLINIUM EXPOSURE

1. Reporter information

Name Address	
Reporter type	☐ Radiologist ☐ Medical specialist in the field of: ☐ Other physician, please specify: ☐ Radiology technician ☐ Consumer/Representative ☐ Other, please specify:

2. Patient information

Patient initials or number:		Gender:	Age:
Height (cm):	Weight (kg):	Race/Ethnicity:	Occupation:

Indication which made the MRI necessary:

Please describe the medical history of this indication:

Does the patient have any of the following?

☐ inflammatory disorders; please specify

☐ immune system disorders; please specify

☐ autoimmune system disorders; please specify

☐ disorders of the central nervous system; please specify

☐ allergies / asthma / intolerances; please specify

Are or were there any other disorders / concurrent conditions (including genetic disorders)? Please specify

Are or were there any concomitant or recent treatments for the pre-existing medical condition(s)? Please specify

☐ no ☐ yes; please specify, including dates:

☐radiation therapy ☐chemotherapy ☐nuclear medicine scans ☐physical therapy ☐pacemaker ☐implants ☐ parenteral nutrition

☐other/additional, please specify:

Tests of renal function

Normal renal function prior administration of gadolinium-based contrast agents? ☐ no ☐ yes ☐ unknown

Patient on dialysis? ☐ no ☐ yes ☐ unknown

Renal function at the time of gadolinium-based contrast agent administration**:** ☐ unknown ☐ known, please specify:

Serum creatinine: Date:

Estimated glomerular filtration rate: Date:

Creatinine clearance: Date:

Phosphate concentration (please specify: blood or urine): Date:

History of reactions to contrast media

In the past, did the patient experience any adverse reactions to contrast media prior to the current reactions?

☐ no ☐ yes, please specify: it was

☐ a gadolinium-based contrast agent, please specify:

☐ no gadolinium-based contrast agent, but (specify):

☐ unknown

Date of administration / dose / route of administration / indication:

Type of adverse reaction

If the patient experienced any symptoms after administration of a contrast agent, please describe the symptoms in chronological order and indicate in what time frame after administration they appeared and how long they lasted

☐ Immediate adverse reactions ☐ no ☐ yes, please specify:

☐ Delayed adverse reactions ☐ no ☐ yes, please specify:

Indication which made the MRI necessary:

Please describe the medical history of this indication:

Does the patient have any of the following?

☐ inflammatory disorders; please specify

☐ immune system disorders; please specify

☐ autoimmune system disorders; please specify

☐ disorders of the central nervous system; please specify

☐ allergies / asthma / intolerances; please specify

Are or were there any other disorders / concurrent conditions (including genetic disorders)? Please specify

Are or were there any concomitant or recent treatments for the pre-existing medical condition(s)? Please specify

☐ no ☐ yes; please specify, including dates:

☐radiation therapy ☐chemotherapy ☐nuclear medicine scans ☐physical therapy ☐pacemaker ☐implants ☐ parenteral nutrition

☐other/additional, please specify:

Tests of renal function

Normal renal function prior administration of gadolinium-based contrast agents? ☐ no ☐ yes ☐ unknown

Patient on dialysis? ☐ no ☐ yes ☐ unknown

Renal function at the time of gadolinium-based contrast agent administration**:** ☐ unknown ☐ known, please specify:

Serum creatinine: Date:

Estimated glomerular filtration rate: Date:

Creatinine clearance: Date:

Phosphate concentration (please specify: blood or urine): Date:

History of reactions to contrast media

In the past, did the patient experience any adverse reactions to contrast media prior to the current reactions?

☐ no ☐ yes, please specify: it was

☐ a gadolinium-based contrast agent, please specify:

☐ no gadolinium-based contrast agent, but (specify):

☐ unknown

Date of administration / dose / route of administration / indication:

Type of adverse reaction

If the patient experienced any symptoms after administration of a contrast agent, please describe the symptoms in chronological order and indicate in what time frame after administration they appeared and how long they lasted

☐ Immediate adverse reactions ☐ no ☐ yes, please specify:

☐ Delayed adverse reactions ☐ no ☐ yes, please specify:

Further information:

Diet, Use of multi-vitamins, supplements, minerals, etc. / Exposure to metals, pollutants, harmful substances, etc.

☐ Diet, if yes, please specify:

Use of (specify): Exposure to (specify):

☐ Nicotine ☐ Alcohol ☐ Other abuse:

Other details:

3. Current symptoms associated with recent exposure to gadolinium-based contrast agent

Do you believe that the adverse reaction(s) are related to gadolinium-based contrast agents? Patient: ☐ no ☐ yes / Physician: ☐ no ☐ yes

Do you wish to report persistent symptoms, currently known as "gadolinium deposition disease" (GDD)? ☐ no ☐ yes

Adverse reaction	**Start**	**End**	**Severity**	**Outcome**	**Causality in terms of gadolinium**	**Adverse reaction details**
			☐ Resulted in death ☐ Life-threatening ☐ Required inpatient hospitalisation or prolongation of existing hospitalisation ☐ Persistent or significant disability/ incapacity ☐ Congenital anomaly/ birth defect ☐ medically relevant	☐ Resolved/Recovered ☐ Resolved/Recovered with sequela, please specify: ☐ Not resolved / Not recovered ☐ Exitus, cause of death: ☐ Unknown	☐ Certain ☐ Probable/Likely ☐ Possible ☐ Unlikely ☐ Conditional/ Unclassified ☐ Unassessable/ Unclassifiable	Was the adverse reaction assigned to a different diagnosis? ☐ no ☐ yes; please specify: How was the diagnosis made? Which tests were performed to evaluate the symptoms or to determine the cause of them? Please specify: Was there any treatment of the reactions? ☐ no ☐ yes; please specify (1): How long did the symptoms last?

(1) Please describe type, duration, dosage of treatment and effect on the adverse reaction (improvement/recovery, aggravation, no change)

4. Administration of gadolinium-based contrast agents

Please describe as complete as possible, when gadolinium-based contrast agents were administered to you. The name of the contrast agents, the indication for the MRI examinations and the symptoms associated with the MRI indication are of particular importance.

Date	Contrast agent (product name / Active substance)	Institution / Facility	Dosage and route of administration	Indication / Reason for MRI	Description of symptoms associated with indication and MRI/test results

5. Use of medications (incl. non-prescription / herbal / homeopathic medicines, etc.)

Medication / product	Indication / reason for use	Dosage and route of administration	Start / End / Duration of use

6. Tests of gadolinium presence in the body

Were concentrations of gadolinium measured in tissues/body fluids?

☐ no ☐ yes; please specify (attach laboratory test reports, if available)

Tissue / Body fluid	Gadolinium concentration measured (please indicate units and reference range)	Laboratory / Facility	Date of sampling

Was an increased signal intensity seen on radiological scans of the brain?

☐ no ☐ yes; please specify (attach radiological reports, if available)

Brain area	Contrast agent / Dose / number of administrations / Cumulative dose	Institution / Facility	Date of examination

Did the patient seek medical treatment for any of the <u>reported symptoms associated with exposure to gadolinium-based contrast agents</u>?

☐ no ☐ yes; please specify type and outcome of treatment:

Medication / treatment	Start	End	Institution / Facility	Outcome / Laboratory findings / Other investigations (attach reports, if available)

Further explanations:

7. Additional relevant information

Further important information for assessment, in particular diagnoses of exclusion, epicrisis Clinical observations / findings (attach examination reports, if available)

City/Date: Signature:

- Pregnancy forms and follow-up forms are provided below:

HISTORY AND START OF PREGNANCY

Guerbet AER Nb: _____

Protocol nb:
Subject nb:

PREGNANT WOMAN:

Last name *(Initial)*	First name *(Initial)*	Birth date *(DD/MM/YYYY)*	Age (years)	Height *(cm)*	Weight *(kg)*	Occupation
|_|	|_|					

PARTNER ***(if exposed to contrast product):***

Age (years)	If chemotherapy treatment, name of product(s) used:	Date of administration *(DD/MM/YYYY)*	Indication	Other medical history

MEDICAL HISTORY:

Arterial hypertension: ❑ Yes ❑ No

Diabetes: ❑ Yes ❑ No
Epilepsy: ❑ Yes ❑ No
Psychiatric illness: ❑ Yes ❑ No
Other:

- *Previous immunisations:*

Rubella: ❑ Yes ❑ No
Toxoplasmosis: ❑ Yes ❑ No

Tobacco:____ cig./day Alcohol:..... glasses/day Drug addiction;.....

OBSTETRICAL HISTORY:

➢ Previous pregnancy(ies): ❑ Yes ❑ No

- Number of pregnancy(ies): |__|
- Number of full-term delivery (ies): |__|
- Number of premature delivery (ies): |__|
- Number of abortion(s): |__|
  - ❑ Spontaneous abortion(s), number: |__|
  - ❑ Voluntary Interruption Pregnancy(ies), number: |__|
  - ❑ Therapeutic abortion(s), number: |__|, Etiology: .....
  - ❑ Death(s) in utero, number: | |, Etiology: .....
- Number of healthy living children without abnormality: |__|
- Number of children died at birth |__| or shortly after: |__|
- Number of malformed living children |__| or genetic abnormality(ies) |__|, Specify:
- Complications during previous pregnancies: ❑ No ❑ Yes, specify:.....

➢ Family history (mother and/or father):

- Malformations: ❑ No ❑ Yes, specify : ❑ Unknown
- Children died in infancy: ❑ No ❑ Yes, specify : ❑ Unknown
- Psychomotor retardation: ❑ No ❑ Yes, specify : ❑ Unknown
- Consanguinity: ❑ No ❑ Yes, specify : ❑ Unknown
- Hereditary disease(s): ❑ No ❑ Yes, specify : ❑ Unknown
- Other: _____

CURRENT PREGNANCY:

- Date of last period |_|_|-|_|_|-|_|_| Pregnancy start date |_|_|-|_|_|-|_|_|
  - → Date of pregnancy test positive: |_|_|-|_|_|-|_|_|, Type of test:.....
  - → Ultrasound age: |___| weeks of amenorrhea
- Multiple pregnancy: ❑ No ❑ Yes, number of embryos/foetuses: |__|
- Predicted delivery date: |_|_|-|_|_|-|_|_|
- First results of examinations if available (echography, lab tests…):

_____

_____

_____

EXPOSURE TO CONTRAST PRODUCT:

Contrast product	Batch number	Route of administration	Dose/day	First intake *(DD/MM/YY)*	Last intake *(DD/MM/YY)*	Type of examination	Indication

If X-rays have been used: Number of images |__| Estimated dose received *(specify unit)* |___|

EXPOSURE OF THE PREGNANT WOMAN TO CONCOMITANT MEDICATIONS:

(specify here: any premedication administered as well as all the usual or occasional treatments received by the patient since the start of the pregnancy).

Name of product	Route of administration	Dose / day	First intake *(DD/MM/YY)*	Last intake *(DD/MM/YY)*	Indication

Contact details of obstetrician:

.....

.....

- COMMENTS:

.....

.....

.....

Stamp: Date: Signature:

Contact details of affiliate or distributor:

COURSE AND OUTCOME OF PREGNANCY, INFANT DEVELOPMENT HISTORY

Guerbet AER Nb:

Protocol nb:
Subject nb:

PREGNANT WOMAN:

Last name *(First initial)*	First name *(First initial)*	Birth date *(DD/MM/YYYY)*	Age *(Years)*	Last menstruation period *(DD/MM/YYYY)*

COURSE OF PREGNANCY:

- Diseases during pregnancy: ☐ Diabetes ☐ Infection, specify: ..... ☐ Arterial hypertension

  ☐ Other: .....
- Hospitalisation during pregnancy: ☐ No ☐ Yes, for: _____
- Pregnancy follow-up (relevant examinations/biological results):

  .....
- Ultrasound examinations: (Dates (DD.MM.YY) or weeks of amenorrhea, and results):

  → 1st trimester:

  .....

  .....

  → 2nd trimester:

  .....

  .....

  → 3rd trimester:

  .....

  .....

  ☐ Extra-uterine pregnancy

  ☐ Congenital anomalies detected (Date: |_||_|-|_||_|-|_||_|), specify: .....

  ☐ Intrauterine growth retardation (Date: |_||_|-|_||_|-|_||_|), specify: .....

  ☐ Death in utero (Date: |_||_|-|_||_|-|_||_|), specify the aetiology: .....
- Premature pregnancy termination:

☐ Spontaneous abortion, Date: |_D_|_D_|-|_M_|_M_|-|_Y_|_Y_| Term (weeks of amenorrhea): |___|

Specify the aetiology: .....

☐ Therapeutic termination, Date |_D_|_D_|-|_M_|_M_|-|_Y_|_Y_| Term (weeks of amenorrhea): |___|

Specify the reason: .....

☐ Voluntary Interruption Pregnancy, Date: |_D_|_D_|-|_M_|_M_|-|_Y_|_Y_| Term (weeks of amenorrhea |___|

specify the reason *(if specific reason)*: .....

TREATMENTS RECEIVED DURING PREGNANCY (including contrast media/agent):

Name of drug	Batch number	Route of administration	Dose/day	First intake *(DD.MM.YY)*	Last intake *(DD.MM.YY)*	Indication

DELIVERY:

- Date: |_D_|_D_|-|_M_|_M_|-|_Y_|_Y_| Term (weeks of amenorrhea) |___|

☐ Normal ☐ Induced ☐ Caesarean

- Living new-born: ❑ Yes ❑ No

- Foetal distress? ☐ Yes, specify:☐ Chronic or ☐ Acute

☐ No

- Complication(s) during or after delivery:

.....
.....
.....
.....

NEONATAL INFORMATION:

- Date of birth: |_D_|_D_|-|_M_|_M_|-|_Y_|_Y_|
- Gender: ☐ F ☐ M
- Birth weight: |_____| kg Birth height: |_____| cm Birth head circumference: |_____| cm
- Premature: ☐ Yes ☐ No
- Dysmature: ☐ Yes ☐ No
- Apgar score: |____| 1 min |____| 5 min

▪ Physical examination at birth:

☐ No dysmorphic features identified
☐ Minor anomalies, specify: ……..
☐ Major Malformations, specify: ……
☐ Neonatal pathology, specify: ……
☐ Resuscitation
☐ Transfer to intensive care or paediatric unit:
→ Duration: ……

→ Address of the unit: ……

→ Description of interventions and outcome:

……

……

NEWBORN / INFANT INFORMATION:

▪ Breastfeeding:

☐ Yes ☐ No

If applicable, age breastfeeding was stopped: |_____| years

▪ Infant demographics: Age: |_____| years

Weight: |_____| kg Height: |_____| cm
☐ If anomalies, specify:

……..

▪ Infant development history and milestones, comments:

……

……

……

☐ If anomalies, specify:

……

▪ Any information on gadolinium accumulation:

☐ Yes ☐ No

If yes, specify:

……

➢ *COMMENTS:*

…… …… …… …… …… …… …… …… ……
Stamp: Date: Signature:
Contact details of affiliate or distributor:

Annex 5 ***Protocols for proposed and on-going studies in RMP part IV***

None

Annex 6 ***Details of proposed additional risk minimisation activities (if applicable)***

None