HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use GADOPICLENOL safely and effectively. See full prescribing information for GADOPICLENOL.

GADOPICLENOL (gadopiclenol) solution for injection, Injection for intravenous use.
Initial U.S. Approval: YYYY

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

See full prescribing information for complete boxed warning

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities.

- **The risk for NSF appears highest among patients with:**
  - **Chronic, severe kidney disease (GFR <30 mL/min/1.73 m^2), or**
  - **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 (for example, age >60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing (5.1).**

----------INDICATIONS AND USAGE----------
GADOPICLENOL is a gadolinium-based contrast agent indicated in adults and children age 2 years and older for contrast enhanced magnetic resonance imaging (MRI) to improve detection, visualization, and characterization of lesions in:

- the Central Nervous System (brain, spine and surrounding tissues),
- the Body (head and neck, thorax including breast, abdomen including liver and kidneys, pelvis including prostate, and musculo-skeletal system). (1)

----------DOSAGE AND ADMINISTRATION----------
The recommended dose of GADOPICLENOL is, for adult and pediatric patients (2 years of age and older), 0.1 mL/kg body weight (equivalent to 0.05 mmol/kg) administered as an intravenous bolus injection, manually or by power injector, at a flow rate of approximately 1 to 4 mL/s (2).

----------DOSAGE FORMS AND STRENGTHS—----------
GADOPICLENOL contains 485.1 mg/mL gadopiclenol (equivalent to 0.5 mmol/mL) and is available in vials and pre-filled syringes. GADOPICLENOL Pharmacy Bulk Package is available in vials. (3).

----------CONTRAINDICATIONS----------
History of hypersensitivity reactions to GADOPICLENOL (4).

----------WARNINGS AND PRECAUTIONS----------

- Nephrogenic Systemic Fibrosis has occurred in patients with impaired elimination of GBCAs. Higher than recommended dosing or repeat dosing appear to increase the risk. (5.1).
- Hypersensitivity: Anaphylactoid/anaphylactic reactions with cardiovascular, respiratory or cutaneous manifestations, ranging from mild to severe, including death, have been observed with similar products. Monitor patients closely for need of emergency cardiorespiratory support. (5.2).
- Gadolinium is retained for months or years in brain, bone, and other organs. (5.3).

----------ADVERSE REACTIONS----------
Adverse reactions that occurred with a frequency >1% in patients who received GADOPICLENOL include: Injection site pain and Headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS contact GUERBET LLC at 1-877-729-6679 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
Pregnancy: Use only if imaging is essential during pregnancy and cannot be delayed. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: MM/YYYY

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

Commented [BL1]: Note to reviewer: "GADOPICLENOL" corresponds to the Drug Product and "gadopiclenol" to the Drug Substance.

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs 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:**
  - **Chronic, severe kidney disease (GFR < 30 mL/min/1.73 m^2), or**
  - **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 (5.1).**
- **For patients at highest risk for NSF, do not exceed the recommended GADOPICLENOL dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration *[see Warnings and Precautions (5.1)].***

1 INDICATIONS AND USAGE

GADOPICLENOL is a gadolinium-based contrast agent indicated in adults and children age 2 years and older for contrast enhanced magnetic resonance imaging (MRI) to improve detection, visualization, and characterization of lesions in:

- the Central Nervous System (brain, spine and surrounding tissues),
- the Body (head and neck, thorax including breast, abdomen including liver and kidneys, pelvis including prostate, and musculo-skeletal system).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of GADOPICLENOL is 0.1 mL/kg body weight (equivalent to 0.05 mmol/kg) for adult and pediatric patients (2 years of age and older) administered as an intravenous bolus injection.

Due to its high relaxivity, the recommended dose of GADOPICLENOL is a lower (half-dose) quantity of gadolinium administered compared to other GBCAs used in clinical practice. Refer to Table 1 to determine the weight-adjusted dose volumes to be administered.

Table 1: Volume of GADOPICLENOL by Body Weight

Body Weight		Volume
Pounds (lb)	Kilograms (kg)	Milliliters (mL)
22	10	1
44	20	2
66	30	3
88	40	4
110	50	5

132	60	6
154	70	7
176	80	8
198	90	9
220	100	10
242	110	11
264	120	12
286	130	13
308	140	14
330	150	15

2.2 Administration Instructions

GADOPICLENOL is formulated at a concentration of 0.5 mmol/mL and the recommended dose of GADOPICLENOL is 0.05 mmol/kg (0.1 mL/kg). Refer to Table 1 to determine the weight-adjusted dose volume to be administered.

- Visually inspect GADOPICLENOL for particulate matter prior to administration.
- Do not use the solution if any particulate matter is present or if the container appears damaged.
- Do not mix with other medications because of the potential for chemical incompatibility.
- Use sterile technique for all handling and administration of GADOPICLENOL.
- Administer GADOPICLENOL as an intravenous bolus injection, manually or by power injector, at a flow rate of approximately 1 to 4 mL/s.
- To ensure complete administration of GADOPICLENOL, the injection may be followed by a normal saline flush.
- Use the lowest dose necessary to obtain adequate visualization and do not exceed the recommended dose.
- Contrast MRI can begin immediately following the injection of GADOPICLENOL.
- Discard any unused portion of the drug.

Vial
- Do not pierce the rubber stopper more than once.
- Aseptically draw up GADOPICLENOL into a disposable syringe and use immediately.

Pre-filled syringe
- Remove the tip cap of the syringe and use immediately.

Pharmacy Bulk Package Preparation:

- Do not use the Pharmacy Bulk Package for direct intravenous infusion.
- Perform the transfer of GADOPICLENOL from the Pharmacy Bulk Package in an aseptic work area, such as laminar flow hood and using aseptic technique and suitable transfer device. Penetrate the closure only one time.
- Once the container closure is punctured, do not remove the Pharmacy Bulk Package from the aseptic work area.
- The Pharmacy Bulk Package is used as a multiple dose container with an appropriate transfer device for filling empty sterile syringes.
- Use each individual dose of GADOPICLENOL promptly following withdrawal from the Pharmacy Bulk Package.
- Use the contents of the Pharmacy Bulk Package within 24 hours after initial puncture.

3 DOSAGE FORMS AND STRENGTHS

GADOPICLENOL is a sterile, nonpyrogenic, clear, colorless to pale yellow aqueous solution for intravenous injection containing 485.1 mg/mL gadopiclenol (equivalent to 0.5 mmol/mL of gadopiclenol and to 78.6 mg/mL of gadolinium). GADOPICLENOL is available in glass vials and plastic pre-filled syringes. GADOPICLENOL Pharmacy Bulk Package is available in vials.

4 CONTRAINDICATIONS

GADOPICLENOL is contraindicated in patients with history of hypersensitivity reactions to gadopiclenol.

5 WARNINGS AND PRECAUTIONS

5.1 Nephrogenic Systemic Fibrosis

Gadolinium-based contrast agents (GBCAs) increase the risk for nephrogenic systemic fibrosis (NSF) among patients with impaired elimination of the drugs. Avoid use of GBCAs among these patients unless the diagnostic information is essential and not available with non-contrast MRI or other modalities. The GBCA-associated NSF risk appears highest for patients with chronic, severe kidney disease (GFR <30 mL/min/1.73 m^2) as well as patients with acute kidney injury. The risk appears lower for patients with chronic, moderate kidney disease (GFR 30-59 mL/min/1.73 m^2) and little, if any, for patients with chronic, mild kidney disease (GFR 60-89 mL/min/1.73 m^2). NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs. Report any diagnosis of NSF following GADOPICLENOL administration to Guerbet LLC (1-877-729-6679) or FDA (1-800-FDA-1088 or www.fda.gov/medwatch).

Screen patients for acute kidney injury and other conditions that may reduce renal function. Features of acute kidney injury consist of rapid (over hours to days) and usually reversible decrease in kidney function, commonly in the setting of surgery, severe infection, injury or drug-induced kidney toxicity. Serum creatinine levels and estimated GFR may not reliably assess renal function in the setting of acute kidney injury. For patients at risk for chronically reduced renal function (e.g., age >60 years, diabetes mellitus or chronic hypertension), estimate the GFR through laboratory testing.

Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA and the degree of renal impairment at the time of exposure. Record the specific GBCA and the dose administered to a patient. For patients at highest risk for NSF, do not exceed the recommended GADOPICLENOL dose and allow a sufficient period of time for elimination of the drug prior to re-administration. For patients receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of a GBCA in order to enhance the contrast agent's elimination *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].* The usefulness of hemodialysis in the prevention of NSF is unknown *[see Dosage and Administration (2) and Clinical Pharmacology (12)].*

5.2 Hypersensitivity Reactions

No serious hypersensitivity reactions have been reported with GADOPICLENOL during clinical trials.
However, as with other GBCAs, hypersensitivity reactions can occur.
In most cases, initial symptoms occurred within minutes of GBCA administration and resolved with prompt emergency treatment.

- Before GADOPICLENOL administration, assess all patients for any history of a reaction to contrast media, bronchial asthma and/or allergic disorders. These patients may have an increased risk for a hypersensitivity reaction to GADOPICLENOL.
- Administer GADOPICLENOL only in situations where trained personnel and therapies are promptly available for the treatment of hypersensitivity reactions, including personnel trained in resuscitation.
- During and following GADOPICLENOL administration, observe patients for signs and symptoms of hypersensitivity reactions for at least half an hour.

5.3 Gadolinium Retention

Gadolinium is retained for months or years in several organs. The highest concentrations (nanomoles per gram of tissue) have been identified in the bone, followed by other organs (e.g. brain, skin, kidney, liver and spleen). The duration of retention also varies by tissue and is longest in bone. Linear GBCAs cause more retention than macrocyclic GBCAs. At equivalent doses, gadolinium retention varies among the linear agents with Omniscan (gadodiamide) causing greater retention than other linear agents [Eovist (gadoxetate disodium), MultiHance (gadobenate dimeglumine)]. Retention is lowest and similar among the macrocyclic GBCAs [Dotarem (gadoterate meglumine), Gadavist (gadobutrol), ProHance (gadoteridol), GADOPICLENOL (gadopiclenol)].

Consequences of gadolinium retention in the brain have not been established. Pathologic and clinical consequences of GBCA administration and retention in skin and other organs have been established in patients with impaired renal function *[see Warnings and Precautions (5.1)].* There are rare reports of pathologic skin changes in patients with normal renal function. Adverse events involving multiple organ systems have been reported in patients with normal renal function without an established causal link to gadolinium.

While clinical consequences of gadolinium retention have not been established in patients with normal renal function, certain patients might be at higher risk. These include patients requiring multiple lifetime doses, pregnant and pediatric patients, and patients with inflammatory conditions. Consider the retention characteristics of the agent when choosing a GBCA for these patients. Minimize repetitive GBCA imaging studies, particularly closely spaced studies, when possible.

5.4 Acute Kidney Injury

In patients with chronically reduced renal function, acute kidney injury requiring dialysis has occurred with the use of GBCAs. The risk of acute kidney injury may increase with increasing dose of the contrast agent. Administer the lowest dose necessary for adequate imaging.

5.5 Extravasation and Injection Site Reactions

Ensure catheter and venous patency before the injection of GADOPICLENOL. Extravasation into tissues during GADOPICLENOL administration may result in tissue irritation *[see Nonclinical Toxicology (13.2)].*

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Commented [BL2]: Note to reviewer: This section will be updated for the MAA submission with data from two pivotal Phase III studies (GDX-44-010, GDX-44-011) and the paediatric study (GDX-44-007).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.
The data described below reflect GADOPICLENOL exposure in 432 patients exposed to one or two doses of GADOPICLENOL ranging from 0.025 mmol/kg body weight to 0.3 mmol/kg body weight.

Table 2 lists adverse reactions that occurred in > 0.2% patients who received GADOPICLENOL.

Table 2: Adverse Reactions in Clinical Trials

Reaction	Rate (%) (n=432)
Injection site pain	3.9
Headache	2.5
Injection site coldness	0.9
Fatigue	0.9
Diarrhoea	0.9
Nausea	0.9
Abdominal pain	0.7
Injection site oedema	0.7

Adverse reactions that occurred with a frequency ≤ 0.2% in patients who received GADOPICLENOL include: Dysgeusia, Injection site warmth, Injection site haematoma and Injection site erythema.

No NSF case has been observed during the clinical trials.
No serious hypersensitivity reaction has been observed during the clinical trials.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
GBCAs cross the human placenta and result in fetal exposure and gadolinium retention. The human data on the association between GBCAs and adverse fetal outcomes are limited and inconclusive *(see Data)*.
In animal reproduction studies, there were no adverse developmental effects observed in rats or rabbits with intravenous administration of GADOPICLENOL during organogenesis *(see Data)*. Because of the potential risks of gadolinium to the fetus, use GADOPICLENOL only if imaging is essential during pregnancy and cannot be delayed.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20% respectively.

Data

Human Data

Contrast enhancement is visualized in the placenta and fetal tissues after maternal GBCA administration.

Cohort studies and case reports on exposure to GBCAs during pregnancy have not reported a clear association between GBCAs and adverse effects in the exposed neonates. However, a retrospective cohort study, comparing pregnant women who had a GBCA MRI to pregnant women who did not have an MRI, reported a higher occurrence of stillbirths and neonatal deaths in the group receiving GBCA MRI. Limitations of this study include a lack of comparison with non-contrast MRI and lack of information about the maternal indication for MRI. Overall, these data preclude a reliable evaluation of the potential risk of adverse fetal outcomes with the use of GBCAs in pregnancy.

Animal Data

Gadolinium Retention

GBCAs administered to pregnant non-human primates (0.1 mmol/kg on gestational days 85 and 135) result in measurable gadolinium concentration in the offspring in bone, brain, skin, liver, kidney, and spleen for at least 7 months. GBCAs administered to pregnant mice (2 mmol/kg daily on gestational days 16 through 19) result in measurable gadolinium concentrations in the pups in bone, brain, kidney, liver, blood, muscle, and spleen at one-month postnatal age.

Reproductive Toxicology

Animal reproduction studies conducted with gadopiclenol showed some signs of maternal toxicity in rats at 10 mmol/kg and rabbits at 5 mmol/kg (corresponding to 52 and 57 times the recommended dose, respectively). This maternal toxicity was characterized in both species by swelling, decreased activity, lower gestation weight gain and food consumption.

No effect on embryo-fetal development was observed in rats at 10 mmol/kg (corresponding to 52 times the recommended dose). In rabbits, a lower mean fetal body weight was observed at 5 mmol/kg (corresponding to 57 times the recommended dose) and this was attributed as a consequence of the lower gestation weight gain.

8.2 Lactation

Risk Summary

There are no data on the presence of gadopiclenol in human milk, the effects on the breastfed infant, or the effects on milk production.

However, published lactation data on other GBCAs indicate that 0.01 to 0.04% of the maternal gadolinium dose is excreted in breast milk. Additionally, there is limited GBCA gastrointestinal absorption in the breast-fed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for GADOPICLENOL and any potential adverse effects on the breastfed infant from GADOPICLENOL or from the underlying maternal condition.

Data

Animal Data

In lactating rats receiving single intravenous injection of [^{153}Gd]-gadopiclenol, 0.3% and 0.2% of the total administered radioactivity was transferred to the pup via maternal milk at 6 and 24 hours after administration, respectively.

Furthermore, in rats, oral absorption of gadopiclenol is poor.

8.4 Pediatric Use

Data
One Phase II study with single dose of GADOPICLENOL (0.05 mmol/kg) was conducted in 80 pediatric patients aged 2 to 17 years, including 60 patients who underwent a central nervous system (CNS) MRI and 20 patients a Body MRI.
The pharmacokinetic profile of GADOPICLENOL was similar to the one established in adults. Thus, no dose adjustment is needed in this population.
Diagnostic efficacy was evaluated and there was no difference among the pediatric age groups.

Juvenile Animal Data
Single and repeat-dose toxicity studies in neonatal and juvenile rats did not reveal findings suggestive of a specific risk for use in pediatric patients (2 years of age and older).

8.6 Renal impairment
No GADOPICLENOL dosage adjustment is recommended for patients with renal impairment. GADOPICLENOL can be removed from the body by hemodialysis *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

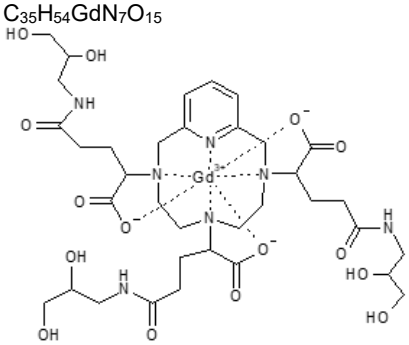
The maximum single dose of GADOPICLENOL tested in humans was 0.3 mmol/kg, which corresponds to 6 times the recommended dose, and was tolerated in a manner similar to lower doses.
No signs of intoxication from an overdose have been reported during clinical use.
GADOPICLENOL can be removed from the body by hemodialysis *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

GADOPICLENOL is a paramagnetic macrocyclic non-ionic complex of gadolinium administered for MRI examinations.

The chemical name for gadopiclenol is *rac*-[(2R,2'Ξ,2''Ξ)-2,2',2''-(3,6,9-triaza-$\kappa^{3}N^{3}$,N^{6},N^{9}-1(2,6)-pyridina-κN^{1}-cyclodecaphane-3,6,9-triyl)tris(5-{[(2Ξ)-2,3-dihydroxypropyl]amino}-5-oxopentanoato-$\kappa^{3}O^{1}$,$O^{1'}$,$O^{1''}$)(3−)]gadolinium.

GADOPICLENOL has a molecular weight of 970.11 g/mol and a molecular formula of $C_{35}H_{54}GdN_{7}O_{15}$



GADOPICLENOL is a sterile, nonpyrogenic, clear, colorless to yellow aqueous solution.
Each mL contains 485.1 mg of gadopiclenol as active ingredient (equivalent to 0.5 mmol and 78.6 mg of gadolinium).
The excipients are tetraxetan, trometamol, hydrochloric acid and/or sodium hydroxide (for pH adjustment, if needed), and water for injection.

GADOPICLENOL does not contain any preservatives.

The main physicochemical properties of GADOPICLENOL are provided in Table 3.

Table 3: Physicochemical properties of GADOPICLENOL

Parameter	Value
Density at 20°C	1.211 g/cm^3
Mean viscosity at 20°C	12.6 mPa.s
Mean viscosity at 37°C	7.6 mPa.s
Osmolality at 37°C	850 mOsm/kg water
pH	7.0 – 7.7
log K_{therm}	18.7

12 CLINICAL PHARMACOLOGY

12.1 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.

12.2 Pharmacodynamics

In MRI, visualization of normal and pathological tissue depends in part on variations in the radiofrequency signal intensity that occurs with:
- differences in proton density
- differences of the spin-lattice or longitudinal relaxation times (T_1)
- differences in the spin-spin or transverse relaxation time (T_2).

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 due to its specific chemical structure. Indeed, gadopiclenol 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.

Due to its high relaxivity, which is presented in Table 4 below, gadopiclenol can be given at half dose of gadolinium compared to other non-specific GBCAs, while providing the same contrast enhancement.

The high relaxivity of gadopiclenol is achieved without *in-vivo* protein interactions since it is comparable in biological medium and it displays only a slight dependence on the strength of the magnetic field (0.47 to 3 T).

Table 4: Relaxivity of GADOPICLENOL at 37°C

	r_1 (L.mmol^{-1}.s^{-1})			r_2 (L.mmol^{-1}.s^{-1})		
Magnetic Field of MRI machine	**0.47 T**	**1.5 T**	**3 T**	**0.47 T**	**1.5 T**	**3 T**
Relaxivity in water	12.6	12.2	11.3	14.6	15.0	11.6
Relaxivity in biological medium	13.2	12.8	13.5	15.1	15.1	14.7

The relaxivity of Gadopiclenol compared to other GBCAs is presented in Table 5.

Table 5: Relaxivity[∞] of GADOPICLENOL and other GBCAs in Water at 1.5 T and 37°C

Gadolinium-Chelate	r_1 (L.mmol^{-1}.s^{-1})	r_2 (L.mmol^{-1}.s^{-1})
GADOPICLENOL	**12.2**	**15.0**
Gadoteric acid	3.0	3.5
Gadobutrol	3.3	3.9
Gadoteridol	2.9	3.4
Gadobenic acid	3.8	4.4
Gadopentetic acid	3.3	3.9
Gadodiamide	3.3	3.9
Gadoxetic acid	4.6	5.3

[∞] Guerbet measurements

Due to its specific macrocyclic structure, gadopiclenol has also a high kinetic stability ($t_{1/2}$ time to observe 50% of decomplexation) (Table 6), which is higher than other macrocyclic GBCAs. That results in a low potential to release gadolinium.

Table 6: Kinetic stability for GADOPICLENOL and other GBCAs at pH 1.2 and 37°C

Gadolinium-Chelate	Structure type	Kinetic stability $t_{1/2}$
GADOPICLENOL	Macrocyclic	~ 20 days
Gadoteric acid	Macrocyclic	~4 days
Gadobutrol	Macrocyclic	~ 18 hours
Gadoteridol	Macrocyclic	~ 4 hours
Gadobenic acid	Linear	<5 s*
Gadopentetic acid	Linear	<5 s
Gadodiamide	Linear	<5 s

** determined at 25°C*

12.3 Pharmacokinetics

Distribution

After intravenous administration, GADOPICLENOL is rapidly distributed in the extracellular fluids. GADOPICLENOL does not undergo protein binding. Mean maximum concentration (C_{max}) and Area Under the Curve (AUC_{inf}) increased proportionally to the dose (0.025 to 0.3 mmol/kg body weight). After a dose of 0.05 and 0.1 mmol/kg body weight, the Cmax was 525 ± 70 µg/mL and 992 ± 233 µg/mL, respectively, and the distribution volume (Vd) was 12.9 ± 1.7 L and 14.3 ± 2.6 L, respectively.

Following GBCA administration, gadolinium is present for months or years in brain, bone, skin, and other organs *[see Warnings and Precautions (5.3)]*.

Elimination

Metabolism

Gadopiclenol is not metabolized.

Excretion

GADOPICLENOL is eliminated rapidly in unchanged form through the kidneys by glomerular filtration. After a dose of 0.05 and 0.1 mmol/kg, 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.

The pharmacokinetic profile of GADOPICLENOL is linear in the studied dose range (0.025 to 0.3 mmol/kg body weight), without difference between males and females.

Specific Populations

Pediatric Patients

One Phase II open-label, uncontrolled, multicenter, single dose of GADOPICLENOL (0.05 mmol/kg) study with age-staggered approach was conducted in 60 paediatric patients aged 2 to 17 years who underwent a CNS MRI.

Individual parameters predicted from a population pharmacokinetic (Pop-PK) model and normalized by body weight were similar between adults and children (Table 7).

Table 7: Pharmacokinetics parameters according to age classes

	2-6 years	**7-11 years**	**12-17 years**	**>18 years**
Cl (L/h/kg)	0.12 [0.05; 0.28]	0.10 [0.04; 0.24]	0.08 [0.04; 0.20]	0.08 [0.05; 0.14]
$t_{1/2}$ (h)	1.29 [0.69; 3.38]	1.48 [0.83; 3.20]	1.77 [1.00; 3.57]	1.82 [0.93; 3.68]
AUC_{inf} (mg.h/L)	403.26 [169.07; 963.83]	477.96 [183.20; 1077.24]	582.09 [267.42; 1290.62]	589.55 [352.98; 937.36]

No dose adjustment is needed in this patient population.

Patients with Renal Impairment

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.

Urinary excretion is delayed with the degree of renal impairment level. In patients with mild or moderate renal impairment, more than 90% of the administered GADOPICLENOL was recovered in urine within 48 hours. In patients with severely impaired renal function about 84% of the administered GADOPICLENOL was recovered in urine within 5 days.

In patients with end stage renal disease (ESRD), haemodialysis effectively removed gadopiclenol from plasma as the percentage of decrease in blood concentrations was 95 to 98% at the end of the first hemodialysis session and 100% after the third hemodialysis session.

No dose adjustment is needed in this patient population.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
No carcinogenicity studies were performed.

Mutagenesis
Gadopiclenol did not demonstrate mutagenic potential in *in vitro* bacterial reverse mutation assays (Ames test), in an *in vitro* chromosome aberration assay in Chinese hamster ovary cells nor in an *in vivo* rat micronucleus assay.

Impairment of Fertility
Gadopiclenol had no effect on fertility and general reproductive performance of male and female rats when given in doses 62 times the human equivalent dose.

13.2 Animal Toxicology and/or Pharmacology

Local intolerance reactions, including slight to moderate erythema and edema were observed after perivenous injection in rabbits suggesting the possibility of local irritation if the contrast medium leaks around the veins in a clinical setting *[see Warnings and Precautions (5.4)]*.

14 CLINICAL STUDIES

Two pivotal phase III studies were conducted and included adult patients undergoing MRI with GADOPICLENOL at 0.05 mmol/kg and MRI with gadobutrol at 0.1 mmol/kg for CNS examination in one study and for examination in other Body regions (head and neck, thorax, abdomen, pelvis and musculo-skeletal system) in the other study.

14.1 CNS Indication

The CNS study included 256 patients with known or highly suspected CNS lesion(s) with a mean age of 57 years (range: 18-84 years), and 53% female patients.

The two primary objectives were achieved:

- All three blinded readers' evaluations demonstrated the superiority of the combined unenhanced/contrast-enhanced MRI (Paired) with GADOPICLENOL over unenhanced MRI (Pre) for all lesion visualization criteria (Table 8).
- For all three blinded readers, non-inferiority of gadopiclenol at 0.05 mmol/kg to gadobutrol at 0.1 mmol/kg was demonstrated for all lesion visualization criteria (Table 9).

Table 8: CNS study - Off-Site Readings - MRI with Gadopiclenol - PAIRED vs PRE – Mixed Model – Full Analysis Set (N=239)

	n	LS Mean (SE)			95% CI difference	p-value
		Paired	Pre	Difference		
Border delineation						
Reader 1	227	3.90 (0.02)	2.08 (0.02)	1.82 (0.03)	[1.76 ; 1.88]	<0.0001
Reader 2	229	3.64 (0.04)	1.74 (0.04)	1.90 (0.05)	[1.81 ; 2.00]	<0.0001
Reader 3	202	3.97 (0.03)	2.61 (0.03)	1.36 (0.04)	[1.29 ; 1.44]	<0.0001
Internal morphology						
Reader 1	227	3.92 (0.03)	1.66 (0.03)	2.26 (0.03)	[2.20 ; 2.33]	<0.0001
Reader 2	229	3.65 (0.03)	1.88 (0.03)	1.77 (0.04)	[1.69 ; 1.85]	<0.0001
Reader 3	202	3.97 (0.04)	2.01 (0.04)	1.96 (0.05)	[1.85 ; 2.06]	<0.0001
Degree of contrast enhancement						
Reader 1	227	3.77 (0.03)	1.00 (0.03)	2.77 (0.04)	[2.69 ; 2.85]	<0.0001
Reader 2	229	3.58 (0.03)	1.00 (0.03)	2.58 (0.05)	[2.49 ; 2.67]	<0.0001
Reader 3	202	3.90 (0.02)	1.00 (0.02)	2.90 (0.03)	[2.84 ; 2.95]	<0.0001

CI: Confidence Interval ; LS: Least Squares ; SE: Standard Error. Only matching lesions are considered.
The models include lesion visualization factor as dependent variable, MRI modality (Pre and Paired MRI) as fixed fact ors, patient as random factor.

Table 9: CNS Study - Off-Site Readings – Comparison Paired Images with Gadopiclenol and Gadobutrol - Mixed Model – Per Protocol Set (N=236)

	n	LS Mean (SE)			95% CI difference	p-value
		GADOPICLENOL	Gadobutrol	Difference		
Border delineation						
Reader 1	227	3.91 (0.02)	3.93 (0.02)	-0.02 (0.02)	[-0.06 ; 0.02]	<0.0001
Reader 2	231	3.64 (0.04)	3.60 (0.04)	0.03 (0.04)	[-0.04 ; 0.11]	<0.0001
Reader 3	220	3.97 (0.01)	3.95 (0.01)	0.02 (0.02)	[-0.01 ; 0.05]	<0.0001
Internal morphology						
Reader 1	227	3.93 (0.02)	3.93 (0.02)	-0.01 (0.02)	[-0.04 ; 0.03]	<0.0001
Reader 2	231	3.64 (0.04)	3.62 (0.04)	0.02 (0.03)	[-0.05 ; 0.09]	<0.0001
Reader 3	220	3.97 (0.02)	3.92 (0.02)	0.05 (0.02)	[0.01 ; 0.08]	<0.0001
Degree of contrast enhancement						
Reader 1	227	3.78 (0.04)	3.77 (0.04)	0.01 (0.03)	[-0.04 ; 0.07]	<0.0001
Reader 2	231	3.57 (0.04)	3.52 (0.04)	0.05 (0.04)	[-0.03 ; 0.12]	<0.0001
Reader 3	220	3.89 (0.03)	3.81 (0.03)	0.09 (0.03)	[0.03 ; 0.15]	<0.0001

CI: Confidence Interval ; LS: Least Squares ; SE: Standard Error.
Only matching lesions are considered. Non-inferiority margin: -0.35
The models include lesion visualization factor as dependent variable, contrast agent and period as fixed factors, patient as random factor.

Lesion-to-Brain Ratio and percentage of lesion enhancement were statistically significantly higher with GADOPICLENOL at 0.05 mmol/kg compared to gadobutrol at 0.1 mmol/kg for all three blinded readers (p<0.0001). For Contrast to Noise Ratio, the difference was statistically significant for two readers (Table 10).

Table 10: CNS Study - Percentage of enhancement , Contrast to Noise Ratio, Lesion to Background Ratio - Off-Site Readings - MRI with Gadopiclenol vs MRI with Gadobutrol - Mixed Model – Full Analysis Set (N=239)

	n	LS Mean (SE) GADOPICLENOL	LS Mean (SE) Gadobutrol	LS Mean Difference (SE)	95% CI	p-value
Percentage of enhancement*						
Reader 1	230	195.01 (7.90)	158.61 (7.90)	36.41 (4.46)	[27.63 ; 45.18]	<0.0001
Reader 2	233	221.52 (9.31)	184.72 (9.31)	36.80 (6.71)	[23.58 ; 50.01]	<0.0001
Reader 3	223	196.55 (8.55)	153.69 (8.55)	42.85 (5.22)	[32.57 ; 53.14]	<0.0001
Contrast to Noise Ratio**						
Reader 1	228	178.32 (12.67)	153.07 (12.67)	25.26 (12.92)	[-0.21 ; 50.72]	0.0519
Reader 2	233	114.60 (7.19)	96.27 (7.19)	18.33 (7.71)	[3.14 ; 33.52]	0.0182
Reader 3	223	60.50 (2.86)	47.04 (2.86)	13.46 (2.41)	[8.70 ; 18.22]	<0.0001
Lesion to Background Ratio**						
Reader 1	228	2.03 (0.04)	1.83 (0.04)	0.20 (0.02)	[0.16 ; 0.24]	<0.0001
Reader 2	233	2.18 (0.04)	1.97 (0.04)	0.21 (0.03)	[0.16 ; 0.26]	<0.0001
Reader 3	223	2.03 (0.04)	1.79 (0.04)	0.24 (0.02)	[0.19 ; 0.28]	<0.0001

CI: Confidence Interval ; LS: Least Squares ; SE: Standard Error; Only matching lesions are considered.
*The models include Percentage of enhancement as dependent variable, contrast agent group and period as fixed factors, patient as random factor.
** The models include Contrast to Noise Ratio (or Lesion to Background Ratio) as dependent variable, contrast agent group, period and the unenhanced value (Pre) as fixed factors, patient as random factor.

The overall diagnostic preference was assessed in a global matched-pairs fashion by three additional blinded readers. The readers expressed in majority a preference for images acquired with GADOPICLENOL (Table 11).

Table 11: CNS study - Overall Diagnostic Preference - Off-Site Readings - MRI with Gadopiclenol vs MRI with Gadobutrol – Extended Full Analysis Set (N=241)

	Reader 4	Reader 5	Reader 6
Overall diagnostic preference			
n	241	241	241
GADOPICLENOL is preferred to gadobutrol	108 (44.8%)	131 (54.4%)	138 (57.3%)
No preference is observed	98 (40.7%)	52 (21.6%)	56 (23.2%)
Gadobutrol is preferred to GADOPICLENOL	35 (14.5%)	58 (24.1%)	47 (19.5%)
p-value*	<0.001	<0.001	<0.001

* Wilcoxon signed-rank test.

14.2 Body Indication

The Body study included 304 patients presenting with known or suspected enhancing abnormality(ies) and/or lesion(s) in at least one body region among head & neck, thorax (including breast), abdomen (including liver, pancreas and kidney), pelvis (including uterus, ovary and prostate) and musculoskeletal (including extremities), with a mean age of 57 years (range: 21-86 years), and 59% female patients.

The two primary objectives were achieved:

- All three blinded readers' evaluations demonstrated the superiority of the combined unenhanced/contrast-enhanced MRI (Paired) with GADOPICLENOL over unenhanced MRI (Pre) for all lesion visualization criteria (Table 12).
- For all three blinded readers, non-inferiority of GADOPICLENOL at 0.05 mmol/kg to gadobutrol at 0.1 mmol/kg was demonstrated for all lesion visualization criteria (Table 13).

Table 12: Body study - Off-Site Readings - MRI with GADOPICLENOL - PAIRED vs PRE – Mixed Model – Full Analysis Set (N=278)

	n	LS Mean (SE)			95% CI difference	p-value
		Paired	Pre	Difference		
Border delineation						
Reader 1	251	3.79 (0.03)	2.26 (0.03)	1.53 (0.04)	[1.46 ; 1.60]	<0.0001
Reader 2	230	3.48 (0.06)	3.01 (0.06)	0.47 (0.06)	[0.36 ; 0.58]	<0.0001
Reader 3	262	3.49 (0.03)	1.78 (0.03)	1.71 (0.04)	[1.65 ; 1.78]	<0.0001
Internal morphology						
Reader 1	251	3.80 (0.02)	1.99 (0.02)	1.81 (0.03)	[1.76 ; 1.87]	<0.0001
Reader 2	230	3.75 (0.05)	3.22 (0.05)	0.53 (0.06)	[0.42 ; 0.64]	<0.0001
Reader 3	262	3.72 (0.03)	1.69 (0.03)	2.03 (0.04)	[1.95 ; 2.11]	<0.0001
Degree of contrast enhancement						
Reader 1	251	3.64 (0.03)	1.00 (0.03)	2.64 (0.04)	[2.56 ; 2.72]	<0.0001
Reader 2	230	2.82 (0.05)	1.00 (0.05)	1.82 (0.07)	[1.68 ; 1.96]	<0.0001
Reader 3	262	3.33 (0.03)	1.00 (0.03)	2.33 (0.04)	[2.26 ; 2.41]	<0.0001

CI: Confidence Interval ; LS: Least Squares ; SE: Standard Error. Only matching lesions are considered.
The models include lesion visualization factor as dependent variable, MRI modality (Pre and Paired MRI) as fixed factors, patient as random factor.

Table 13: Body Study - Off-Site Readings – Comparison Paired Images with GADOPICLENOL and Gadobutrol - Mixed Model – Per Protocol Set (N=260)

	n	LS Mean (SE)			95% CI difference	p-value
		GADOPICLENOL	Gadobutrol	Difference		
Border delineation						
Reader 1	240	3.82 (0.02)	3.81 (0.02)	0.00 (0.03)	[-0.05 ; 0.05]	<0.0001
Reader 2	223	3.56 (0.05)	3.53 (0.05)	0.02 (0.04)	[-0.05 ; 0.10]	<0.0001
Reader 3	243	3.53 (0.03)	3.57 (0.03)	-0.04 (0.03)	[-0.10 ; 0.01]	<0.0001
Internal morphology						
Reader 1	240	3.83 (0.02)	3.83 (0.02)	-0.00 (0.03)	[-0.06 ; 0.05]	<0.0001
Reader 2	223	3.75 (0.04)	3.75 (0.04)	-0.00 (0.04)	[-0.07 ; 0.07]	<0.0001
Reader 3	243	3.74 (0.03)	3.77 (0.03)	-0.03 (0.02)	[-0.08 ; 0.02]	<0.0001
Degree of contrast enhancement						
Reader 1	240	3.69 (0.04)	3.68 (0.04)	0.01 (0.04)	[-0.06 ; 0.09]	<0.0001
Reader 2	223	2.88 (0.07)	2.86 (0.07)	0.03 (0.05)	[-0.07 ; 0.12]	<0.0001
Reader 3	243	3.35 (0.04)	3.37 (0.04)	-0.02 (0.03)	[-0.08 ; 0.04]	<0.0001

CI: Confidence Interval ; LS: Least Squares ; SE: Standard Error.
Only matching lesions are considered. Non-inferiority margin: -0.35
The models include lesion visualization factor as dependent variable, contrast agent and period as fixed factors, patient as random factor.

The percentage of lesion enhancement was statistically significantly higher with GADOPICLENOL at 0.05 mmol/kg compared to gadobutrol at 0.1 mmol/kg for two blinded readers and no differences were observed between the two contrast agents for Lesion to Background Ratio (Table 14).

Table 14: Body Study - Percentage of enhancement and Lesion to Background Ratio - Off-Site Readings - MRI with Gadopiclenol vs MRI with Gadobutrol - Mixed Model – Full Analysis Set (N=273)

	n	LS Mean (SE) Gadopiclenol	LS Mean (SE) Gadobutrol	LS Mean Difference (SE)	95% CI	p-value
Percentage of enhancement*						
Reader 1	249	145.26 (6.95)	116.52 (6.95)	28.73 (7.85)	[13.27 ; 44.20]	0.0003
Reader 2	227	147.78 (6.78)	121.06 (6.78)	26.72 (4.90)	[17.05 ; 36.39]	<0.0001
Reader 3	249	219.95 (40.63)	211.49 (40.63)	8.46 (10.98)	[-13.16 ; 30.08]	0.4415
Lesion to Background Ratio**						
Reader 1	249	2.83 (0.13)	2.74 (0.13)	0.09 (0.12)	[-0.15 ; 0.32]	0.4633
Reader 2	227	3.51 (0.24)	3.72 (0.24)	-0.22 (0.19)	[-0.58 ; 0.15]	0.2418
Reader 3	249	4.36 (0.22)	4.41 (0.22)	-0.04 (0.17)	[-0.38 ; 0.29]	0.7976

CI: Confidence Interval ; LS: Least Squares ; SE: Standard Error; Only matching lesions are considered.
*The models include Percentage of enhancement as dependent variable, contrast agent and period as fixed factors, patient as random factor.
** The models include Lesion to Background Ratio as dependent variable, contrast agent, period and the unenhanced value (Pre) as fixed factors, patient as random factor.

The overall diagnostic preference was assessed in a global matched-pairs fashion by three additional blinded readers. The readers expressed in majority no preference between images with GADOPICLENOL and images with Gadobutrol (Table 15) .

Table 15: Body Study - Overall Diagnostic Preference - Off-Site Readings - MRI with Gadopiclenol vs MRI with Gadobutrol – Extended Full Analysis Set (N=276)

	Reader 4	Reader 5	Reader 6
Overall diagnostic preference			
n	276	276	276
GADOPICLENOL is preferred to gadobutrol	36 (13.0%)	40 (14.5%)	33 (12.0%)
No preference is observed	216 (78.3%)	206 (74.6%)	228 (82.6%)
Gadobutrol is preferred to GADOPICLENOL	24 (8.7%)	30 (10.9%)	15 (5.4%)
p-value*	0.1223	0.2346	0.0079

* Wilcoxon signed-rank test.

14.3 Pediatric population

One Phase II study with single dose of GADOPICLENOL (0.05 mmol/kg) was conducted in 80 pediatric patients aged 2 to 17 years, including 60 patients who underwent a CNS MRI and 20 patients a Body MRI.
The pharmacokinetic profile was similar to the one established in adults. Thus, no dose adjustment is needed in this population.
Diagnostic efficacy was evaluated and there was no difference among the pediatric age groups.

16 HOW SUPPLIED/STORAGE AND HANDLING

GADOPICLENOL is a sterile, clear, colorless to yellow aqueous solution containing 485.1 mg/mL of GADOPICLENOL (equivalent to 0.5 mmol/mL of GADOPICLENOL and to 78.6 mg/mL of gadolinium).

GADOPICLENOL is supplied in the following presentations:

Commented [BL3]: Note to reviewers: The corresponding NDC numbers will be submitted with NDA dossier.

Vial (glass)
- 3 mL vial (filled in 10 mL-vial) packed in a carton box of 1 and 10 (NDC XXXXX-XXX-XX)
- 7.5 mL vial (filled in 10 mL-vial) packed in a carton box of 1 and 10 (NDC XXXXX-XXX-XX)
- 10 mL vial (filled in 10 mL-vial) packed in a carton box of 1 and 10 (NDC XXXXX-XXX-XX)
- 15 mL vial (filled in 20 mL-vial) packed in a carton box of 1 and 10 (NDC XXXXX-XXX-XX)

Prefilled syringe (plastic)
- 7.5 mL prefilled syringe (filled in 15 mL-syringe) packed in a carton box of 1 and 10 (NDC XXXXX-XXX-XX)
- 10 mL prefilled syringe (filled in 15 mL-syringe) packed in a carton box of 1 and 10 (NDC XXXXX-XXX-XX)
- 15 mL prefilled syringe (filled in 15 mL-syringe) packed in a carton box of 1 and 10 (NDC XXXXX-XXX-XX)

Pharmacy Bulk Package
Vial (glass)
- 30 mL vial (filled in 50 mL-vial) packed in a carton box of 1 and 10 (NDC XXXXX-XXX-XX)
- 50 mL vial (filled in 50 mL-vial) packed in a carton box of 1 and 10 (NDC XXXXX-XXX-XX)
- 100 mL vial (filled in 100 mL-vial) packed in a carton box of 1 and 10 (NDC XXXXX-XXX-XX)

Storage
Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP, Controlled Room Temperature (CRT)].
Pre-filled syringes must not be frozen. Frozen pre-filled syringes of GADOPICLENOL should be discarded.
If solidification occur in the vial because of exposure to the cold, vial of GADOPICLENOL should be brought to room temperature before use. If allowed to stand at room temperature for a minimum of 90 minutes, the solution of GADOPICLENOL should return to a clear, colorless to yellow solution.
Before use, visually inspect the solution of GADOPICLENOL.
Do not use the solution in case of severe discoloration, if particulate matter is present or if the container and closure appear damaged.

17 PATIENT COUNSELING INFORMATION

- Advise the patient to read the FDA-approved patient labeling (Medication Guide).

17.1 Nephrogenic Systemic Fibrosis

Instruct patients to inform their healthcare provider if they:
- Have a history of kidney disease, or
- Have recently received a GBCA.

GBCAs increase the risk for NSF among patients with impaired elimination of the drugs. To counsel patients at risk for NSF:
- Describe the clinical manifestations of NSF.
- Describe procedures to screen for the detection of renal impairment.

Instruct the patients to contact their physician if they develop signs or symptoms of NSF following GADOPICLENOL administration, such as burning, itching, swelling, scaling, hardening and tightening of the skin; red or dark patches on the skin; stiffness in joints with trouble moving,

bending or straightening the arms, hands, legs or feet; pain in the hip bones or ribs; or muscle weakness.

17.2 Common Adverse Reactions

Inform patients that they may experience:

- Reactions along the venous injection site, such as mild and transient burning or pain or feeling of warmth or coldness at the injection site.
- Side effects of headache, nausea, abnormal taste and feeling hot.

17.3 General Precautions

- Pregnancy: Advise pregnant women of the potential risk of fetal exposure to GADOPICLENOL *[see Use in Specific Populations (8.1)]*.
- Gadolinium Retention: Advise patients that gadolinium is retained for months or years in brain, bone, skin, and other organs in patients with normal renal function. The clinical consequences of retention are unknown. Retention depends on multiple factors and is greater following administration of linear GBCAs than following administration of macrocyclic GBCAs *[see Warnings and Precautions (5.3)]*.

Guerbet

Manufactured by
Liebel-Flarsheim Company LLC,
8800 Durant Road, Raleigh, North Carolina (NC) 27616, USA

Distributed by
Guerbet LLC
821 Alexander Road, Suite 204, Princeton, NJ 08540, USA

MEDICATION GUIDE
GADOPICLENOL
(gadopiclenol)
Injection for intravenous use

What is GADOPICLENOL?

- GADOPICLENOL is a prescription medicine called a gadolinium-based contrast agent (GBCA). GADOPICLENOL, like other GBCAs, is injected into your vein and used with a magnetic resonance imaging (MRI) scanner.
- A MRI exam with a GBCA, including GADOPICLENOL, helps your doctor to see problems better than an MRI exam without a GBCA.
- Your doctor has reviewed your medical records and has determined that you would benefit from using a GBCA with your MRI exam.

What is the most important information I should know about GADOPICLENOL?

- GADOPICLENOL contains a metal called gadolinium. Small amounts of gadolinium can stay in your body including the brain, bones, skin and other parts of your body for a long time (several months to years).
- The recommended dose of GADOPICLENOL contains twice less quantity of gadolinium compared to other GBCAs used in clinical practice.
- It is not known how gadolinium may affect you, but so far, studies have not found harmful effects in patients with normal kidneys.
- Rarely patients have reported pains, tiredness, and skin, muscle or bone ailments for a long time, but these symptoms have not been directly linked to gadolinium.
- There are different GBCAs that can be used for your MRI exam. The amount of gadolinium that stays in the body is different for different gadolinium medicines. Gadolinium stays in the body more after linear GBCA agents and among them, more after Omniscan than after Eovist or MultiHance. Gadolinium stays in the body the least after GADOPICLENOL, Clariscan, Dotarem, Gadavist or ProHance.
- People who get many doses of gadolinium medicines, women who are pregnant and young children may be at increased risk from gadolinium staying in the body.
- Some people with kidney problems who get gadolinium medicines can develop a condition with severe thickening of the skin, muscles and other organs in the body (nephrogenic systemic fibrosis). Your healthcare provider should screen you to see how well your kidneys are working before you receive GADOPICLENOL.

Do not receive GADOPICLENOL if you have had a severe allergic reaction to GADOPICLENOL.

Before receiving GADOPICLENOL, tell your healthcare provider about all your medical conditions, including if you:

- have had any MRI procedures in the past where you received a GBCA. Your healthcare provider may ask you for more information including the dates of these MRI procedures.
- are pregnant or plan to become pregnant. It is not known if GADOPICLENOL can harm your unborn baby. Talk to your healthcare provider about the possible risks to an unborn baby if a GBCA such as GADOPICLENOL is received during pregnancy.
- have kidney problems, diabetes, or high blood pressure.
- have had an allergic reaction to dyes (contrast agents) including GBCAs.

What are possible side effects of GADOPICLENOL?

- **See "What is the most important information I should know about GADOPICLENOL?"**
- **Allergic reactions. GADOPICLENOL can cause allergic reactions that can sometimes be serious. Your healthcare provider will monitor you closely for symptoms of an allergic reaction.**

The most common side effects of GADOPICLENOL include: injection site pain, headache, fatigue, injection site coldness, nausea and diarrhoea.
These are not all the possible side effects of GADOPICLENOL.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective uses of GADOPICLENOL.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your healthcare provider for information about GADOPICLENOL that is written for health professionals.

What are the ingredients in GADOPICLENOL?
Active ingredient: gadopiclenol
Inactive ingredients: tetraxetan, trometamol, hydrochloric acid and/or sodium hydroxide, water for injection
Manufactured by: Liebel-Flarsheim Company LLC
Distributed by: Guerbet LLC
For more information, go to www.guerbet-us.com or call 1-877-729-6679.