▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

# AUSTRALIAN PRODUCT INFORMATION

WARNING: RISK ASSOCIATED WITH NEPHROGENIC SYSTEMIC FIBROSIS (NSF)
Gadolinium-Based Contrast Agents (GBCAs) increase the risk for nephrogenic systemic fibrosis (NSF) among patients with impaired elimination of the drugs. Avoid use of VUEWAY in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.
The risk for NSF appears highest among patients with:
- o Chronic, severe kidney disease (GFR < 30 mL/min/1.73 m2), or
- o Acute kidney injury.

Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age > 60 years, hypertension, diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.
For patients at highest risk for NSF, do not exceed the recommended VUEWAY dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration [see Special Warnings and Precautions for Use (4.4)].

# VUEWAY® (GADOPICLENOL) SOLUTION FOR INJECTION

## 1 NAME OF THE MEDICINE

Gadopiclenol

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial or pre-filled syringe contains the active ingredient gadopiclenol 485.1 mg/mL (equivalent to 0.5 mmol/mL of gadopiclenol and to 78.6 mg of gadolinium).

For the full list of excipients see Section 6.1 List of excipients.

## 3 PHARMACEUTICAL FORM

Solution for injection.

VUEWAY is a clear, colourless to pale yellow solution.

The main physiochemical properties are presented in Table 1.

**Table 1: Physicochemical properties of gadopiclenol**

| Parameter | Value |
|---|---|
| Osmolality at 37°C | 850 mOsm/kg water |
| pH | 7.0-7.8 |

| | |
|---|---|
| Viscosity at 20°C | 12.5 mPa s |
| Viscosity at 37°C | 7.7 mPa s |

# 4 CLINICAL PARTICULARS

## 4.1 THERAPEUTIC INDICATIONS

This medicinal product is for diagnostic use only.

VUEWAY (gadopiclenol) is indicated in adults and children aged 2 years and older for contrast-enhanced magnetic resonance imaging (MRI) to detect and visualise lesions with abnormal blood brain barrier or abnormal vascularity in:

- the central nervous system (brain, spine, and associated tissues);
- the body (head and neck, thorax, abdomen, pelvis and musculoskeletal system).

## 4.2 DOSE AND METHOD OF ADMINISTRATION

VUEWAY should only be administered by trained healthcare professionals with technical expertise in performing gadolinium enhanced MRI.

**DOSAGE**

Adults (≥ 18 years)

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.

Paediatrics (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.

Dose Calculation

The lowest dose that provides sufficient enhancement for diagnostic purposes should be used. 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.

Table 2 below indicates the volume to be administered according to BW.

**Table 2: Volume of VUEWAY to be administered per BW**

| BW kilograms (kg) | **Volume** millilitres (mL) | **Quantity** millimoles (mmol) |
|---|---|---|
| 10 | 1 | 0.5 |
| 20 | 2 | 1.0 |
| 30 | 3 | 1.5 |
| 40 | 4 | 2.0 |
| 50 | 5 | 2.5 |
| 60 | 6 | 3.0 |
| 70 | 7 | 3.5 |
| 80 | 8 | 4.0 |
| 90 | 9 | 4.5 |
| 100 | 10 | 5.0 |
| 110 | 11 | 5.5 |
| 120 | 12 | 6.0 |
| 130 | 13 | 6.5 |
| 140 | 14 | 7.0 |

**METHOD OF ADMINISTRATION**

VUEWAY is for intravenous use only.

The recommended dose is administered intravenously as a bolus injection at approximatively 2 mL/second 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).

Paediatric population

Depending on the amount of gadopiclenol to be given to the child, it is preferable to use gadopiclenol vials with a single use syringe adapted to the amount to be administered, in order to have better precision of the injected volume.

Handling Instructions Before Administration

Use aseptic technique for all handling and administration of VUEWAY.

VUEWAY should be inspected visually prior to use. Do not use the solution if any particulate matter is present or the solution is discoloured.

Solution with visible signs of deterioration (such as particles in the solution, fissures in the vial) must not be used.

*Vials for single-use setting*

- The vial stopper should be pierced only once.
- Aseptically draw up VUEWAY into a disposable syringe and use immediately.
- If solidification occurs in the vial because of exposure to the cold, bring the vial of VUEWAY to room temperature before use and inspect that the solution is clear, colourless to yellow without any particulate matter and discoloration.
- Discard any unused portion.

*Vials for multi-use setting*

- For use only with an automated contrast injection system approved for multi-patient use.
- The vial stopper should be pierced only once.
- Once pierced, do not remove the multi-use vial from the aseptic work area.
- The multi-use vial can be used with an appropriate transfer device for filling empty sterile syringes or an automated injector. The manufacturer's instructions for use for the device must be followed.
- Change the single-use tubing between patients.
- Use each individual dose of VUEWAY promptly following withdrawal from the multi-patient vial.
- Use the contents of the multi-use vial within 24 hours at room temperature after initial puncture.
- If solidification occurs in the vial because of exposure to the cold, bring the vial of VUEWAY to room temperature before use and inspect that the solution is clear, colourless to yellow without any particulate matter and discolouration.
- Discard any unused portion.

*Pre-filled syringes for single-use setting*

- Remove the tip cap of the syringe, screw the plunger rod and use immediately.
- Pre-filled syringes must not be frozen. Frozen pre-filled syringes of VUEWAY should be discarded.
- Discard any unused portion.

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.

**DOSAGE ADJUSTMENT**

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 $m^2$) 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 *Renal impairment* above).

Elderly

No dose adjustment is necessary. Caution should be exercised in elderly patients (see section 4.4).

## 4.3 CONTRAINDICATIONS

Hypersensitivity to the active ingredient or 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.

Intrathecal administration of gadolinium-containing contrast agents can cause serious adverse reactions including death, coma, encephalopathy, and seizures. Do not use by the intrathecal route.

MRI images produced with VUEWAY should only be analysed and interpreted by healthcare professionals trained in interpretation of gadolinium enhanced MRI.

Gadolinium retention

The current evidence suggests that gadolinium may accumulate in the brain after multiple administration of GBCAs. Increased signal intensity on non-contrast T1-weighted images of the brain has been observed after multiple administrations of GBCAs in patients with normal renal function. Gadolinium has been detected in brain tissue after multiple exposures to GBCAs, particularly in the dentate nucleus and globus pallidus. The evidence suggests that the risk of gadolinium accumulation is higher after repeat administration of linear than after repeat administration of macrocyclic agents. The clinical significance of gadolinium accumulation in the brain is presently unknown; however, gadolinium accumulation may potentially interfere with the interpretation of MRI scans of the brain. In order to minimise potential risks associated with gadolinium

accumulation in the brain, it is recommended to use the lowest effective dose and perform a careful benefit risk assessment before administering repeated doses.

Hypersensitivity or anaphylactic reactions

- As with other gadolinium-containing contrast agents, hypersensitivity reactions can occur, including life-threatening reactions. 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 a hypersensitivity reaction occurs, 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. oxygen, adrenaline, and antihistamines), an endotracheal tube and a ventilator 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 $m^2$). 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.

Seizures

As with other gadolinium-containing contrast agents, special caution is necessary in patients with a lowered threshold for seizures. All equipment and medication 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.

**Use in the 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).

**Paediatric use**

The safety and efficacy of VUEWAY in children less than 2 years have not yet been established. No data are available.

**Effects on laboratory tests**

Interactions with laboratory tests have not been observed.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed.

Concomitant 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

**Effects on fertility**

No impairment of fertility was observed in male and female rats dosed IV with up to 10 mmol/kg/day gadopiclenol (60 times the clinical exposure based on AUC) (see section 5.3).

**Use in pregnancy**

There are no data from the use of gadopiclenol in pregnant women. Gadopiclenol should not be used during pregnancy unless the clinical condition of the woman requires use of gadopiclenol.

It is unknown whether exposure to gadolinium is associated with adverse effects in the fetus.

Studies in rats showed little placental transfer. No effects on embryofetal development were observed in rats at 10 mmol/kg/day (53 times the clinical exposure based on AUC) or in rabbits at 2.5 mmol/kg/day (23 times the clinical exposure based on AUC). Decreased fetal weights were observed in rabbits at 5 mmol/kg/day, associated with maternal toxicity.

### Use in lactation

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 gadopiclenol, should be at the discretion of the healthcare professional and breast-feeding mother.

## 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

### Clinical Trial

The safety of VUEWAY was evaluated in 1047 patients who received at least one dose of VUEWAY. The dose ranged from 0.025 mmol/kg to 0.3 mmol/kg. A total of 708 patients received the recommended dose of 0.05 mmol/kg.

The most frequent common adverse events reported with gadopiclenol were headache, injection site pain, nausea, injection site haematoma and dizziness. Most adverse events were mild to moderate in intensity.

Tabulated list of adverse reactions

Adverse reactions listed below were reported during clinical trials, including 1047 subjects exposed to gadopiclenol.

Table 3 below presents adverse reactions reported by SOC (System Organ Class) and by frequency with the following guidelines: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000).

**Table 3: Adverse Reactions obtained from Clinical Trials – All Subjects Exposed to Gadopiclenol, All doses (N=1047)**

| System Organ Class | Frequency | |
|---|---|---|
| | Common | Uncommon |
| Immune system disorders | - | Hypersensitivity* |
| Nervous system disorders | Headache, dizziness | Dysgeusia |
| Gastrointestinal disorders | - | Diarrhoea, Nausea, Abdominal pain, Vomiting |
| General disorders and administration site conditions | Injection site reaction** | Fatigue, Feeling hot |
| Investigations | | Increase in creatinine levels |

* Including immediate (dermatitis allergic, erythema, dyspnoea, dysphonia, throat tightness, and throat irritation) and delayed (periorbital oedema, swelling, rash and pruritus) reactions.

** Injection site reaction includes the following terms: injection site pain, injection site oedema, injection site coldness, injection site warmth, injection site haematoma and injection site erythema.

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 of the start of shock and rarely results in death.

*Nephrogenic systemic fibrosis (NSF)*

Isolated cases of NSF have been reported with GBCAs (see section 4.4).

*Acute pancreatitis*

Isolated cases of acute pancreatitis with onset within 48 hours after GBCA administration have been reported with other GBCAs.

Paediatric population (2 years and older)

A total of 80 paediatric patients aged 2 years to 17 years were included in the clinical trial. As compared to adults, the safety profile of 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%).

Among these TEAEs, 1 event in 1 patient (1.25%) from the CNS cohort was considered related to gadopiclenol (maculopapular rash of moderate intensity). Ù

**Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

### 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 been reported.Gadopiclenol can be removed by haemodialysis. However, there is no evidence that haemodialysis is suitable for prevention of NSF.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

## 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 $T_1$ and $T_2$ relaxation times in targeted tissues. The extent to which a contrast agent can affect the relaxation rate of tissue water ($1/T_1$ or $1/T_2$) is termed relaxivity ($r_1$ or $r_2$).

Relaxivity is directly proportional to the number of water molecules linked to the gadolinium. Gadopiclenol has high relaxivity due to its specific structure (see Table 4). Two water molecules are linked to gadolinium in gadopiclenol, in contrast to one water molecule in the other currently available gadolinium-containing contrast agents. Therefore, gadopiclenol given at half dose of gadolinium compared to other non-specific gadolinium-containing contrast agents, may provide the same contrast enhancement.

Cardiac Electrophysiology

At 6 times the recommended dosage in adult patients, gadopiclenol does not prolong the QT interval to any clinical relevant extent.

**Table 4: Relaxivity at 37°C for gadopiclenol**

| | $r_1$ ($mmol^{-1}.l.s^{-1}$) | | | $r_2$ ($mmol^{-1}.l.s^{-1}$) | | |
|---|---|---|---|---|---|---|
| **Magnetic field** | **0.47 T** | **1.5 T** | **3 T** | **0.47 T** | **1.5 T** | **3 T** |
| Relaxivity in water | 12.5 | 12.2 | 11.3 | 14.6 | 15.0 | 13.5 |
| Relaxivity in biological medium | 13.2 | 12.8 | 11.6 | 15.1 | 15.1 | 14.7 |

## Clinical trials

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). Study 1 (PICTURE) included 256 patients presenting with known or highly suspected CNS lesions with focal areas of disrupted blood brain barrier (BBB) (e.g. primary and secondary tumours). The majority of patients (72%), presented with brain tumours, 20% had brain or spine metastases and 8% presented with other pathologies.

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 tumours (23%) and liver tumours (21%).

The primary endpoint was the evaluation of lesion visualisation, based on 3 co-criteria (border delineation**,** internal morphology and degree of contrast enhancement) by 3 independent blinded readers, using a 4-point scale. The mean of scores for each of the 3 lesion visualisation 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 visualisation 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 0.2 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 3 readers, and for each lesion visualisation criterion also demonstrated the non-inferiority of gadopiclenol at 0.05 mmol/kg to gadobutrol at 0.1 mmol/kg in both studies, as shown in Table 5 below.

**Table 5: Lesion visualisation – Off-site readings – Full analysis set**

| | Number of patients | LS Mean (SE) | | | 95% CI difference | *p*-value |
|---|---|---|---|---|---|---|
| | | Gadopiclenol | Gadobutrol | Difference | | |
| **Study 1 (PICTURE)** | | | | | | |
| Border delineation | 239 | 3.83 (0.02) | 3.82 (0.02) | 0.01 (0.02) | [-0.02 ; 0.05] | 0.5025 |
| Internal morphology | 239 | 3.83 (0.02) | 3.81 (0.02) | 0.02 (0.02) | [-0.01 ; 0.05] | 0.2006 |
| Degree of contrast enhancement | 239 | 3.73 (0.03) | 3.68 (0.03) | 0.05 (0.02) | [0.01 ; 0.09] | 0.0172 |
| **Study 2 (PROMISE)** | | | | | | |
| Border delineation | 273 | 3.60 (0.03) | 3.60 (0.03) | -0.00 (0.02) | [-0.05 ; 0.04] | 0.8987 |
| Internal morphology | 273 | 3.75 (0.02) | 3.76 (0.02) | -0.01 (0.02) | [-0.05 ; 0.03] | 0.6822 |
| Degree of contrast enhancement | 273 | 3.30 (0.04) | 3.29 (0.04) | 0.01 (0.03) | [-0.05 ; 0.07] | 0.8546 |

*CI: Confidence Interval ; LS: Least Squares ; SE: Standard Error.*

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.

*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.

## 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 maximum concentration ($C_{max}$) was 525 ± 70 µg/mL and 992 ± 233 µg/mL, respectively.

The $C_{max}$ increased 1.1-fold, 1.1-fold and 1.4-fold and the area under plasma concentration-time curve from time 0 to infinity ($AUC_{inf}$) 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 $C_{max}$ and $AUC_{inf}$ 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.

**Metabolism**

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.

**Excretion**

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 ($t_{1/2}$) in healthy volunteers with a normal renal function was 1.5 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 elimination half-life equivalent to 0.025 to 0.3 mmol/kg elimination half-life), without difference between males and females. Mean maximum concentration ($C_{max}$) and Area Under the Curve ($AUC_{inf}$) 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/hr/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 ($t_{1/2}$) 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 $t_{1/2}$ 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 $C_{max}$ increased 1.1-fold, 1.1-fold and 1.4-fold and the $AUC_{inf}$ 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 $C_{max}$ and $AUC_{inf}$ 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 , 4 hours 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.

## 5.3 PRECLINICAL SAFETY DATA

### Genotoxicity

Gadopiclenol was negative in the *in vitro* bacterial reverse mutation (Ames) assay, the *in vitro* mouse lymphoma cell gene mutation assay, and the *in vivo* micronucleus test. Gadopiclenol is therefore not considered genotoxic.

### Carcinogenicity

No data available.

# 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

36 months

*For vials*

Chemical and physical in-use stability has been demonstrated for 24 hours at up to 25°C.

Single use vials/syringes should be used immediately after opening and remaining contents discarded after use. Multi dose vials may be held at 25°C for no more than 24 hours after opening.

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

*For vials*

Store below 25°C.

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*

Store below 25°C.

Do not freeze.

## 6.5 NATURE AND CONTENTS OF CONTAINER

*For vials*

3 mL, 7.5 mL, 10 mL and 15 mL vials in packs of 1 or 25.

30 mL, 50 mL and 100 mL in packs of 1.

Type I clear glass vials sealed with an elastomeric chlorobutyl stopper and sealed with an aluminium crimped cap.

*For pre-filled syringes*

7.5 mL, 10 mL and 15 mL pre-filled syringes in packs of 1 and 10.

Plastic (polypropylene) pre-filled syringe, graduated every 0.5 mL, with an elastomeric bromobutyl plunger stopper and capped with an elastomeric bromobutyl tip cap.

Not all presentations may be available.

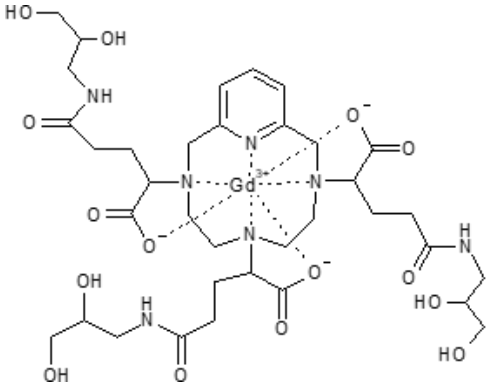
### 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

### 6.7 PHYSICOCHEMICAL PROPERTIES

#### Chemical structure

The structural formula of gadopiclenol is:




#### CAS number

The CAS Registry Number is 933983-75-6.

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

Not scheduled.

## 8 SPONSOR

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Guerbet

## 9 DATE OF FIRST APPROVAL

DD MMM YYYY

## 10 DATE OF REVISION

DD MMM YYYY

### SUMMARY TABLE OF CHANGES

| Section Changed | Summary of new information |
|---|---|
| | |