SEE THE DIFFERENCE, MAKE A DIFFERENCE.

EFFECTIVE ENHANCEMENT AT HALF THE GD DOSE.*[1-3]

*Half the gadolinium dose compared to other macrocyclic GBCAs at a Gd dose of 0.1 mmol/kg in approved indications.

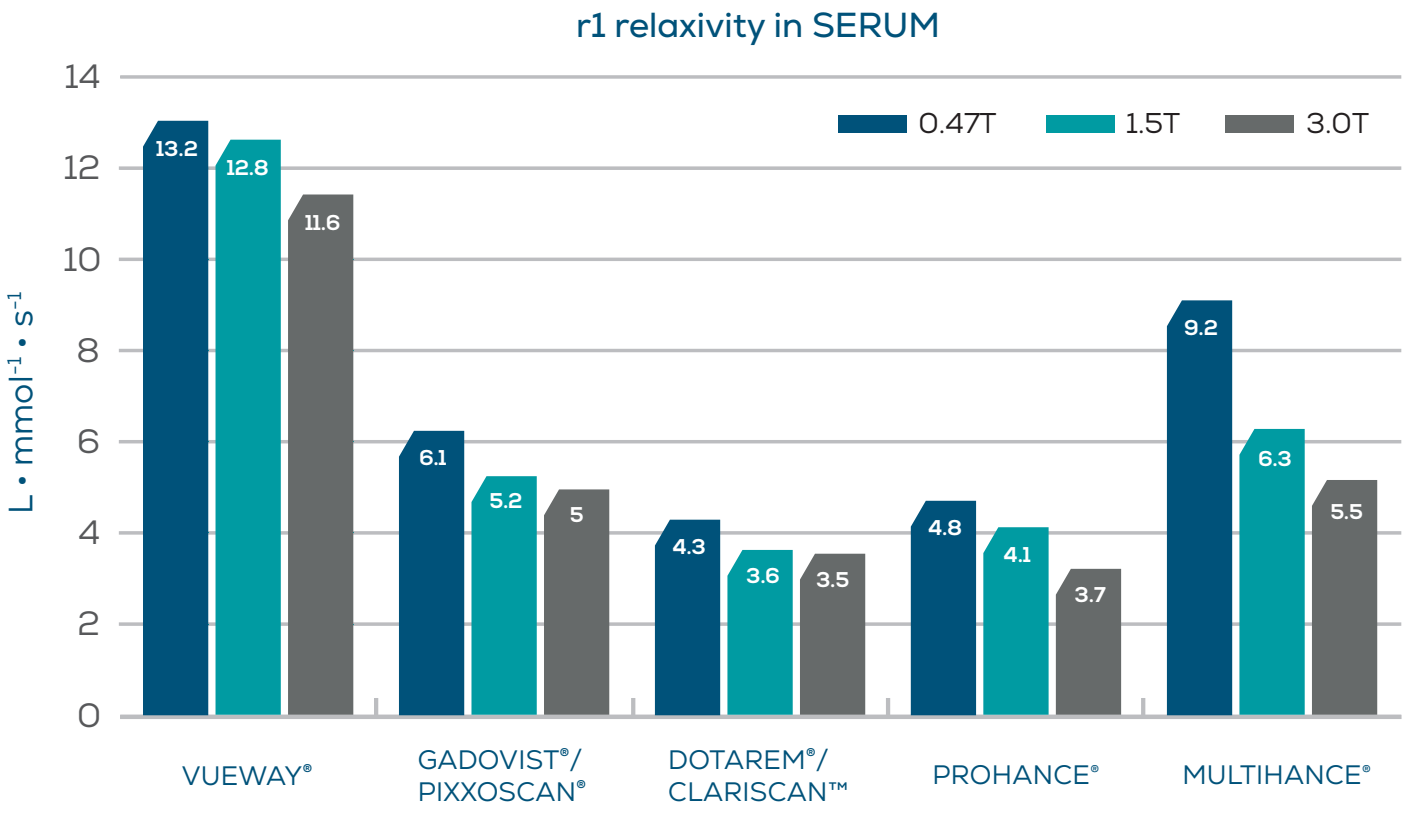
Vueway®
(gadopiclenol) injection

BRACCO
LIFE FROM INSIDE

GL-VW-2300016

SEE THE DIFFERENCE,

VUEWAY® has the **highest relaxivity** of all GBCAs today **combined with high stability**,*[4] making effective MRI contrast enhancement possible at **half the Gd dose (0.05 mmol/kg)** vs. standard macrocyclic GBCAs at the dose of 0.1 mmol/kg.[1-3]



Adapted from Robic et al. Invest Radiol. 2019

High relaxivity is synonymous with **high potency**, which **means high efficacy**. A high-potency GBCA can achieve the **same desired contrast effect even at a reduced Gd dose**.[5-8]

*In addition to Elucirem™ (gadopiclenol).
GBCA, gadolinium-based contrast agent; Gd, gadolinium; MRI, magnetic resonance imaging; T, tesla.

MAKE A DIFFERENCE.

A macrocyclic GBCA offering similar visualization at a reduced Gd dose can **make a difference to your patients** because:

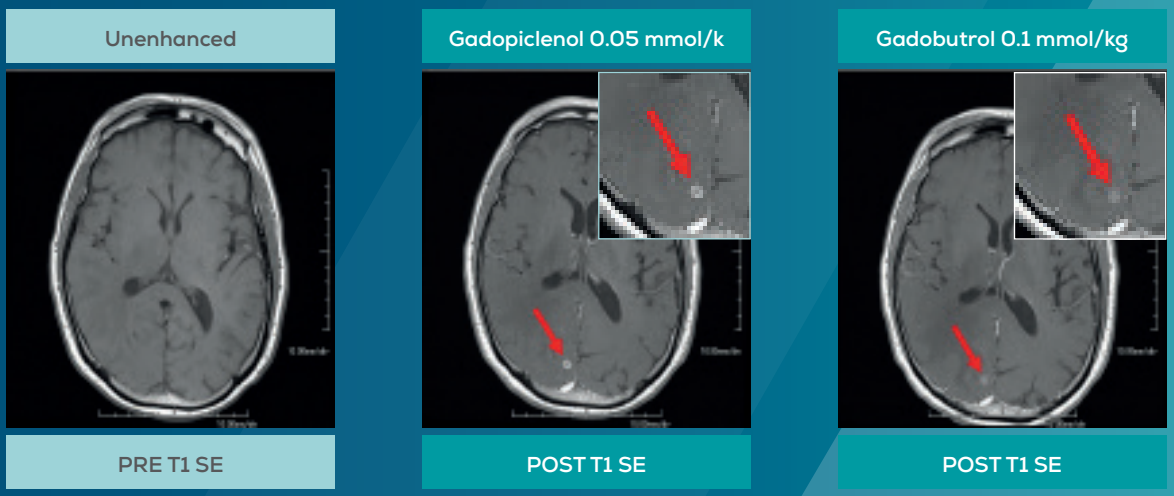
- **Less gadolinium** is injected per MRI procedure.
- **Gd exposure is minimized** per procedure for all patients, including **pediatrics**.
- The **cumulative lifetime dose is reduced**, which may be of clinical value, especially in vulnerable patients undergoing repeated or closely-spaced MRIs.[3,7,9]
- The **rate of lesion detection and characterization is comparable** to a standard macrocyclic GBCA at the dose of 0.1 mmol/kg.[1-3]

GBCA, gadolinium-based contrast agent; Gd, gadolinium; MRI, magnetic resonance imaging.

MAKING A DIFFERENCE IN POTENCY

GADOPICLENOL HAS THE HIGHEST

The **degree of contrast enhancement** and diagnostic efficacy produced by GBCAs on MR images **depends on relaxivity** and injected dose (time-dependent, local concentration in tissue). A high-relaxivity GBCA can achieve at least the same contrast efficacy at the **reduced Gd dose** as a standard GBCA at the dose of 0.1 mmol/kg.[5-8]



High-relaxivity VUEWAY® at half the Gd dose vs. Gadovist® at 0.1 mmol/kg: *Clinical case of a 65-year-old man with brain metastasis from lung adenocarcinoma at 3.0 T* *†*

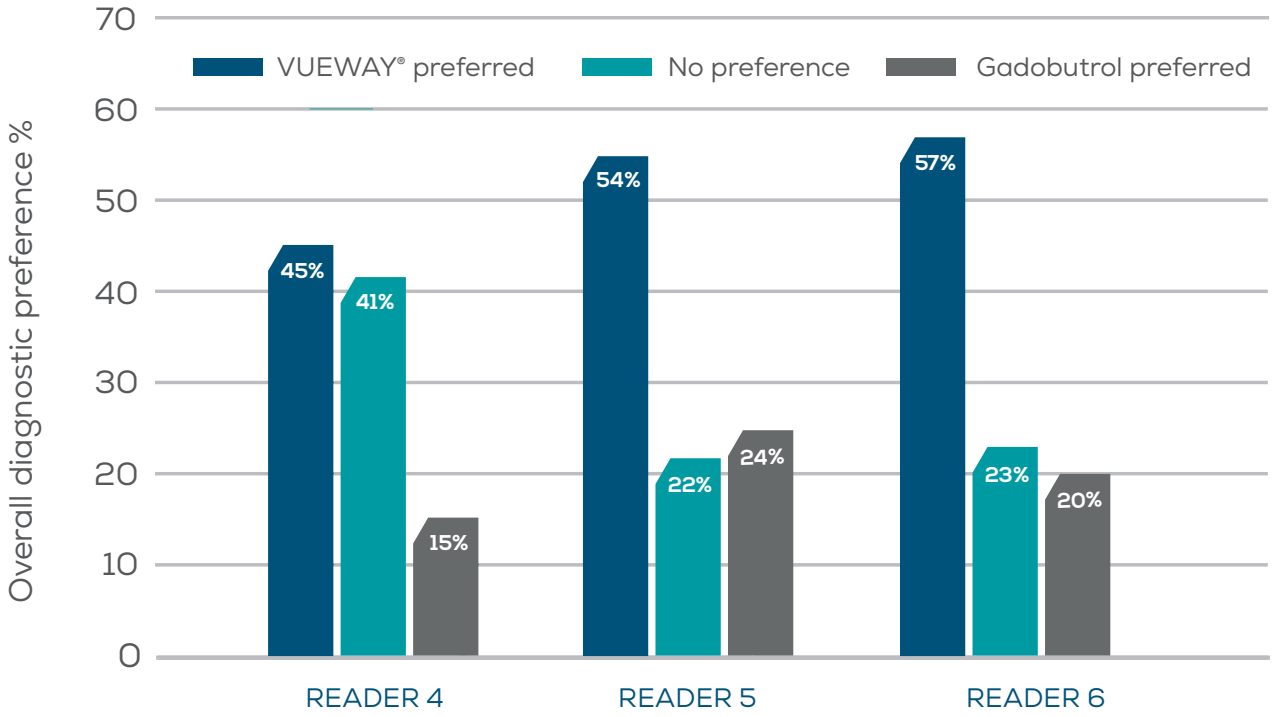
- LOW-FIELD MAGNETS
- ABBREVIATED EXAMS
- HIGH-FIELD MAGNETS

*From Phase III PICTURE Clinical Trial of MRI in the CNS: Study GDX-44-010. Data on file.
†Presented studies in their primary outcomes proved non-inferiority of VUEWAY® (0.05 mmol/kg) in half Gd dose compared to gadobutrol (0.1 mmol/kg) in full Gd dose.
CNS, central nervous system; GBCA, gadolinium-based contrast agent; MR, magnetic resonance; MRI, magnetic resonance imaging; SE, spin echo; T, tesla.

RELAXIVITY OF ALL GBCAs TODAY[1]

VUEWAY® demonstrates **2-to-3-fold higher relaxivity** than all current **macrocyclic GBCAs** at all relevant MRI field strengths.*[4]

Thanks to VUEWAY®'s high potency, **diagnostic results can be achieved at a reduced Gd dose across a broad spectrum of field strengths, MRI machines** and examinations.[1-3]



Adapted from Loevner et al. Invest Radiol. 2022

ALL SCANNER TYPES

CANCER SCREENING

ONGOING MONITORING

Primary outcomes of the Phase III CNS showed non-inferiority of gadopiclenol at 0.05 mmol/kg to gadobutrol at 0.1 mmol/kg for MRI of the CNS.[2] **Key secondary outcomes of the Phase III CNS study included overall diagnostic preference**. These data are presented as bar graphs above. In this side-by-side comparison of paired images of 241 patients from MRI with gadopiclenol (VUEWAY®) at a Gd dose of 0.05 mmol/kg vs. gadobutrol (Gadovist®) at double the dose (0.1 mmol/kg), the preference for images with gadopiclenol was statistically significant for all 3 readers ($P<0.001$).[†1,2]

*Together with Elucirem™ (gadopiclenol).
†Overall diagnostic preference was evaluated in a global matched pairs fashion (a reader evaluates paired images with gadopiclenol and gadobutrol from the same patient side by side).[1,2]
CNS, central nervous system; GBCA, gadolinium-based contrast agent; Gd, gadolinium; MRI, magnetic resonance imaging.

MAKING A DIFFERENCE IN Gd EXPOSURE[10]

VUEWAY® IS A STABLE LOWER-DOSE GBCA

VUEWAY® offers a **similar safety profile** in the general population vs. **sensitive patients** such as children, the **elderly**,* the **renally impaired** patients,† and those with **liver impairment**.‡[1,11] A lower Gd dose for similar visualization can help **to minimize Gd exposure per MRI procedure** in vulnerable patient populations and reduce the overall lifetime dose for those likely to undergo multiple examinations.[3,7,9]

Pediatrics (2-17 years of age).

Patients with impaired renal function:

- No dosage adjustment recommended for patients with renal impairment.†
- In patients with mild or moderate renal impairment, more than 90% of the administered dose was recovered in the urine within 48 hours.†[1]

Patients requiring multiple lifetime doses.[3]

Persons requiring cancer screening or surveillance with MR:

- e.g. breast cancer screening in high-risk women.[3]
- e.g. prostate cancer surveillance.

VUEWAY® adheres to recommendations to minimize gadolinium exposure (ALARA principle).[12,13]

"For all Gd contrast agents … 'As Low As Reasonably Achievable' (ALARA) principles should be used and that the exposure to all GdCAs should be minimised, either by reducing the dose or using alternative diagnostic methods, if possible."[14]

Statement by the expert group during EMA gadolinium deposition evaluation process in 2017

*Caution should be exercised in elderly patients. Refer to sections 4.2, 4.4 and 5.2 of the VUEWAY® (gadopiclenol) SmPC.[1]
†The elimination half-life (t1/2) is prolonged in subjects with renal impairment, increasing with the degree of renal impairment. There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of some gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR<30 mL/min/1.73 m^2). Refer to sections 4.2 and 5.2 of the VUEWAY® (gadopiclenol) SmPC.[1]
‡Caution is recommended for patients with hepatic impairment. Refer to section 4.2 of the VUEWAY® (gadopiclenol) SmPC.[1]
EMA, European Medicines Agency; GBCA, gadolinium-based contrast agent; Gd, gadolinium; GdCA, gadolinium-containing contrast agent; MR, magnetic resonance; MRI, magnetic resonance imaging; SmPC, Summary of Product Characteristics.

HELPING TO MEET PATIENT MEDICAL NEEDS

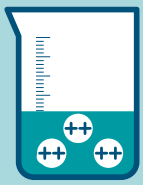
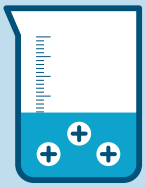
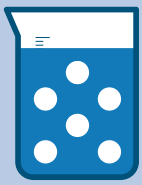
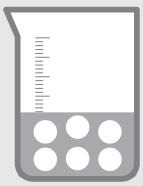
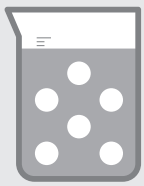
The uniquely **high relaxivity** of gadopiclenol[4] can **help radiologists apply the ALARA principle to contrast-enhanced MRI**.[12,15]

HIGH RELAXIVITY VS. STANDARD RELAXIVITY[16-19]

Relaxivity: Gadopiclenol offers the highest relaxivity today vs. the standard relaxivity of other macrocyclic GBCAs.*†‡[1]

Dose: VUEWAY® allows comparable contrast enhancement at half the Gd dose of another macrocyclic GBCA at 0.1 mmol/kg (vs. Gadovist®).[2,3]

Concentration: A higher Gd concentration of the contrast agent solution does not provide any discernible benefit, neither in static nor dynamic imaging. For clinical diagnosis, of more importance than concentration is the relaxivity of the agent.[20,21]

CONTRAST AGENT	Gadopiclenol (VUEWAY®+ Elucirem™)	Gadobenate dimeglumine (MULTIHANCE®)	Gadoteridol (PROHANCE®)	Gadobutrol (Gadovist® + Pixxoscan®)	Gadoteric acid (Dotarem®+ Clariscan™)
RELAXIVITY	HIGHEST‡‡	HIGH†	STANDARD	STANDARD*	STANDARD*
DOSE (mmol/kg)	0.05	0.05§	0.1	0.1‖	0.1
VOLUME (mL/kg)	0.1	0.1	0.2	0.1	0.2
CONCENTRATION	STANDARD	STANDARD	STANDARD	DOUBLE	STANDARD
					

*Standard relaxivity: an r1 of 1.9-6.2 L·mmol^{-1}·s^{-1} , i.e. similar (+/- 50%) to the reference value of Magnevist® at 1.5T (4.1 L·mmol^{-1}·s^{-1}).[16-19]
†High-Relaxivity GBCAs: an r1 of 6.3-8.2 L·mmol^{-1}·s^{-1} or higher than the reference value of Magnevist® at 1.5T. [16-19]
‡Highest relaxity GBCA: a significantly higher r1 (>100%) than the reference value of Magnevist® at 1.5T, i.e. > 8.2 L·mmol^{-1}·s^{-1}.[1,16-19]
§MultiHance® has been indicated at an approved dose of 0.05 mmol/kg for liver scans in the EU since 2017.[22]
‖A dose of 0.075 mmol gadobutrol per kg body weight may be administered at minimum for imaging of the CNS.[23]
ALARA, as low as reasonably possible; CNS, central nervous system; EU, European Union; GBCA, gadolinium-based contrast agent; Gd, gadolinium; MRI, magnetic resonance imaging.

EFFECTIVE ENHANCEMENT AT HALF THE GD DOSE*

DIAGNOSTIC EFFICACY AT A REDUCED GD DOSE TH

Preclinical studies confirmed the extremely high relaxivity and good stability of gadopiclenol,[4] whereas a Phase IIb dose-finding study indicated VUEWAY®'s clinical effectiveness at a reduced Gd dose in MRI of the CNS vs. the high-relaxivity agent MultiHance® (gadobenate dimeglumine) in patient case studies from this trial.[†12]
Subsequent to positive safety data from Phases I & II,[12,24,25] over 500 adult patients were included in two pivotal Phase III studies to undergo MRI with both VUEWAY® (gadopiclenol) at 0.05 mmol/kg and Gadovist® (gadobutrol) at 0.1 mmol/kg.[2,3]

In the CNS study (PICTURE), primary endpoints were met:

- Demonstrating that **VUEWAY®** provides non-inferior, or **comparable contrast enhancement at half the gadolinium dose (0.05 mmol/kg) vs. gadobutrol in qualitative assessments** by experienced readers for all lesion visualization criteria.[1,2]
  - Selected **secondary endpoints** were also met, inter alia demonstrating **a significantly higher degree of contrast enhancement for gadopiclenol vs. gadobutrol** for **quantitative measurements (ROI) and overall diagnostic preference (all readers)**.[‡2]

In the Body study (PROMISE), primary endpoints were met:

- Superiority of VUEWAY® at 0.05 mmol/kg to unenhanced MRI **AND** non-inferiority of VUEWAY® at 0.05 mmol/kg to gadobutrol at 0.1 mmol/kg was demonstrated for all lesion visualization endpoints.[1,3]

*Half the gadolinium dose compared to other macrocyclic GBCAs at a Gd dose of 0.1 mmol/kg in approved indications.
†Phase IIb study to determine a safe and effective dose of gadopiclenol: international, multicenter, double-blind, randomized, controlled, parallel dose groups, and crossover study.[12]
‡Contrast-to-noise ratio, enhancement percentage and lesion-to-background ratio were calculated for each patient (mean for up to 3 most representative lesions) by 3 offsite independent blinded readers. Overall diagnostic preference was evaluated in a global matched pairs fashion (a reader evaluates paired images with gadopiclenol and gadobutrol from the same patient side by side).[2]
CNS, central nervous system; Gd, gadolinium; MRI, magnetic resonance imaging.

ANKS TO VUEWAY®'S UNPARALLELED POTENCY

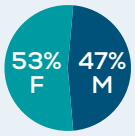
Phase III CNS study: Intra-individual, crossover comparison vs. gadobutrol[1,2]

256 PATIENTS

Patients with known or highly suspected CNS lesions

AGE:
MEAN: 57 years
RANGE: 18-84 years

SEX:



0.05 mmol/kg VUEWAY® injection

vs.

0.1 mmol/kg Gadovist®

ENDPOINTS

Endpoints: Primary Endpoints:
Superiority of VUEWAY® at 0.05 mmol/kg to unenhanced MRI across lesion visualization criteria

Non-inferiority of VUEWAY® injection at 0.05 mmol/kg to gadobutrol at 0.1 mmol/kg for all lesion visualization criteria in qualitative assessments by readers

Selected Secondary Endpoints:
Were also met, i.e. a significantly higher contrast enhncement in quantitative ROI measurements for VUEWAY® vs. Gadovist®

The PICTURE trial results: Non-inferior/comparable contrast enhancement for VUEWAY® in the CNS at half the Gd dose of Gadovist® at 0.1 mmol/kg

Phase III Body study: Intra-individual, crossover comparison vs. gadobutrol[1,3]

304 PATIENTS

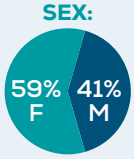
Presenting with known or suspected enhancing focal lesion(s) in at least one body region

For MRI of the:

- Head and neck, thorax (incl. breast)
- Abdomen
- Pelvis
- Musculoskeletal

AGE:
MEAN: 57 years
RANGE: 21-86 years

SEX:



0.05 mmol/kg VUEWAY® injection

vs.

0.1 mmol/kg Gadovist®

PRIMARY ENDPOINTS

Superiority of VUEWAY® at 0.05 mmol/kg to unenhanced MRI across lesion visualization criteria

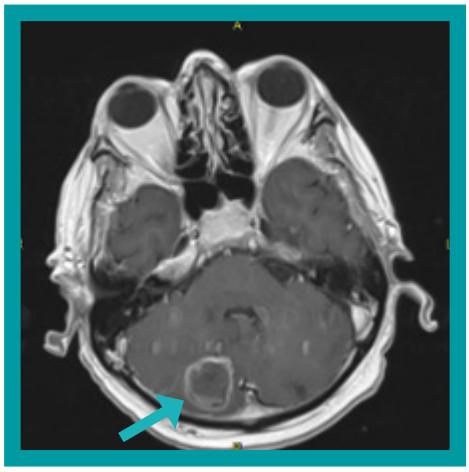
Non-inferiority of VUEWAY® at 0.05 mmol/kg to gadobutrol at 0.1 mmol/kg across lesion visualization criteria

The PROMISE trial results: Comparable contrast enhancement for VUEWAY® in body areas at half the Gd dose of Gadovist® at 0.1 mmol/kg

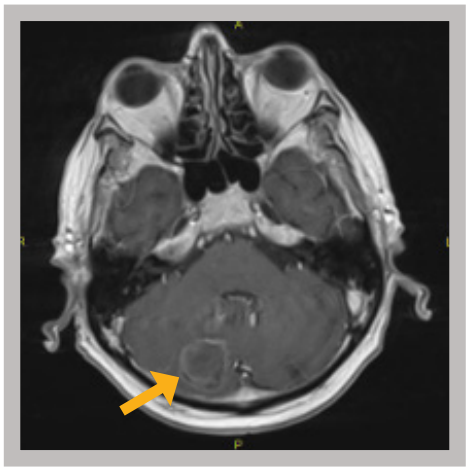
CNS, central nervous system; Gd, gadolinium; MRI, magnetic resonance imaging.

VUEWAY® - ENHANCED MRI OF THE CNS AND BODY AT

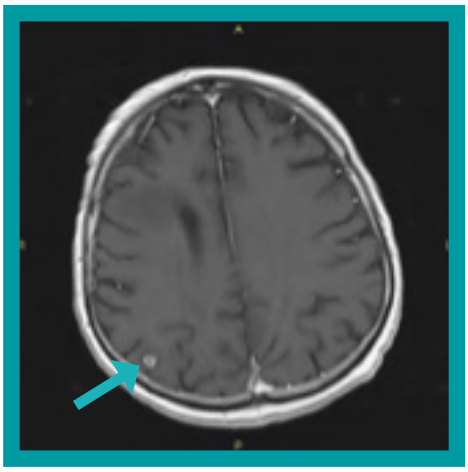
MRI of the CNS: Clinical case of an 80-year-old patient with cerebellar metastasis‡



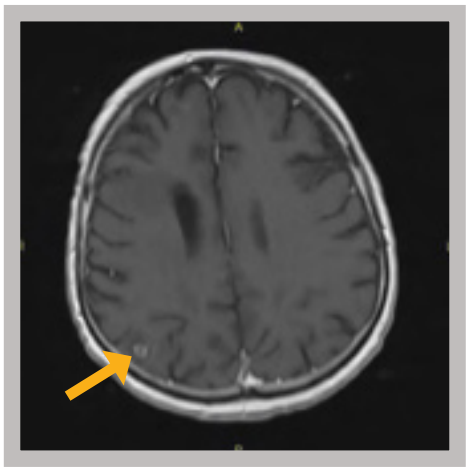
Gadopiclenol 0.05 mmol/kg (T1 SE)



Gadobutrol 0.1 mmol/kg (T1 SE)



Gadopiclenol 0.05 mmol/kg (T1 SE)

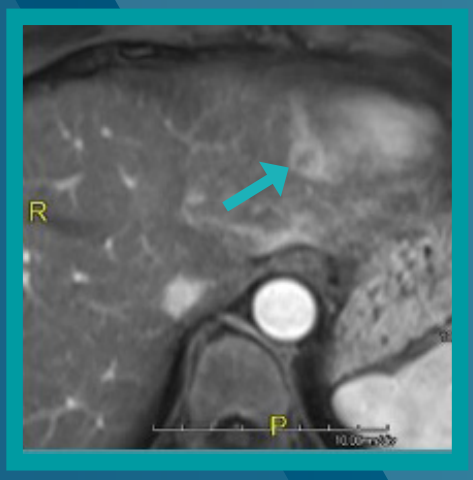


Gadobutrol 0.1 mmol/kg (T1 SE)

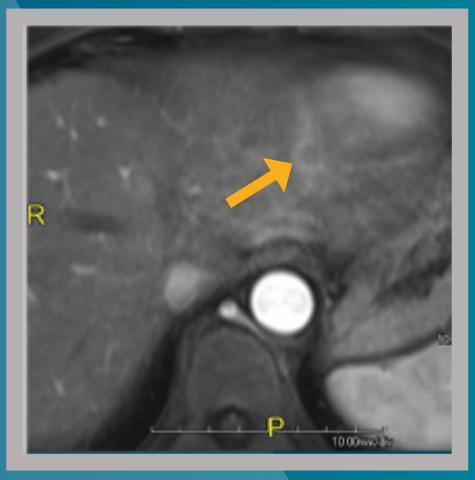
*All images shown are representative images from referenced studies. Individual results may vary.
†Presented studies in their primary outcomes proved non-inferiority of VUEWAY® (0.05 mmol/kg) in half Gd dose compared to gadobutrol (0.1 mmol/kg) in full Gd dose.
‡From Phase III PICTURE Clinical Trial of MRI in the CNS: Study GDX-44-010. Data on file.
CNS, central nervous system; MRI, magnetic resonance imaging; SE, spin echo; T, tesla.

0.05 MMOL/KG VS. GADOBUTROL AT 0.1 MMOL/KG*†

MRI of the Body: Clinical case of a 68-year-old female patient with liver metastasis from rectal cancer (enhancing lesion in left liver lobe, arterial phase)‡

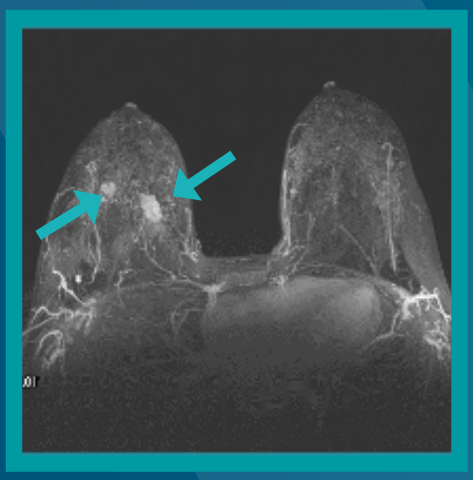


Gadopiclenol 0.05 mmol/kg

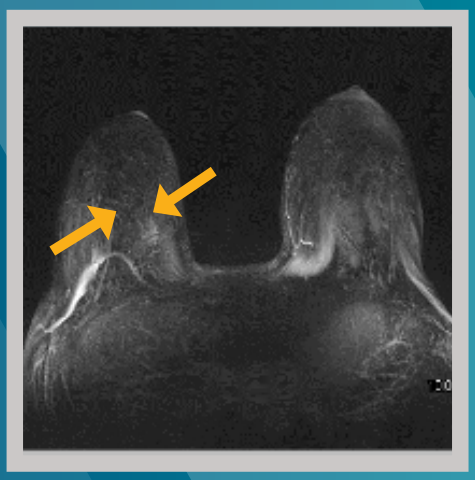


Gadobutrol 0.1 mmol/kg

MRI of the Body: Clinical case of a 44-year-old woman with right breast cancer and breast implants (1st dynamic MIP)‡



Gadopiclenol 0.05 mmol/kg



Gadobutrol 0.1 mmol/kg

CONTRAST ENHANCEMENT

*All images shown are representative images from referenced studies. Individual results may vary.
†Presented studies in their primary outcomes proved non-inferiority of VUEWAY® (0.05 mmol/kg) in half Gd dose compared to gadobutro (0.1 mmol/kg) in full Gd dose.
‡From Phase III PROMISE Clinical Trial of MRI in the Body: Study GDX-44-011. Data on file.
Gd, gadolinium; MIP, maximum intensity projection; MRI, magnetic resonance imaging.

VUEWAY® OFFERS A GOOD SAFETY PROFILE

In clinical trials VUEWAY® (gadopiclenol) has shown a good safety profile in adults and children (2-17 yrs).[1-3,11]

- Clinical trials included a total of 1047 subjects exposed to gadopiclenol.[1]
  The safety of VUEWAY® was evaluated in multiple clinical studies, including:
  - A pharmacokinetics study of subjects with impaired renal function.[2,4]
  - A Phase IIb clinical study in pediatric patients.[11]
  - 2 pivotal Phase III studies vs. gadobutrol in the CNS and Body.[2,3]
- VUEWAY® at a Gd dose of 0.05 mmol/kg is well tolerated in children aged 2 to 17 years.[1,11]
- The Phase III CNS and Body studies in adults showed that the type and severity of AEs between VUEWAY® and Gadovist® were similar between the two GBCAs.[2,3]
  - In the CNS study, the AE rate was slightly lower following the administration of VUEWAY® (4.9%) versus Gadovist® (6.9%).[2]

EU SKUs available

3 mL
7.5 mL
10 mL
15 mL
30 mL
50 mL
100 mL

AE, adverse event; CNS, central nervous system; ; EU, European Union; GBCA, gadolinium-based contrast agent; Gd, gadolinium; MRI, magnetic resonance imaging; SKU, Stock Keeping Unit.

Phase IIb exploratory study in pediatric patients: prospective, multicenter, open-label design[1,11]

80 PATIENTS

Pediatric patients scheduled to undergo a clinically indicated MRI exam for:

60 patients
With known or suspected lesions of the CNS

20 patients
With known or suspected lesions of body organs (head & neck, thorax, abdomen or musculoskeletal system)

3 sequential groups by age

- 12-17 years
- 7-11 years
- 2-6 years

Phase IIb study results in pediatric patients:

VUEWAY ® at 0.05 mmol/kg seems to have a good safety profile in these patients and could improve lesion detection and visualization, therefore providing better diagnostic confidence.[11]

- Overall in the CNS cohort, lesions were identified in 32 patients (53.3%) with pre-contrast images and in 34 patients (56.7%) with paired images. Overall in the Body cohort, 12 lesions were detected in 11 patients (55.0%) both with pre-contrast and paired images.

- No serious AEs or AEs of severe intensity; only 2 non-serious AEs related to gadopiclenol.*[11]

*Among the treatment-emergent adverse events (TEAEs), 1 event in 1 patient (1.25%) from the CNS cohort was considered related to gadopiclenol.[1]
AE, adverse event; CNS, central nervous system; MRI, magnetic resonance imaging.

MAKING A DIFFERENCE THROUGH PARTNERSHIP

HALF THE DOSE* IS ONLY HALF THE STORY – BRA

An experienced partner in diagnostic imaging committed to quality contrast agents and relaxivity research, Bracco prides itself on providing continuing education and technological support.
Bracco consults with customers to decrease imaging costs and increase revenue and product value.

The Bracco Group operates in a variety of pharmaceutical business areas, with a central focus on diagnostic imaging and contrast agents.
For more than 95 years, Bracco has been an innovator in radiology, dedicated to developing products that help advance the standard of care.

*Half the gadolinium dose compared to other macrocyclic GBCAs at a Gd dose of 0.1 mmol/kg in approved indications.
GBCA, gadolinium-based contrast agent; Gd, gadolinium.

CCO'S PEERLESS SUPPORT IS THE UNTOLD STORY

- The Bracco Group is committed to environmental sustainability through the principles of circular economy and clean chemistry.[26]

- A GBCA at the dose of 0.05 mmol/kg could help reduce the release of anthropogenic gadolinium into the environment via hospital wastewater.[2,27]

SEE THE DIFFERENCE.
MAKE A DIFFERENCE.

Vueway®
(gadopiclenol) injection

GL-VW-2300016

ABBREVIATED SUMMARY OF

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT - Vueway 0.5 mmol/mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION - 1 mL of solution contains 485.1 mg gadopiclenol (equivalent to 0.5 mmol of gadopiclenol and to 78.6 mg of gadolinium). For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM - Solution for injection. Clear, colourless to pale yellow solution.

4. CLINICAL PARTICULARS - **4.1 Therapeutic indications** - This medicinal product is for diagnostic use only. Vueway 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. **4.2 Posology and method of administration** - This medicinal product should only be administered by trained healthcare professionals with technical expertise in performing gadolinium enhanced MRI. Posology - The recommended dose of Vueway is 0.1 mL/kg body weight (BW) (equivalent to 0.05 mmol/kg BW) to provide diagnostically adequate contrast for all indications. The dose should be calculated based on the patient's BW and should not exceed the recommended dose per kilogram of BW detailed in this section. Elderly - No dose adjustment is necessary. Caution should be exercised in elderly patients (see section 4.4 and 5.2). Renal impairment - No dose adjustment is necessary for patients with any level of renal impairment. Gadopiclenol should only be used in patients with severe renal impairment (GFR < 30 mL/min/1.73 m2) and in patients in the perioperative liver transplantation period after careful risk/benefit assessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI (see section 4.4). If it is necessary to use gadopiclenol, the dose should not exceed 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW). More than one dose should not be used during a scan. Because of the lack of information on repeated administration, gadopiclenol injections should not be repeated unless the interval between injections is at least 7 days. Hepatic impairment - No dose adjustment is considered necessary for patients with hepatic impairment. Caution is recommended, especially in the case of perioperative liver transplantation period (see above "renal impairment"). Paediatric population (2 years and older) - The recommended and maximum dose of Vueway is 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW) for all indications. More than one dose should not be used during a scan. The safety and efficacy of Vueway in children less than 2 years has not yet been established. No data are available. Method of administration - The medicinal product is for intravenous use only. The recommended dose is administered intravenously as a bolus injection at approximatively 2 mL/sec followed by a flush of sodium chloride 9 mg/ml (0.9%), solution for injection via manual injection or power injector. Intravenous administration of contrast agent should, if possible, be done with the patient lying down. Since experience shows that most undesirable effects occur within minutes after administration, the patient should be kept under observation during and following administration for at least half an hour (see section 4.4). For instructions on the medicinal product before administration, see section 6.6. Paediatric population - In children, Vueway in vials with a single use syringe of a volume adapted to the amount to be injected should be used in order to have better precision of the injected volume.Image acquisition - Contrast-enhanced MRI can start after the injection depending on the pulse sequences used and the protocol for the examination. Optimal signal enhancement is generally observed during arterial phase and within a period of about 15 minutes after injection. Longitudinal relaxation times (T1)-weighted sequences are particularly suitable for contrast-enhanced examinations. **4.3 Contraindications** - Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. **4.4 Special warnings and precautions for use** - The usual precautions for MRI examination should be applied, such as exclusion of patients with pacemakers, ferromagnetic vascular clips, infusion pumps, nerve stimulators, cochlear implants, or suspected intracorporal metallic foreign bodies, particularly in the eye. MRI images produced with this medicinal product should only be analysed and interpreted by the healthcare professionals trained in interpretation of gadolinium enhanced MRI. There are no or limited clinical data investigating the performance of gadopiclenol for CNS imaging in patients with inflammatory, infectious, autoimmune or demyelinating disorders (such as multiple sclerosis), patients with acute or chronic infarct, or patients with intramedullary spine lesions.There are also no or limited clinical data investigating the performance of gadopiclenol for body imaging in patients with inflammatory, infectious and autoimmune conditions, including acute/chronic pancreatitis, inflammatory bowel disease, inflammatory diseases of head and neck region and endometriosis. Potential for hypersensitivity or anaphylactic reactions - As with other gadolinium-containing contrast agents, hypersensitivity reactions can occur, including life-threatening. Hypersensitivity reactions may be either allergic (described as anaphylactic reactions when serious) or non-allergic. They can occur either immediately (less than 60 minutes) after injection or delayed (up to 7 days). Anaphylactic reactions occur immediately and can be fatal. They are independent of the dose, can occur after even the first dose of the product, and are often unpredictable; During the examination, supervision by a physician is necessary. If hypersensitivity reactions occur, administration of the contrast agent must be discontinued immediately and – if necessary – a specific therapy must be instituted. A venous access should thus be kept during the entire examination. To permit immediate emergency countermeasures, appropriate drugs (e.g. epinephrine and antihistamines), an endotracheal tube and a respirator should be ready at hand; The risk of hypersensitivity reaction may be higher in patients with a history of previous reaction to gadolinium-containing contrast agents, bronchial asthma or allergy. Renal impairment and nephrogenic systemic fibrosis (NSF) - Prior to administration of gadopiclenol, it is recommended that all patients are screened for renal dysfunction by obtaining laboratory tests. There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of some gadolinium- containing contrast agents in patients with acute or chronic severe renal impairment (GFR < 30 mL/min/1.73 m2). Patients undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. As there is a possibility that NSF may occur with gadopiclenol, it should only be used in patients with severe renal impairment and in patients in the perioperative liver transplantation period after careful benefit/risk assessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI. Haemodialysis shortly after gadopiclenol administration may be useful at removing it from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis. Elderly - As the renal clearance of gadopiclenol may be impaired in the elderly, it is particularly important to screen patients aged 65 years and older for renal dysfunction. Caution should be exercised in patients with renal impairment (see section 4.2). Seizures - As with other gadolinium-containing contrast agents, special caution is necessary in patients with a lowered threshold for seizures. All equipment and drugs necessary to counter convulsions occurring during the MRI examination must be made ready for use beforehand. Extravasation - Caution during administration is necessary to avoid any extravasation. In case of extravasation, the injection must be stopped immediately. In case of local reactions, evaluation and treatment should be carried out as necessary. Cardiovascular disease - In patients with severe cardiovascular disease gadopiclenol should only be administrated after careful risk benefit assessment because no data are available so far. Excipients - This medicinal product contains less than 1 mmol sodium (23 mg) per 15 mL, that is to say essentially 'sodium- free'. **4.5 Interaction with other medicinal products and other forms of interaction** - No interaction studies have been performed.

PRODUCT CHARACTERISTICS*[1]

oncomitant medicinal products to be taken into account - Beta-blockers, vasoactive substances, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists decrease the efficacy of the mechanisms of cardiovascular compensation for blood pressure disorders. The physician must obtain information before injection of gadopiclenol about the concomitant intake of those medicinal products. **4.6 Fertility, pregnancy and lactation** - Pregnancy - There are no data from the use of gadopiclenol in pregnant women. Animal studies showed little placental transfer and do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Vueway should not be used during pregnancy unless the clinical condition of the woman requires use of gadopiclenol. Breast-feeding - Gadolinium-containing contrast agents are excreted into breast milk in very small amounts. At clinical doses, no effects on the infant are anticipated due to the small amount excreted in milk and poor absorption from the gut. Continuing or discontinuing breast feeding for a period of 24 hours after administration of Vueway, should be at the discretion of the doctor and breast-feeding mother. Fertility - Animals studies do not indicate impairment of fertility (see section 5.3). **4.7 Effects on ability to drive and use machines** - Vueway has no or negligible influence on the ability to drive and use machines. **4.8 Undesirable effects** - Summary of the safety profile - The most frequent adverse reactions were injection site pain, headache, nausea, injection site coldness, fatigue and diarrhoea. Description of selected adverse reactions - Hypersensitivity: Immediate reactions include one or more effects, which appear simultaneously or sequentially, which are most often cutaneous, respiratory and/or vascular reactions. Each sign may be a warning sign of a starting shock and go very rarely to death. Nephrogenic systemic fibrosis (NSF) - Isolated cases of NSF have been reported with other gadolinium- containing contrast agents (see section 4.4). Paediatric population (2 years and older) - A total of 80 paediatric patients aged 2 years and older were included in the clinical trial. As compared to adults, the safety profile of gadopiclenol in this population did not show any specific safety concern. A total of 31 Treatment Emergent Adverse Events (TEAEs) occurred during and/or after gadopiclenol administration for 14 patients (17.5%). Twelve TEAEs were reported in the CNS cohort and 2 in the Body cohort. Among these TEAEs, 1 event in 1 patient (1.25%) from the CNS cohort was considered related to gadopiclenol. Reporting of suspected adverse reactions - Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system **4.9 Overdose** - The maximum daily single dose tested in humans was 0.6 mL/kg BW (equivalent to 0.3 mmol/kg BW), which corresponds to 6 times the recommended dose. No signs of intoxication from an overdose have so far been reported. Gadopiclenol can be removed by haemodialysis. However, there is no evidence that haemodialysis is suitable for prevention of nephrogenic systemic fibrosis (NSF).

5. PHARMACOLOGICAL PROPERTIES – 5.1 Pharmacodynamic properties - Pharmacotherapeutic group: paramagnetic contrast media, ATC code: V08CA12. Gadopiclenol is a paramagnetic agent for Magnetic Resonance Imaging (MRI).Mechanism of action - The contrast-enhancing effect is mediated by gadopiclenol which is a macrocyclic non-ionic complex of gadolinium, the active moiety which enhances the relaxation rates of water protons in its vicinity in the body, leading to an increase in signal intensity (brightness) of tissues. When placed in a magnetic field (patient in MRI machine), gadopiclenol shortens the T1 and T2 relaxation times in targeted tissues. The extent to which a contrast agent can affect the relaxation rate of tissue water (1/T1 or 1/T2) is termed relaxivity (r1 or r2). Gadopiclenol presents a high relaxivity in water (see Table 3) due to its chemical structure, because it can exchange two water molecules, which are linked to the gadolinium to complete its coordination number in addition to the four nitrogens and the three oxygens of the carboxylate functions of the gadopiclenol chelate. This explains that, gadopiclenol given at half dose of gadolinium compared to other non-specific gadolinium-containing contrast agents, may provide the same contrast enhancement.

Clinical efficacy and safety - Two pivotal studies included adult patients undergoing MRI with gadopiclenol at 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW) and MRI with gadobutrol at 0.1 mL/kg BW (equivalent to 0.1 mmol/kg BW). One study (Study 1; PICTURE) included 256 patients presenting with known or highly suspected CNS lesions with focal areas of disrupted BBB (e.g. primary and secondary tumors). The majority of patients (72%) presented with brain tumors, 20% had brain or spine metastases and 8% presented with other pathologies. The other study (Study 2; PROMISE) included 304 patients with known or suspected abnormalities or lesions in other body regions (8% in head and neck, 28% in thorax, 35% in abdomen, 22% in pelvis and 7% in musculo-skeletal system) both based on results of a previous imaging procedure such as CT or MRI. The most frequent pathologies were breast tumors (23%) and liver tumors (21%). The primary endpoint was the evaluation of lesion visualization, based on 3 co-criteria (border delineation, internal morphology and degree of contrast enhancement) by three independent blinded readers, using a 4-point scale. The mean of scores for each of the 3 lesion visualization co-criteria was calculated as the sum of scores for up to 3 most representative lesions divided by the number of lesions. Both studies demonstrated: Superiority of the combined unenhanced/contrast-enhanced MRI (Paired) with gadopiclenol over unenhanced MRI (Pre) for all 3 lesion visualization criteria ($p < 0.0001$ for all three readers, paired t-tests on matching lesions); Non-inferiority of gadopiclenol at 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW) to gadobutrol at 0.1 mL/kg BW (equivalent to 0.1 mmol/kg BW) ($p < 0.0001$ for all three readers, paired t-tests on matching lesions). The pooled analysis of the primary outcome over the three readers, and for each lesion visualization criterion also demonstrated the non-inferiority of gadopiclenol at 0.05 mmol/kg to gadobutrol at 0.1 mmol/kg in both studies. The secondary criteria evaluated included quantitative evaluations (Contrast to Noise Ratio, Lesion to Brain (background) Ratio and percentage of lesion enhancement), overall diagnostic preference and impact on patient management.In Study 1, Lesion to Brain Ratio, and percentage of lesion enhancement were statistically significantly higher with gadopiclenol at 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW) compared to gadobutrol at 0.1 mL/kg BW (equivalent to 0.1 mmol/kg BW) for all 3 readers. Contrast to Noise Ratio was statistically significantly higher for 2 readers. In Study 2, percentage of lesion enhancement was significantly higher for with gadopiclenol at 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW) compared to gadobutrol at 0.1 mL/kg BW (equivalent to 0.1 mmol/kg BW) and no statistically significant difference was observed for Lesion to Background Ratio.Lesion visualisation parameters (e.g., co-primary endpoints and quantitative assessments, such as, Contrast to Noise Ratio, Lesion to Brain (background) Ratio and percentage of lesion enhancement) were assessed in all the lesions identified by the blinded readers, independently of their size, in more than 86% of patients in CNS study and in more than 81% of patients in Body study, who had no more than 3 lesions. In the remaining patients with more than 3 lesions visible, a subset of 3 most representative lesions were selected for assessment of the co-primary endpoints. Therefore, in those patients, the additional lesions were not assessed. Consequently, the technical capability of lesion visualisation for both contrast agents cannot be extrapolated for those non-selected lesions. The overall diagnostic preference was assessed in a global matched-pairs fashion (reading of images from both MRI assessed side by side) by three additional blinded readers in each study. The results are summarized in the Table 5 below. In Study 1, in majority, the readers expressed a preference for images acquired with gadopiclenol. In Study 2, in majority, the readers expressed no diagnostic preference between images acquired with gadopiclenol and with gadobutrol. Paediatric population - One exploratory study (Study 3) with a single dose of gadopiclenol (0.1 mL/kg BW equivalent to 0.05 mmol/kg BW) included 80 paediatric patients aged 2 to 17 years old with 60 patients undergoing CNS MRI and 20 patients undergoing Body MRI. Diagnostic efficacy was evaluated and there was no difference among the paediatric age groups. The European Medicines Agency has deferred the obligation to submit the results of studies with Vueway in one or more subsets of the paediatric population in the detection and visualisation of disorders or lesions with

suspected abnormal vascularity in various body regions for diagnostic purposes. (see section 4.2 for information on paediatric use). **5.2 Pharmacokinetic properties** – Absorption - The absolute bioavailability of gadopiclenol (in humans) is 100%, as it is only administered via the intravenous route. After an intravenous dose of 0.1 to 0.2 mL/kg BW (equivalent respectively to 0.05 and 0.1 mmol/kg BW), the Cmax was 525 ± 70 mcg/mL and 992 ± 233 mcg/mL, respectively. The Cmax increased 1.1-fold, 1.1-fold and 1.4-fold and the AUCinf increased 1.5-fold, 2.5-fold and 8.7- fold in patients with mild, moderate and severe renal impairment, respectively after a dose of 0.2 mL/kg BW (equivalent to 0.1 mmol/kg BW). In addition, the increase in Cmax and AUCinf is expected to be similar with a dose of 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW) based on the results of population pharmacokinetic simulations. Distribution - After intravenous administration gadopiclenol is rapidly distributed in the extracellular fluids. After a dose of 0.1 ml/kg BW (equivalent to 0.05 mmol/kg BW) the distribution volume Vd was 12.9 ± 1.7 L.The in vitro binding of 153Gd-gadopiclenol to human plasma proteins is negligible and independent of the gadopiclenol concentration, as 153Gd-gadopiclenol bound 0.0–1.8% to human plasma proteins and 0.0-0.1% to human red blood cells. Biotransformation - Gadopiclenol is not metabolised. The lack of metabolism is confirmed by in vitro data using pooled human liver microsomes incubated with 153Gd-gadopiclenol. After 120 minutes ≥ 95% of the 153Gd-gadopiclenol remained in unchanged form. The results were similar when heat inactivated pooled human liver microsomes (negative controls) were incubated with 153Gd-gadopiclenol, indicating that 153Gd-gadopiclenol is not metabolised. Elimination - Gadopiclenol is eliminated rapidly in unchanged form through the kidneys by glomerular filtration. After a dose of 0.1 to 0.2 mL/kg BW (equivalent respectively to 0.05 and 0.1 mmol/kg BW), the mean plasma elimination half-life (t1/2) in healthy volunteers with a normal renal function was1.5 and 1.7 hour, respectively, and the clearance was 100 ± 10 mL/min and 96 ± 12 mL/min, respectively. Urinary excretion is the major route of elimination of gadopiclenol, with approximately 98 % of the dose excreted in urine after 48 hours regardless of the dose administered. Linearity/non-linearity - The pharmacokinetic profile of gadopiclenol is linear in the studied dose range (0.05 to 0.6 mL/kg BW equivalent to 0.025 to 0.3 mmol/kg BW), without difference between males and females. Mean maximum concentration (Cmax) and Area Under the Curve (AUCinf) increased proportionally to the dose. Paediatric population - One Phase II study (Study 3) with a single dose of gadopiclenol at 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW) was conducted and included 60 paediatric patients aged 2 to 17 years old undergoing CNS MRI. Individual parameters predicted from the population pharmacokinetic model and normalised by BW were similar between adults and children. The terminal half-life was 1.77 hour for age group 12-17 years old, 1.48 hour for age group 7-11 years old and 1.29 hour for age group 2-6 years old. The median clearance ranged from 0.08 l/h/kg (for age group 12-17 years old) to 0.12 l/h/kg (for age group 2-11 years old). The pharmacokinetics of gadopiclenol in children aged 2 to 17 years are comparable to the pharmacokinetics in adults. Renal impairment and dialysability - The elimination half-life (t1/2) is prolonged in subjects with renal impairment, increasing with the degree of renal impairment. In patients with mild (60 ≤ eGFR < 90 mL/min), moderate (30 ≤ eGFR < 60 mL/min) and severe (15 ≤ eGFR < 30 mL/min) renal impairment, the mean t1/2 was 3.3, 3.8 and 11.7 hours, respectively and the clearance was 1.02, 0.62 and 0.17 mL/min/kg, respectively. The Cmax increased 1.1-fold, 1.1-fold and 1.4-fold and the AUCinf increased 1.5-fold, 2.5-fold and 8.7-fold in patients with mild, moderate and severe renal impairment, respectively after a dose of 0.2 mL/kg BW (equivalent to 0.1 mmol/kg BW). In addition, the increase in Cmax and AUCinf is expected to be similar with a dose of 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW) based on the results of population pharmacokinetic simulations. Urinary excretion is delayed with the progression of renal impairment level. In patients with mild or moderate renal impairment, more than 90 % of the administered dose was recovered in the urine within 48 hours. In patients with severely impaired renal function about 84 % of the administered dose was recovered in the urine within 5 days. In patients with End Stage Renal Disease (ESRD), 4 hour haemodialysis effectively removed gadopiclenol from plasma as the percentage of decrease in blood concentrations was 95 to 98 % at the end of the first haemodialysis session. Weight - The effect of weight was investigated with population pharmacokinetic simulations of patients with a BW ranging from 40 kg to 150 kg receiving a gadopiclenol dose of 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW). The ratios of median AUCinf of gadopiclenol between a typical healthy subject of 70 kg and subjects weighing 40 kg and 150 kg was 0.86 and 2.06, respectively. The ratios of the plasma concentrations 10, 20 and 30 minutes after administration between a typical healthy subject of 70 kg and subjects weighing 40 kg and 150 kg ranged from 0.93 to 1.26. 5.3 Preclinical safety data - Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development. Juvenile animal toxicity studies have not revealed any relevant findings.

6. PHARMACEUTICAL PARTICULARS – 6.1 List of excipients - Tetraxetan Trometamol, Hydrochloric acid (for pH adjustment) , Sodium hydroxide (for pH adjustment), Water for injections. **6.2 Incompatibilities** - In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. **6.3 Shelf life** - 3 years. For vials - Chemical and physical in-use stability has been demonstrated for 24 hours at up to 25 °C. From a microbiological point of view, the product should be used immediately.If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless the opening has taken place in controlled and validated aseptic conditions. **6.4 Special precautions for storage** - For vials - This medicinal product does not require any special storage conditions. For storage conditions after first opening of the medicinal product, see section 6.3.For pre-filled syringes - Do not freeze. **6.5 Nature and contents of container** - Not all pack sizes may be marketed. **6.6 Special precautions for disposal and other handling** - Do not use if the medicinal product including packaging is opened or damaged. The solution for injection should be inspected visually prior to use. Solution with visible signs of deterioration (such as particles in the solution, fissures in the vial) must not be used. Before and during the use of the product, follow the safety, hygiene and asepsis rules. For vials - The vial stopper should be pierced only once. For pre-filled syringes - Do not use the pre-filled syringe if there are any signs of leakage.The pre-filled syringe is for single use only. Do not attempt to re-use even after cleaning or sterilizing the single use pre-filled syringe. Screw the push rod into the syringe plunger. It is important to rotate and push the push rod an additional ½ turn so that the plunger can rotate freely. Before using the pre-filled syringe, remove the tip cap by spinning it. Connection is compatible with luer 6%. All luer connections should be gently hand tightened without over tightening to ensure secure connection and to prevent damage to the device. Before connecting to the patient, prime completely the intravenous line and check the absence of air: hold the syringe erect and push plunger forward until all of the air is evacuated and fluid either appears at the tip of the needle or the tubing is filled. The dose volume accuracy has been checked and is conform to ISO 7886-1. The delivered dose accuracy for 15 mL syringes, graduated every 0.5 mL, depends on the injected volume. For a volume range of 5 to 15 mL, it may vary up to ± 0.6 mL. When used with a power injector, follow injector instructions for use. Any unused product should be discarded at the end of the examination session. The peel-off tracking label available on the vial or the pre-filled syringe should be stuck onto the patient record to enable accurate recording of the gadolinium contrast agent used. The dose used should also be recorded. If electronic patient records are used, the name of the product, the batch number and the dose should be entered into the patient record. Any unused portions and waste material derived from disposal and items which come into contact with the product when administering this product with an automatic application system should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER - Bracco Imaging SPA Via Egidio Folli, 50 20134 Milan, Italy

8. MARKETING AUTHORISATION NUMBER(S) - EU/1/23/1773/001-025

9. DATE OF REVISION OF THE TEXT : Oct 2023

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