SUMMARY OF PRODUCT CHARACTERISTICS

▼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. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Elucirem 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

Mean osmolality at 37°C	850 mOsm/kg H_2O
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.

Elucirem 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 Elucirem 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.

Table 1 below indicates the volume to be administered according to BW.

Table 1: Volume of Elucirem 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

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 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 above “renal impairment”).

Paediatric population (2 years and older)

The recommended and maximum dose of Elucirem 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 Elucirem 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, Elucirem 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

Gadopiclenol must not be used intrathecally. Serious, life-threatening and fatal cases, primarily with neurological reactions (e.g. coma, encephalopathy, seizures), have been reported with intrathecal use of gadolinium-based contrast agents.

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 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.

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.

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

Pregnancy

Data on the use of gadolinium-based contrast agents including gadopiclenol in pregnant women is limited. Gadolinium can cross the placenta. It is unknown whether exposure to gadolinium is associated with adverse effects in the foetus. Animal studies showed little placental transfer and do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Elucirem 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 Elucirem, 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

Elucirem has no or negligeable 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.

Tabulated list of adverse reactions

Table 2 below presents adverse reactions based on clinical trials including 1047 subjects exposed to gadopiclenol ranging from 0.05 mL/kg BW (equivalent to 0.025 mmol/kg BW) to 0.6 mL/kg BW (equivalent to 0.3 mmol/kg BW).

The adverse reactions are listed below by SOC (System Organ Class) and by frequency with the following guidelines: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000).

Table 2: Adverse reactions reported following gadopiclenol administration

System Organ Class	**Frequency**	
	Common	**Uncommon**
Immune system disorders	-	Hypersensitivity*
Nervous System Disorders	Headache	Dysgeusia
Gastrointestinal Disorders	-	Diarrhoea, Nausea, Abdominal pain, Vomiting

General Disorders and Administration Site Conditions	Injection site reaction**	Fatigue, Feeling hot

* Including immediate (dermatitis allergic, erythema, dyspnoea, dysphonia, throat tightness, throat irritation, paraesthesia oral and flushing) 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 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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 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).

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.

Table 3: 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 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 0.2 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 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, as shown in table 4 below.

Table 4: Lesion visualization – Off-site readings – Full analysis set

	n patients	**LS Mean (SE)**		**Difference**	**95% CI difference**	**p-value**
		Gadopiclenol	**Gadobutrol**			
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.

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.

Table 5: Results on overall diagnostic preference for Study 1 (CNS) and Study 2 (Body)

	Reader	N	gadopiclenol preferred	No preference	gadobutrol preferred	p-value*
Study 1 (CNS)	4	241	108 (44.8 %)	98 (40.7 %)	35 (14.5 %)	< 0.0001
	5	241	131 (54.4 %)	52 (21.6 %)	58 (24.1 %)	< 0.0001
	6	241	138 (57.3 %)	56 (23.2 %)	47 (19.5 %)	< 0.0001
Study 2 (Body)	4	276	36 (13.0 %)	216 (78.3 %)	24 (8.7 %)	0.1223
	5	276	40 (14.5 %)	206 (74.6 %)	30 (10.9 %)	0.2346
	6	276	33 (12.0 %)	228 (82.6 %)	15 (5.4 %)	0.0079

* Wilcoxon signed-rank test.

A change in patient treatment plan was reported after administration of gadopiclenol at 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW) in 23.3 % and 30.1 % of patients in Study 1 and Study 2, respectively.

Analysis per subgroups in Study 1 revealed that treatment plan could be changed for 64 % of the 22 patients for whom the investigator considered that diagnosis was not assessable (or grade of glial tumor could not be determined) based on unenhanced MRI, 28 % of 81 patients with malignant diagnosis and about 12 % of 111 patients with non-malignant diagnosis.

In Study 2, treatment plan could be changed after MRI with gadopiclenol for 41 % of the 22 patients with non-assessable diagnosis based on unenhanced MRI, 32 % of 165 patients with malignant diagnosis and 14 % of 64 patients with non-malignant diagnosis.

A post-hoc reading of all images from both pivotal studies for CNS and Body indications was conducted in a fully blinded, unpaired, randomised manner . A high level of concordance in lesion detectability between gadopiclenol at 0.05 mmol/kg and gadobutrol at 0.1 mmol/kg was observed at lesion and at patient level. The results are summarized in Table 6 below.

Table 6: Concordance in lesion detectability between gadopiclenol at 0.05 mmol/kg and gadobutrol at 0.1 mmol/kg

	Perfect match at lesion level*	Perfect match at patient level*
Study 1 (CNS)	88.0% to 89.8%	84.3% to 86.0%
Study 2 (Body) overall	92.3% to 95.5%	81.3% to 85.0%
Head & Neck	89.5% to 100%	70.6% to 94.1%
Thorax	88.3% to 93.2%	69.8% to 73.2%
Pelvis	91.7% to 100%	87.5% to 94.6%
Abdomen	94.6% to 95.2%	84.0% to 87.2%
Musculoskeletal	100%	100%

*Range of values according to the reader (3 readers per region)

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 Medicines and Healthcare products Regulatory Agency (MHRA) has deferred the obligation to submit the results of studies with Elucirem 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 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 C_{max} 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 ($t_{1/2}$) 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 (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/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 ($t_{1/2}$) is prolonged in subjects with renal impairment, increasing with the degree of renal impairment. In patients with mild ($60 \leq$ eGFR < 90 mL/min), moderate ($30 \leq$ eGFR < 60 mL/min) and severe ($15 \leq$ 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 (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 AUC_{inf} 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.

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

This medicinal product does not require any special storage conditions.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

3 mL solution for injection in a 10 mL vial (glass type I) with elastomeric stopper in pack size of 1.

7.5 mL solution for injection in a 10 mL vial (glass type I) with elastomeric stopper in pack sizes of 1 or 25.

10 mL solution for injection in a 10 mL vial (glass type I) with elastomeric stopper in pack sizes of 1 or 25.

15 mL solution for injection (in a 20 mL vial (glass type I) with elastomeric stopper in pack sizes of 1 or 25.

30 mL solution for injection in a 50 mL vial (glass type I) with elastomeric stopper in pack size of 1.

50 mL solution for injection in a 50 mL vial (glass type I) with elastomeric stopper in pack size of 1.

100 mL solution for injection in a 100 mL vial (glass type I) with elastomeric stopper in pack size of 1.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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.

The vial stopper should be pierced only once.

Any unused product should be discarded at the end of the examination session.

The peel-off tracking label available on the vial 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

Guerbet

BP 57400

95943 Roissy CdG Cedex

France

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 12308/0014

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/12/2023

10 DATE OF REVISION OF THE TEXT

02/02/2025