swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Elucirem

International non-proprietary name: gadopiclenol
Pharmaceutical form: solution for injection
Dosage strength(s): 0.5 mmol/mL
Route(s) of administration: intravenous use
Marketing authorisation holder: Guerbet AG
Marketing authorisation no.: 68791
Decision and decision date: approved on 21 December 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical classification system
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BLQ	Below limit of quantification
BW	Body Weight
CI	Confidence interval
CL	Clearance
CM	Contrast media
C_{max}	Maximum observed plasma/serum concentration of drug
CNR	Contrast to noise ratio
CNS	Central nervous system
CT	Computed tomography
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOTA	Tetraxetan (dodecane tetraacetic acid)
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ERA	Environmental risk assessment
FAS	Full analysis set
FDA	Food and Drug Administration (USA)
GBCAs	Gadolinium-based contrast agents
Gd	Gadolinium
GI	Gastrointestinal
GLP	Good Laboratory Practice
hERG	Human ether-a-go-go related gene
HPLC	High-performance liquid chromatography
IA	Intra-arterial
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IMP	Investigational medicinal product
INN	International non-proprietary name
ITT	Intention-to-treat
IV	Intravenous
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
MDRD	Modification of diet in renal disease
Min	Minimum
MRHD	Maximum recommended human dose
MRI	Magnetic resonance imaging
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
NSF	Nephrogenic systemic fibrosis
NYHA	New York Heart Association

PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PPS	Per protocol set
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SUSAR	Suspected unexpected serious adverse reaction
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TGF-β	Transforming growth factor-beta
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
Vd	Volume of distribution

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for gadopiclenol in the above-mentioned medicinal product.

2.2 Indication and dosage

2.2.1 Requested indication

Magnetic resonance imaging (MRI) contrast media for central nervous system (CNS) diagnostics and other body regions.

2.2.2 Approved indication

In adults
ELUCIREM is a gadolinium-based contrast agent indicated in adults for use with magnetic resonance imaging (MRI) to detect and visualise lesions with abnormal vascularity
- in the CNS area (see warnings and precautions and properties/effects),
- in other areas of the body (see warnings and precautions and properties/effects).

ELUCIREM should be used only if diagnostic information is significant and cannot be obtained by non-contrast-enhanced magnetic resonance imaging (MRI).

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dose of gadopiclenol is 0.05 mmol/kg body weight, equivalent to 0.1 mL/kg body weight for all indications. This dose is equivalent to half the standard dose of a non-specific gadolinium-containing contrast agent.
The lowest dose that provides sufficient enhancement for diagnostic purposes should be used. The dose should be calculated based on the patient's body weight and should not exceed the recommended dose per kilogram of body weight.

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	16 May 2022
Formal objection	14 June 2022
Response to formal objection	13 July 2022
Formal control completed	8 August 2022
List of Questions (LoQ)	28 February 2023
Response to LoQ	29 May 2023
Preliminary decision	26 July 2023
Response to preliminary decision	20 September 2023
Labelling corrections	20 November 2023
Response to labelling corrections	24 November 2023
Final decision	21 December 2023
Decision	approval

3 Medical context

Contrast media (CM) enhance the visualisation of structures and functions of the body in imaging procedures such as X-ray diagnostics, magnetic resonance imaging (MRI) and sonography (ultrasound).
According to the ATC code, 4 groups of CM are distinguished; Elucirem, with the active ingredient gadopiclenol, belongs to the group of paramagnetic contrast media for magnetic resonance imaging. The contrast-enhancing effect is mediated by gadopiclenol as in other paramagnetic contrast media. The active moiety enhances the relaxation rates of water protons in its vicinity in the body, leading to an increase in signal intensity (brightness) of tissues.

Within the paramagnetic gadolinium-containing CM, a distinction is made between linear and macrocyclic CM. Elucirem belongs to the newer group of macrocyclic paramagnetic contrast media. It is a non-ionic macrocyclic gadolinium (Gd) complex with the excipient tetraxetan (USAN), which is equivalent to DOTA. Another excipient, trometamol, is also known as tromethamine.

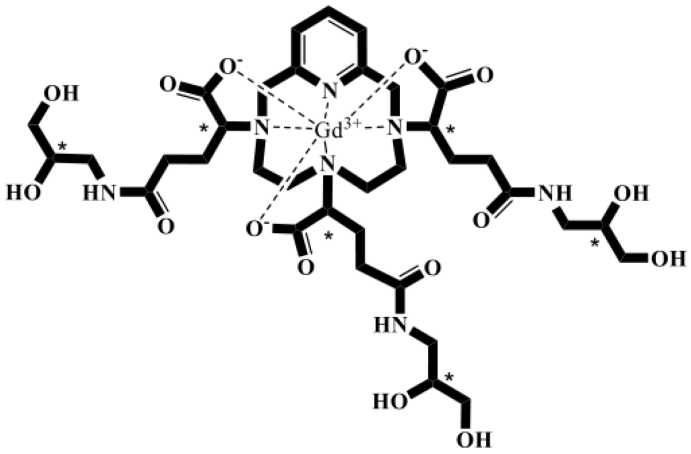
In 2018, the European Medicines Agency (EMA) reported that small amounts of gadolinium were found to be deposited in the brain after the use of gadolinium-containing contrast agents. Due to the unknown long-term risks of gadolinium deposition in the brain, the suspension of marketing authorisations for intravenous linear gadolinium-containing contrast agents in the EU was recommended, with the exception of the agents gadoxetic acid and gadobenic acid, which remain available, but only for MRI imaging of the liver.
Since then, the rule for all gadolinium-containing CM approved in Switzerland is that they should only be used if the diagnostic information is necessary and cannot be obtained with MRI without contrast enhancement.

Several gadolinium-containing preparations are currently available in Switzerland, including gadoterate (Dotarem®), gadobutrol (Gadovist®), and gadoteridol (ProHance®), each belonging to the class of gadolinium-containing macrocyclic contrast agents, which are mostly used for examination of different body regions, whole body, MR-angiography etc. (for details see the information for healthcare professionals). Gadopiclenol (Elucirem®) will be a further additional macrocyclic product for different body regions. Some older preparations belonging to the class of gadolinium-containing linear contrast agents are now limited for use in special situations/organ systems like liver or MR-arthrography.

4 Quality aspects

4.1 Drug substance

INN: gadopiclenol
Chemical name: rac-[(2R,2'Ξ,2''Ξ)-2,2',2''-(3,6,9-triaza-κ3N3,N6,N9-1(2,6)-pyridina-κN1-cyclodecaphane-3,6,9-triyl)tris(5-{[(2Ξ)-2,3-dihydroxypropyl]amino}-5-oxopentanoato-κ3O1,O1',O1'')(3−)]gadolinium
Molecular formula: $C_{35}H_{54}GdN_7O_{15}$
Molecular mass: 970.11 g/mol
Molecular structure:



Gadopiclenol, drug substance, is a white to off-white powder.

Gadopiclenol is manufactured in five chemical reaction steps using well-defined starting materials with acceptable specifications.
The crude active substance is purified by three purification operations performed before drying to yield pure gadopiclenol.

Appropriate proof-of-structure data have been supplied for the active substance.
All potential and actual impurities have been well discussed with regards to their origin and have been characterised and monitored appropriately.

An appropriate specification is provided for the active substance. Analytical methods have been correctly validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis date are provided and comply with the proposed specification.

Appropriate stability data have been provided supporting a suitable retest period when stored in the proposed packaging.

4.2 Drug product

The drug product gadopiclenol 0.5 mmol/mL is supplied as a clear, colourless to pale yellow sterile aqueous solution.
The drug product gadopiclenol 0.5 mmol/mL is presented in vials (7 different filled volumes) and syringes (3 different filled volumes) for single use only. Both presentations offer the same dosages and compositions.
The composition is adequately described, qualitatively and quantitatively.

Suitable pharmaceutical development data have been provided for the finished product formulation and manufacturing process.

A satisfactory batch formula has been provided for the manufacture of the product, together with an appropriate account of the manufacturing process, which is described in sufficient detail.
The manufacturing process has been validated on three commercial scale batches. The results are satisfactory. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

The finished product specification is satisfactory. The test methods have been described and validated adequately. Batch data have been provided that comply with the release specifications.

The primary packaging is either a single-use 10 mL, 20 mL, 50 mL or 100 mL type I clear glass vial with a rubber stopper and an aluminium overseal or a single-use 15 mL polypropylene syringe with a rubber plunger stopper and capped with a rubber tip.

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.
Samples were tested according to the shelf-life specifications.
Based on the results, a shelf-life of 2 years for the unopened vial or syringe is set, with the storage recommendation “Store at room temperature (15 to 25°C)”. This is satisfactory.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

5.1 Pharmacology

Gadopiclenol enhances a signal in magnetic resonance imaging due to the specific chemical structure that allows binding of two water molecules to gadolinium, whereas only one water molecule is present for the other gadolinium-based contrast agents (GBCAs).
The proof of concept was investigated in rodent models of brain tumour and brain metastasis. Other GBCA products were used in comparison. Studies showed that gadopiclenol at half-dose (0.05 mmol/kg) was as effective as commercial products at 0.1 mmol/kg. Higher signal intensity allowed detection of a significantly higher number of brain metastasis in the mouse model.
Gadopiclenol induced a concentration-dependent inhibition of hERG tail current amplitude that was statistically significant at ≥5 mmol/kg. A NOEL of 2.5 mmol/L was established. However, the effect was considered to be non-specific, caused by the high molecular weight of gadopiclenol molecule and hyperosmolarity of the test article solution, as described for the other GBCAs. No significant effects on action potential parameters were observed in the rabbit Purkinje fiber model. No effect of gadopiclenol on the cardiovascular system was seen in conscious dogs up to 13-fold the clinical exposure. Slight and transient increases in arterial blood pressure, QT, QTc interval and in QRS complex duration, without a change in the HR, RR and PR intervals, were observed in anaesthetised dogs at 2 mmol/kg. However, there were no effects on the ECG parameters in single- and repeat-dose toxicity studies in dogs up to the maximum dose, corresponding to 26 times the intended human exposure. Taken together, the potential for gadopiclenol to induce QT prolongation and cardiac repolarisation problems in humans seems very low. No effects on a battery of behavioural and physiological parameters covering the main central and peripheral nervous system functions were observed in rats after single intravenous administration up to 5 mmol/kg. A proconvulsant effect of gadopiclenol was observed in Wistar rats at 5 mmol/kg only (19 times the intended human exposure). Seizure is a known adverse side effect of the GBCA class of molecules. A warning note is included in the information for healthcare professionals. There were no effects on respiratory parameters in rats up to the highest dose level, corresponding to 19 times the intended human dose. Bronchoconstriction (associated with transitory episodes of muscular spasms) was observed at the dose level of 5 mmol/kg in guinea pigs. The NOAEL is determined at 2.5 mmol/kg (10 times the intended human dose, based on the body surface area). In rats with saline overload, gadopiclenol induced an increase in urine osmolality and significant decreases in free water clearance at ≥2.5 mmol/kg. However, there was no change in the glomerular filtration rate and no relevant changes in the excretion fractions of sodium, potassium and chloride.

5.2 Pharmacokinetics

Gadopiclenol shows linear kinetics after single IV administration in rats and dogs. Peak exposure is reached 5 min post-dose. The elimination phase in both species was linear, with the difference that single-phase elimination is observed in dogs, whereas in rats a rapid initial phase followed by a slower elimination phase is observed. $T_{1/2}$ was approximately 0.3-1.5 h in all nonclinical species and in humans. Clearance (CL) and volume of distribution (Vd) were similar across the animal species and ranged from 200 to 468 mL/h/kg and 193 to 312 mL/kg, respectively. Vd indicated that gadopiclenol distribution to the extracellular space was similar to that for other GBCAs. There were no gender differences. *In vitro* binding of gadopiclenol to plasma proteins and red blood cells was low in all nonclinical species and in humans. Gadopiclenol was metabolically stable *in vitro* in hepatic microsomes from rats, rabbits, dogs, monkeys, and humans (no metabolites found). Renal clearance represents the main route of excretion in all species. Unchanged gadopiclenol was measured in

plasma and urine of rats, dogs and humans. Radioactively labelled gadopiclenol is widely distributed in all body tissues 10 minutes after a single IV injection. The highest concentration of radioactivity is measured in kidneys and bladder wall. After 1 hour, the level of radioactivity starts to decline and was detectable only in kidneys after 336 hours. Distribution to the brain was minor, indicating little penetration through the blood-brain barrier. Gadopiclenol crosses the placenta and is detectable in the fetus at low levels. This is adequately described in the information for healthcare professionals. Gadopiclenol is excreted in the milk of lactating female rats and detected in lactating pups. In a pre- and postnatal development study, gadolinium was detected in all examined tissues of gadolinium-dosed animals (dams and pups), and its concentration increased dose-dependently. In decreasing order of exposure, the exposed tissues for dams and pups were the kidneys, the femur/skin/liver, the brain/cerebellum, and the plasma. The gadolinium concentrations in pups compared with dams was negligible in kidney, liver, femur and skin, up to 14% in cerebellum and brain, and up to 11% in plasma. A similar pattern of distribution was observed in the juvenile toxicity study in rats. In the gadolinium retention study in juvenile and adult animals, two days after single dosing, gadolinium concentrations compared to adult animals were lower in kidney, higher in brain and cerebellum, and similar in other tissues. This is probably due to the immaturity of the kidneys and the brain in juvenile animals. After repeated dosing, these values were equivalent between juvenile and adult animals. After an 8-week treatment-free recovery period, the recovery was complete in all adult and juvenile groups. A long-term retention study in rats did not show any difference between gadopiclenol and other macrocyclic GBCAs and confirmed the well-known toxicological properties of GBCAs, with the linear form being less stable and more toxic compared to the macrocyclic GBCAs. According to the totality of data, it can be concluded that gadopiclenol will not pose a higher risk of neurotoxicity than other approved GBCAs. The information for healthcare professionals contains a warning note with regard to Gd retention.

5.3 Toxicology

Rats and dogs were considered as relevant species based on similar PK as in humans. As gadopiclenol is intended for diagnostic purposes and will be administered to humans as a single dose, results of the acute toxicity studies are considered more relevant. Rabbits were used as a second species for the embryofetal development study. Additional studies included juvenile toxicity studies, local tolerance and hypersensitivity studies. Animals were dosed IV, corresponding to the intended human administration route. Across all nonclinical studies in rodents, decreased activity, swelling of the face/muzzle or limbs was observed at high doses (≥10 mmol/kg/day), appearing 1-4 hours post-dosing with complete resolution of symptoms. Similar symptoms were only occasionally observed in dogs at a dose of 4 mmol/kg/day and in rabbits at 5 mmol/kg/day.
Kidney was the main target organ in rats and dogs in acute and repeated dose toxicity studies, which correlates with its excretory role. After single-dose administration, a statistically higher kidney weight, associated with minimal to mild tubular cell vacuolation and with a dose-related increase in severity, was observed in rats. No related cellular necrosis or inflammation was apparent. Due to the partial reversibility (minimal tubular vacuolation remained), the NOAEL of 10 mmol/kg was accepted in the acute dose toxicity study. This corresponds to 59 times the intended human exposure.
In dogs, completely reversible minimal to mild vacuolation of the tubular epithelium, characterised by a foamy appearance of the epithelium, was found at 4 mmol/kg (safety margin: 25). The same findings were observed across repeated dose studies with dose-and time-dependent increases in severity in both species. The findings were partially reversible in the recovery period. The NOAELs were 5 mmol/kg/day and 2.5 mmol/kg/day for 2 weeks and 28-day repeat-dose toxicity studies in rats, respectively. The safety margins based on findings from 14-day and 28-day repeat-dose toxicity studies in rats were 16-fold and 9-fold, respectively, for a proposed clinical dose of 0.05 mmol/kg.
Gadopiclenol was negative in the Ames test in the *in vitro* mouse lymphoma assay and in the *in vivo*, mammalian erythrocyte micronucleus test in rats. Carcinogenicity studies were not conducted, which is accepted considering the single diagnostic use. There were no effects on male and female reproductive performance and fertility in rats up to 10 mmol/kg/day, corresponding to 62-fold the

proposed clinical dose. The effect of gadopiclenol on embryofetal development (EFD) was evaluated in rats (0, 2.5, 5 and 10 mmol/kg) and rabbits (0, 1, 2.5 and 5 mmol/kg) up to the maternal toxic dose. In both studies there were no effects on pregnancy parameters or fetal viability. There were no visceral variations or malformations. In rats, NOAELs were 5 mmol/kg for maternal toxicity and 10 mmol/kg/day for developmental toxicity, corresponding to the safety margins of 26 and 52, respectively. In rabbits, the NOAEL for maternal and developmental toxicity was 2.5 mmol/kg/day, giving a safety margin of 24. No gadopiclenol-related effects on reproductive or developmental parameters were observed in the postnatal developmental study in rats up to the dose of 10 mmol/kg (safety margin 55). Gadopiclenol was well tolerated in juvenile animals after single- and repeat-dose administration. There were no effects on development, sexual maturation or neurobehavioural development. Cortical tubular vacuolation in the kidneys was noted at all dose levels, but was completely reversible after the treatment-free period. The NOAEL for juvenile toxicity was 2.5 mmol/kg/day, with a safety margin of 8-fold for a proposed clinical dose. Injection of gadopiclenol was well tolerated following a single administration in rats (IV), dogs (IV) and rabbits (IV, IA), and following repeated IV injections in rats and dogs. Since irritation was observed following single perivenous and repeated IV administrations in rabbits, misadministration should be avoided. Studies in renally impaired rats confirmed that the risk of nephrogenic systemic fibrosis is associated with previous exposure to the linear form of GBCA. No profibrotic risk was determined after gadopiclenol administration. No increase in TGF-β was observed in immunohistochemistry staining of dorsal lumbar skin sections of rats during the repeat-dose toxicity study. According to the investigational studies in rats, gadopiclenol is not expected to pose a higher risk of neurotoxicity than other approved GBCAs. There is no concern with respect to excipients or impurities. The description of the safety findings from the nonclinical studies and their evaluation in Module SII of the RMP is considered adequate. A significant risk for the environment by the introduction of gadopiclenol on the market is not expected.

5.4 Nonclinical conclusions

The submitted documentation was sufficient to conduct a risk assessment.
Overall, the pharmacology and toxicological profile of gadopiclenol were adequately characterised in the nonclinical studies. From the nonclinical side, the application is approvable.

6 Clinical aspects

6.1 Clinical pharmacology

The evaluation of the clinical pharmacology data in this application has been based on previous regulatory decisions by the FDA. The available assessment report and respective product information from FDA were used as a basis for the clinical pharmacology evaluation.

For further details concerning clinical pharmacology, see the information for healthcare professionals in the appendix of this report.

6.2 Dose finding and dose recommendation

Dose finding was based on two studies (Phase 1/2a Study GDX-44-003, Phase IIb Study GDX-44-004).

The Phase 1/2a Study GDX-44-003 was a two-part single-centre dose-finding study with PK assessment and pharmacodynamics with brain MRI. The requested dose of 0.05 mmol/kg produced sufficient information mostly, and safety was acceptable, with headache being the most common adverse event followed by injection pain.

The Phase 2b Study GDX-44-004 was a multi-centre (28), double-blind, 1:1:1:1 randomised, controlled, parallel-group, crossover dose-finding study with brain MRI. A comparison was made with gadobenate dimeglumine (MultiHance®) at the standard dose of 0.1 mmol/kg. Subjects with brain metastasis were included, making up an actual percentage of 22.5%. Subjects presenting with acute or chronic grade III (at least) renal insufficiency, defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m² based on one eGFR assessment performed on the day of the MRI prior to the first contrast agent injection, and patients with class III/IV congestive heart failure (NYHA) were excluded.
252 subjects in subset 2 were randomly assigned in a 1:1:1:1 ratio to receive 0.025, 0.05, 0.1 or 0.2 mmol/kg body weight (BW) of gadopiclenol and 0.1 mmol/kg BW of MultiHance®. The primary criterion was the contrast-to-noise ratio (CNR).
For all 3 independent off-site readers, gadopiclenol at the doses of 0.1 and 0.2 mmol/kg demonstrated significant superiority for CNR as compared with MultiHance® at the dose of 0.1 mmol/kg.
Gadopiclenol at the dose of 0.05 mmol/kg showed a similar CNR as compared with MultiHance® at the dose of 0.1 mmol/kg. Gadopiclenol at the dose of 0.025 mmol/kg showed inferior CNR results compared to MultiHance®.
Safety data suggest a dose-effect relationship mostly associated with an increased number of reports of injection site pain with increasing doses of gadopiclenol and more gastrointestinal disorders at the dose of 0.2 mmol/kg.
One SAE was assessed as related to gadopiclenol, involving a young adult patient who experienced an increase of creatinine >25 % within 24h after a dose of 0.1 mmol/kg, but with blood values of creatinine that remained in the normal ranges. Additionally, eGFR (MDRD) was diminished. Another subject receiving a dose of 0.1 mmol/kg showed a non-serious blood urea and creatinine increase after 24 hours too. All SAEs resolved. No deaths were reported among the subjects of the safety set.

In summary, these studies identified a dose of 0.05 mmol/kg gadopiclenol as sufficient (compared to the standard dose of 0.1 mmol/kg MultiHance®). Higher doses of gadopiclenol (0.1 mmol/kg, 0.2 mmol/kg) seemed to show higher diagnostic accuracy (Phase 2b Study GDX-44-004). However, potentially first signs of nephrotoxicity were seen in single non-elderly adults with normal renal function at baseline with higher doses of gadopiclenol, e.g. 0.1 mmol/kg (Phase 2b Study GDX-44-004).

Due to its high relaxivity (measured in vitro), the recommended dose of gadopiclenol is lower (half-dose) compared to other contrast agents used in clinical practice, thus reducing the amount of

gadolinium administered for the same examination session. For further details regarding relaxivity, please refer to the information for healthcare professionals.

6.3 Efficacy

Two Phase 3 studies with a similar design were pivotal: GDX-44-010 and GDX-44-011.

GDX-44-010 Phase 3 study - MRI of brain or spine lesions
GDX-44-010 was a prospective, multi-centre (33), randomised, double-blind, controlled and crossover Phase 3 study. The study included 256 adult patients with brain or spine lesions who underwent two MRI scans, one with gadopiclenol at 0.05 mmol/kg and the other with gadobutrol at 0.1 mmol/kg. 250 patients were analysed for safety, and between 236 and 251 patients, depending on the analysis sets, were analysed for efficacy. The blinded centralised image evaluations (off-site reading) were performed by 3 independent blinded radiologists.
The main inclusion criteria were the following: Female or male adult patients presenting with known or highly suspected CNS lesion(s) with focal areas of disrupted blood-brain barrier (BBB) (e.g. primary and secondary tumours) based on results of a previous imaging procedure such as Computed Tomography (CT) or MRI.
Subjects presenting with an estimated Glomerular Filtration Rate (eGFR) <30 mL/min/1.73m² based on eGFR assessment performed one day prior to each contrast agent injection (V1, V2, V4), patients with class III/IV congestive heart failure (NYHA) and patients with liver failure or liver transplantation were excluded.

Primary objective 1 was to demonstrate the superiority of gadopiclenol-enhanced MRI at 0.05 mmol/kg body weight (BW) compared to unenhanced MRI for patients referred for contrast-enhanced MRI of CNS, in terms of 3 lesion visualisation co-primary criteria (border delineation, internal morphology and degree of contrast enhancement) using the patient as his/her own control. Primary criteria 1 was done in the full analysis set FAS 1 (extended FAS 1, including all patients who had both gadopiclenol pre contrast and Paired images assessable).

Primary objective 2 was to demonstrate the non-inferiority of gadopiclenol at 0.05 mmol/kg compared to gadobutrol at 0.1 mmol/kg in terms of the same lesion visualisation co-primary criteria as mentioned above for patients referred for contrast-enhanced MRI of CNS. Primary criteria objective 2 was analysed in the per-protocol set (PPS 2), which included all patients from FAS 2 who had no major protocol deviations for primary criteria 2.

There were no pivotal secondary analyses. Thus, all secondary analyses used descriptive statistics only and can only be considered supportive.

256 patients were randomised: 128 in each arm. 14 patients prematurely discontinued the study: 6 before receiving the first contrast agent and 8 before receiving the second contrast agent. These numbers of completers were in an acceptable range and nearly equally distributed between both groups.
Major protocol deviations were reported for 27 randomised patients (10.5%). As the cases were low, a significant impact on results is unlikely.
According to the baseline disease characteristics, the most frequent diseases were meningioma (29.7%), metastases in the central nervous system (18.0%), glioblastoma (10.9%) and acoustic neuroma (8.4%).
The most frequent medical history consisted of surgical and medical procedures, mostly radiotherapy to brain (20.8%), brain tumour operation (16.0%), chemotherapy (15.6%), radiotherapy (7.6%), hysterectomy (6.4%), and craniotomy (5.2%).
eGFR was locally measured at Visit 2 and Visit 4. In agreement with the inclusion/exclusion criteria, no patient had an eGFR below 30 mL/min/1.73m². Among the patients who received gadopiclenol at V2 and gadobutrol at V4, 6.4% had an eGFR <60 mL/min/1.73m² at V2 and 5.8% at V4. Among the

patients who received gadobutrol at V2 and gadopiclenol at V4, 10.4% had an eGFR <60 mL/min/1.73m² at V2 and 8.2% at V4.

Results

Primary criteria 1: The differences in the mean scores for border delineation, internal morphology and degree of contrast enhancement were significantly different from zero, with a type 1 error set at 0.025 in favour of paired images compared to pre-contrast images for all three readers ($p<0.0001$ in all cases). Therefore, the null hypothesis was rejected, and the primary objective 1 was achieved.
Primary criteria 2: When comparing images with gadopiclenol to images with gadobutrol, the differences in the mean scores for border delineation, internal morphology and degree of contrast enhancement were close to 0 in all cases, with a lower limit of the 95% CI of the difference not lower than -0.06. That is well above the non-inferiority margin of -0.35 for all three readers ($p<0.0001$ in all cases). Therefore, the null hypothesis was rejected and the primary objective 2 was achieved.
As most of the 95% CI of the difference included the value “0”, superiority of gadopiclenol at 0.05 mmol/kg over gadobutrol at 0.1 mmol/kg could not be concluded.
Supportive analyses showed similar results. However, the group of patients with spine examination, with 5 (2.1%) patients, was too small to allow meaningful conclusions on efficacy of gadopiclenol in spine examination.
For further details, please refer to the information for healthcare professionals.

Phase 3 Study GDX-44-011 – MRI of different body regions

GDX-44-011 was a prospective, multi-centre (33), randomised, double-blind, controlled and crossover Phase 3 study with 300 patients (randomised with administration of gadopiclenol/gadobutrol), which had a similar design to that of the Phase 3 study conducted for CNS imaging (GDX-44-010). However, there were some relevant differences in the sample size calculation and quantity of off-site readers. 301 patients were analysed for safety, and between 260 and 300 patients, depending on analysis sets, were analysed for efficacy.

The main inclusion criteria were the following. Female or male adult patients presenting with known or suspected enhancing abnormality(ies) and/or lesion(s) in at least one of the following body regions: head & neck, thorax (including breast), abdomen (including liver, pancreas and kidneys), pelvis (including uterus, ovary and prostate) and musculoskeletal (including extremities). This was based on a previous imaging procedure performed within 12 months prior to informed consent form signature. The main exclusion criteria were the same as those mentioned above in the description of study GDX-44-010 (eGFR <30 mL/min/1.73m², class III/IV congestive heart failure (NYHA), liver failure or liver transplantation).

In contrast to GDX-44-010, more blinded readers were recruited (due to different body regions) in GDX-44-011. The blinded centralised image evaluations (off-site reading) were performed by 3 independent blinded radiologists per body region, which were pooled together from all body regions for the primary endpoint analyses (pooled readers 1, 2, and 3), respectively.
Sample size in GDX-44-011 was slightly adapted because of a suggested higher drop-out rate.

Primary objectives 1 and 2 were similarly defined as in study GDX-44-010.

There were no pivotal secondary analyses. Thus, all secondary analyses used descriptive statistics only and can only be considered supportive.

Overall, 304 patients were randomised: 152 in each arm.
The 304 randomised patients underwent MRI for imaging of different body regions: abdomen for 108 patients, head & neck for 25, musculoskeletal for 23, pelvis for 65 and thorax for 79.

29 patients prematurely discontinued the study: 4 before receiving the first contrast agent, 23 before receiving the second contrast agent and 2 after receiving the second contrast agent. Although premature discontinuation in study GDX-44-011 was about twice as high as in study GDX-44-010, these numbers of completers were still in the acceptable range with more or less similar distribution between both groups.
Major protocol deviations were reported for 50 randomised patients (16.4%). Major deviations occurred more frequently in study GDX-44-011, by a factor of about 1.5, than in study GDX-44-010. However, as the number of cases was low, a major impact on the results is unlikely.

In accordance with the inclusion criteria, the patients presented with known or suspected enhancing abnormality(ies) and/or lesion(s) in at least one of the following body regions: head & neck, thorax (including breast), abdomen (including liver, pancreas and kidney), pelvis (including uterus, ovary and prostate) and musculoskeletal (including extremities). In both FAS 1, 66.3% of the patients presented with neoplasms (benign, malignant and unspecified [including cysts and polyps]), the most frequent being metastasis to liver (9.5%), and breast cancer (9.2%). The other most frequent diseases according to preferred terms were breast mass (9.0%) and hepatic lesions (4.7%). The imaging procedures documenting the diseases were mainly CT (42.4%) and ultrasound (25.5%). The imaging procedure had been performed within a median of 1 month before the first injection of study contrast agent.
Among the 301 patients of the Safety Set, 6 (2.0%) reported previous intolerance to a contrast agent: iodinated contrast agent for 5 patients, diagnostic radiopharmaceutical for one patient.
eGFR was measured in a local laboratory at Visit 2 and Visit 4. In agreement with the inclusion/exclusion criteria, no patient had an eGFR below 30 mL/min/1.73m². Among the patients who received gadopiclenol at V2 and gadobutrol at V4, 8.6% had an eGFR <60 mL/min/1.73m² at V2 and 9.5% at V4. Among the patients who received gadobutrol at V2 and gadopiclenol at V4, 8.1% had an eGFR <60 mL/min/1.73m² at V2 and 7.1% at V4.

Results
Primary criteria 1: The differences in the mean scores for border delineation, internal morphology and degree of contrast enhancement were significantly different from zero, with a type 1 error set at 0.025 in favour of paired images compared to pre-contrast images for all three readers ($p<0.0001$ in all cases). Therefore, the null hypothesis was rejected, and the primary objective 1 was achieved. As pooled off-site readers were used, differences between the pooled three readers seemed to be higher than in study GXD-44-010 without pooled readers, especially with regard to pre-contrast images. Different body areas may have further enhanced heterogeneity.
Primary criteria 2: When comparing images with gadopiclenol to images with gadobutrol, the differences in the mean scores for border delineation, internal morphology and degree of contrast enhancement were close to 0 in all cases, with a lower limit of the 95% CI of the difference not lower than -0.10. That was largely above the non-inferiority margin of -0.35 for all three readers ($p<0.0001$ in all cases). Therefore, the null hypothesis was rejected, and the primary objective 2 was achieved. With regard to the comparison of gadopiclenol and gadobutrol, there were no differences between both groups regarding heterogeneity within each group.
As all 95% CI of the difference included the value “0”, superiority of gadopiclenol at 0.05 mmol/kg over gadobutrol at 0.1 mmol/kg could not be concluded.
Supportive analyses showed similar results including some heterogeneity. Study GDX-44-011 was insufficiently powered for any robust sub-analyses of body regions.
For further details, please refer to the information for healthcare professionals.

6.4 Safety

The safety of gadopiclenol was evaluated in eight clinical studies in 1047 subjects.
Electrocardiograms (ECG) were analysed in four studies. The majority of patients (67.6%) received

gadopiclenol at the dose of 0.05 mmol/kg. A single dose was administered except in the thorough QT study where healthy volunteers received one dose at 0.1 mmol/kg and one dose at 0.3 mmol/kg.
A total of 92 healthy volunteers and 955 patients were exposed to gadopiclenol. CNS imaging was performed for 515 adults while body imaging was performed for 328 adults.
Among the subjects exposed to gadopiclenol, there were more female patients (54%), with a median age of 55 years. The large majority of subjects (82.9%) were White, 9.5% were Asian, 4.8% American Indian or Alaska native, 2.5% Black or African American.
There were no relevant differences in demographic characteristics between patients receiving different doses of gadopiclenol.
The overall population included 5.5% of patients with moderate renal impairment and 1.5% with severe renal impairment, 11.6% with hypersensitivity, 9.1% with cardiac diseases, 8.6% with a medical history of convulsions and 6.1% with hepatic insufficiency. Patients with severe renal impairment were only included in the GDX-44-005 study and therefore received the dose of 0.1 mmol/kg only. The rate of patients with a history of convulsions was higher among patients receiving gadopiclenol at 0.2 mmol/kg (20.0%).

Overall, 367 subjects (33.5%) experienced at least one adverse event (AE), and the AEs were considered related to the study product for 151 patients (13.8%). Serious AEs (SAEs) were reported in 15 patients (1.4%), and only two were considered related to the contrast agent (one with gadopiclenol reported as a SUSAR and one with gadobenate dimeglumine). Two deaths occurred, neither related to the contrast agent, and 10 patients had to discontinue the investigational medicinal product (IMP) due to an AE. Furthermore, no nephrogenic systemic fibrosis (NSF) was reported during any study. The rates of adverse events were similar between contrast agents.
Out of the 699 reported AEs, 672 (96.1%) resolved, 1 (0.1%) worsened, 2 (0.3%) led to death and 24 (3.4%) were not resolved at the end of the study.

When analysed by dose of gadopiclenol, the frequency of patients experiencing at least one AE related to gadopiclenol was higher with high doses. A higher frequency of headache and gastrointestinal disorders related to gadopiclenol was reported among subjects receiving a dose of 0.2 or 0.3 mmol/kg, and a higher frequency of injection site pain was also reported among patients receiving gadopiclenol at 0.2 mmol/kg. In addition, 0.1 mmol/kg led to more frequent AEs too. Thus, no dose higher than 0.05 mmol/kg was accepted.
The most frequently reported AEs considered related to gadopiclenol by the investigators were reactions at the injection site (pain, coldness, oedema, haematoma, erythema), gastrointestinal disorders (nausea, diarrhoea, vomiting, abdominal pain) and other nervous or general disorders such as headache, fatigue, dizziness.

Two deaths post-contrast injection were reported in the clinical studies. One death occurred 22 days after administration of gadopiclenol 0.1 mmol/kg, in a patient with severe renal impairment, due to cardiopulmonary failure. After gadopiclenol administration at 0.1 mmol/kg, a slight deterioration in renal function was seen. Another death after gadobutrol was considered not related; this event was reported in a patient with disseminated (including cerebral) metastatic disease.

Eleven patients experienced non-fatal SAEs after gadopiclenol administration, of which only one (blood creatinine increase) was considered related to gadopiclenol. Non-fatal SAEs occurred after gadopiclenol at 0.05 mmol/kg in 7 patients, after gadopiclenol 0.075 mmol/kg in 1 patient, after gadopiclenol 0.1 mmol/kg in 2 patients, and after gadopiclenol 0.2 mmol/kg in 1 patient. A further not related serious AE “cardiac failure congestive” was reported in the Phase 1 study GDX-44-005 in a patient with renal failure and showed characteristics similar to those observed in the death of a patient within the same study. After gadopiclenol administration at 0.1 mmol/kg, a slight deterioration in renal function was seen in this case too. A further case of drug-related creatinine increases with gadopiclenol 0.1 mmol/kg from Phase 2 study GDX-44-004 was seen in a young adult patient without pre-existing cardiovascular or renal disease.

There was a higher rate of AEs leading to withdrawal, discontinuation of IMP and/or study with gadopiclenol. Among the 70 patients (6.4%) withdrawn from clinical study after contrast agent administration, 7 were withdrawn due to non-fatal AE: 5 patients after gadopiclenol, 1 after gadobenate dimeglumine and 1 after gadobutrol. The main safety problems of gadopiclenol associated with higher doses are renal failure and different laboratory signs of diminished renal function, supporting the restriction of the maximum dose to 0.05 mmol/kg.

No relevant or consistent changes in median values of blood pressure and heart rate were observed in any clinical study. As this was true for the means and the medians, more cases of increased blood pressure were seen after gadopiclenol: 9 patients (0.9%) after gadopiclenol. One event of increased blood pressure (0.1%) was considered related to gadopiclenol.
Two events of increased blood pressure (0.8%) after gadobenate dimeglumine were considered as treatment-related. Two events of increased blood pressure (0.4%) were reported after gadobutrol, neither considered related to gadobutrol. All these AEs were of mild to moderate intensity, did not lead to any change in IMP administration and resolved. None was serious. Since more events, which were also related to the drug, were observed with gadopiclenol, hypertension is mentioned in the information for healthcare professionals.

Safety in Special Groups and Situations:
Patients with Impaired Renal Function: The incidence of AEs was higher in patients with severe renal impairment. The low numbers of patients (moderate renal impairment=57, severe renal impairment=16) hampered robust comparisons. The incidence of AEs related to gadopiclenol was mostly similar for patients with or without slight renal impairment.

Patients with Hepatic Diseases: The incidence of adverse events was similar for patients with or without hepatic diseases. Serious AEs were reported in 3 patients (4.5%) with hepatic diseases, none considered related to gadopiclenol. However, the numbers (n=67) were too low for robust comparisons.

There were no differences in the proportion of patients with at least one AE, including in Patients with Allergies and Patients with History of Convulsions.

Patients with Cardiac Diseases: No difference in the proportion of patients with at least one AE was observed in patients with cardiac diseases (n=100). Among the AEs related to gadopiclenol, QT interval abnormal and blood pressure increase were reported in patients with cardiac diseases. Serious AEs were reported for 2 patients with cardiac diseases (congestive cardiac failure and cardiopulmonary failure), neither related to gadopiclenol. However, the case of congestive cardiac failure in a context of worsening renal function is suggestive of a correlation.

Dialysability of gadopiclenol following intravenous administration: In the GDX-44-005 study, the dialysability of gadopiclenol following a single intravenous injection (0.1 mmol/kg BW) was assessed in a cohort of 8 patients with end stage renal disease (ESRD) requiring haemodialysis. Three sessions of haemodialysis effectively removed gadopiclenol from plasma. For most of the subjects, the first session of haemodialysis managed to remove most of the gadopiclenol from the body. No gadopiclenol was detected (BLQ) in any of the plasma and urine follow-up samples available at 1, 3 and 6 months. Four dialysed patients (50%) experienced at least one AE: muscle spasms (2 patients), systolic blood pressure increase (1 patient), nausea and vomiting (1 patient). None of these events were considered related to gadopiclenol, and none was serious. Muscle spasms were considered related to the procedure of haemodialysis.

Drug Interactions: No interactions with other medicinal products have been observed. However, since formal drug interaction studies have not been carried out, gadopiclenol should not be mixed with other compounds.

6.5 Final clinical benefit risk assessment

Contrast media (CM) enhance the visualisation of structures and functions of the body in imaging procedures such as X-ray diagnostics, magnetic resonance imaging (MRI) and sonography (ultrasound).
Elucirem, with the active ingredient gadopiclenol, belongs to the group of paramagnetic contrast media for magnetic resonance imaging. The contrast-enhancing effect is mediated by gadopiclenol as in other paramagnetic contrast media.
Within the paramagnetic gadolinium-containing CM, a distinction is made between linear and macrocyclic CM. Elucirem belongs to the group of macrocyclic paramagnetic contrast media. It is a non-ionic macrocyclic gadolinium (Gd) complex with the excipient tetraxetan (USAN), which is equivalent to DOTA.

Gadolinium-containing CM should only be used if the diagnostic information is necessary and cannot be obtained with MRI without contrast enhancement, given the unknown long-term risk of gadolinium retention in tissue.

There are already several well-known macrocyclic gadolinium-containing contrast agents available in Switzerland, which cover all patients from birth up to a very high age. Therefore, the medical need for a fourth product is limited. There is substantial clinical experience with the already approved macrocyclic gadolinium-containing contrast agents, which cover almost all needs.

A potential theoretical benefit of gadopiclenol could be the lower dosage of 0.05 mmol/kg. This dose contains half the amount of gadolinium compared to the standard dose of 0.1 mmol/kg, e.g. for gadobutrol. Theoretically, this reduced dose of 0.05 mmol/kg could lead to less gadolinium retention in the tissues, e.g. the brain. However, all macrocyclic gadolinium-containing contrast agents on the Swiss market have a substantially lower gadolinium retention in the human tissues, including the brain, compared to the older linear gadolinium-containing contrast agents. Furthermore, no human data on tissue distribution have been submitted for gadopiclenol. Thus, there is no proven clinical benefit for gadopiclenol regarding gadolinium retention.

Two studies (Phase 1/2a Study GDX-44-003, Phase 2b Study GDX-44-004) finally identified a dose of 0.05 mmol/kg gadopiclenol as sufficient (compared to the standard dose of 0.1 mmol/kg for the comparator). Although higher doses of gadopiclenol (0.1 mmol/kg, 0.2 mmol/kg) appear to have a higher diagnostic accuracy, also more AEs were observed with those doses. More fatal, serious cases and discontinuation due to adverse events and laboratory values were observed with doses >0.05 mmol/kg. Several cases of a certain deterioration of renal function (concerning different parameters, observed in patients with/without renal disease, as well as those with heart disease) gave a hint that a relationship with gadopiclenol doses >0.05 mmol/kg cannot be excluded. Thus, no doses higher than 0.05 mmol/kg should be used.
Therefore, 0.05 mmol/kg was considered the optimal dose. This was further confirmed in the pivotal phase 3 studies.

Efficacy of gadopiclenol in contrast-enhanced MRI of CNS and other body regions was demonstrated in two well-designed and adequately controlled studies in adults (Phase 3 Study GDX-44-010, Phase 3 Study GDX-44-011), which were submitted to support approval for adults in CNS and other body regions. The main exclusion criteria in both studies were the following: Patients presenting with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m² based on eGFR assessment performed one day prior to each contrast agent injection (V1, V2, V4), patients with class III/IV congestive heart failure (NYHA) and patients with liver failure or liver transplantation were excluded.

Both studies met their primary objective of showing superiority over non-enhanced images and non-inferiority compared to gadobutrol-enhanced images. However, the demonstration of superiority over gadobutrol failed.
The proportion of patients in study GDX-44-010 with spine examination (n=5, 2.1%) was considered too small to allow meaningful conclusions on efficacy of gadopiclenol in spine examination.

Study GDX-44-011 was insufficiently powered for any robust sub-analyses of body regions. For further details, please refer to the information for healthcare professionals.

Safety in the Phase 3 adult studies GDX-44-010 and GDX-44-011 was acceptable overall, with only small hints of diminishing renal function due to 0.05 mmol/kg gadopiclenol. For further details, please refer to the information for healthcare professionals.

Overall, based on the submitted data, the standard dose of 0.05 mmol/kg gadopiclenol compared to gadobutrol 0.1 mmol/kg is efficacious and safe.
Superiority over unenhanced scans was demonstrated. Non-inferiority to gadobutrol was shown, but superiority over gadobutrol 0.1 mmol/kg was not demonstrated. In light of the tolerable safety profile, the overall benefit risk assessment is therefore positive.
There remain some uncertainties, as adult patients with acute relapses of demyelinating diseases like multiple sclerosis and naïve symptomatic patients (without pre-examination e.g. by CT or MRI before the start of studies) were not included, and the studies were not powered for robust sub-analyses of different body regions. The number of patients with moderate and severe chronic kidney disease and liver insufficiency was sparse. Post-marketing data will follow in the future (see below post-approval requirement).

Post-approval requirement:
The clinical prospective longitudinal cohort study 4341-4 (expected completion: 4th quarter 2028) must be submitted to Swissmedic by 31 December 2028.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Elucirem was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

ELUCIREM®, solution for injection

Composition

Active substances

Gadopiclenol

Excipients

Tetraxetan, trometamol, hydrochloric acid, sodium hydroxide, water for injections
Sodium content: Max. 0.46 mg/mL (0.02 mmol/mL) taking into account the variable sodium hydroxide additives.

Pharmaceutical form and active substance quantity per unit

Solution for injection for intravenous administration in a pre-filled syringe or in a vial.
1 mL contains 485.1 mg gadopiclenol equivalent to 0.5 mmol gadopiclenol and 78.6 mg gadolinium.

Pack sizes	3 mL	7.5 mL	10 mL	15 mL	30 mL
Gadopiclenol	1.46 g	3.64 g	4.85 g	7.28 g	14.55 g
mmol	1.5	3.75	5.0	7.5	15.0

Gd-concentration	0.5 mmol Gd/mL
Osmolality at 37 °C	850 mOsm/kg H_2O
pH value	7.0 – 7.8

Indications/Uses

In adults

ELUCIREM is a gadolinium-based contrast agent indicated in adults for use with magnetic resonance imaging (MRI) to detect and visualise lesions with abnormal vascularity
- in the CNS area (see warnings and precautions and properties/effects)
- in other areas of the body (see warnings and precautions and properties/effects)

ELUCIREM® should be used only if diagnostic information is significant and cannot be obtained by non-contrast-enhanced magnetic resonance imaging (MRI).

Dosage/Administration

General Dosing

The recommended dose of gadopiclenol is 0.05 mmol/kg body weight corresponding to 0.1 mL/kg body weight for all indications. No higher doses than 0.05 mmol/kg body weight may be used, as the safety of higher doses has not been established. The lowest possible dose needed to achieve sufficient contrast enhancement for diagnostic purposes shall be used. The required dose should be calculated on the basis of the patient's body weight and should not exceed the following dose information:

Body weight Kilograms (kg)	**Volume** in millilitres (mL)	**Quantity** in millimol (mmol)
10	1	0.5
20	2	1
30	3	1.5
40	4	2
50	5	2.5
60	6	3
70	7	3.5
80	8	4
90	9	4.5
100	10	5
110	11	5.5
120	12	6
130	13	6.5
140	14	7

General hygiene requirements for sterile solutions always need to be observed when using contrast media (see “Other warnings”).

Administration:

The recommended dose is administered intravenously as a bolus injection. Contrast-enhanced MRI may begin shortly after injection depending on pulse sequences used and examination protocol. T1-weighted sequences are particularly suitable for contrast-enhanced examinations.

If possible, intravenous administration of the contrast medium should be performed while lying down. As experience shows that most undesirable effects occur shortly after administration, the patient should be observed for at least half an hour during and after administration of ELUCIREM® (see Warnings and Precautions).

Special patient groups

Paediatric population

The safety and efficacy of ELUCIREM® in children and adolescents has not yet been sufficiently established.

Elderly patients (65 years old and over)

No dose adjustment is considered necessary. Caution should generally be exercised in elderly patients.

Patients with renal insufficiency

No dose adjustment is considered necessary in patients with any degree of renal impairment. ELUCIREM® should only be used after careful risk-benefit assessment in patients with severe renal impairment (estimated creatinine clearance eGFR < 30 mL/min/1.73 m^2) and in patients in the perioperative liver transplant phase, as the rate of adverse effects is increased. Use is only indicated when diagnostic information is essential and is not available with non-contrast-enhanced MRI. If the use is indicated, the dose of 0.05 mmol/kg body weight must not be exceeded. No more than one dose should be used during an MRI examination. In the absence of information on repeated administration, ELUCIREM® injection should not be repeated *(see also "Warnings and precautions, renal insufficiency and nephrogenic systemic fibrosis (NSF)").*

Contraindications

Hypersensitivity to gadopiclenol or any other ingredient.
Do not inject in the subarachnoid (or epidural) region.

Warnings and precautions

Hypersensitivity

As with other gadolinium-containing contrast agents, life-threatening hypersensitivity reactions may occur. These can either be allergic (anaphylactic if they are severe) or non-allergic. They can be immediate (within 60 minutes) or delayed (up to 7 days later). Anaphylactic reactions occur immediately and can

be fatal. They are independent of the dose, can occur immediately during the first administration of the medicine and are often unpredictable.
During the examination, monitoring by a physician is required. In the event of hypersensitivity reactions, administration of the contrast medium must be discontinued immediately and, if necessary, specific therapy initiated. Venous access should therefore be maintained throughout the entire examination. In order to be able to initiate immediate emergency measures, the necessary resuscitation material (oxygen, adrenaline, antihistamines or other medications depending on the comedication, infusion material, intubation and ventilation option) should therefore be ready for use during each examination, in addition to the personnel requirements for emergency therapy. It is essential to be familiar with the use of emergency measures. In particular, it is necessary to comply with the special circumstances in a MRI system (poor accessibility of the patient, danger of high magnetic fields).
As most undesirable effects are experienced within minutes of administration, the patient should be observed for at least half an hour during and after administration of ELUCIREM® (see also “Undesirable Effects”).
Patients with allergic predisposition, asthma or a history of contrast medium reaction are at increased risk of a reaction. The patient should therefore be asked about existing allergies (e.g. hay fever, contrast agent intolerance, urticaria), asthma or other risks before injecting a contrast medium. Symptoms of existing asthma may worsen as a result of contrast medium injection. In such patients, the decision to use ELUCIREM® should be taken after careful risk-benefit assessment.

Renal insufficiency and nephrogenic systemic fibrosis (NSF)

It is recommended that all patients undergo laboratory tests for renal dysfunction before administration of ELUCIREM®.
Nephrogenic systemic fibrosis (NSF) has been reported in association with the use of some gadolinium-containing contrast agents in patients with acute or chronic severe renal insufficiency (GFR < 30 mL/min/1.73 m^2).
Patients undergoing liver transplants are especially at risk, since the incidence of acute renal failure is high in this group. Since administration of ELUCIREM® may be associated with NSF, in patients with severe renal impairment or in the peri-operative phase of liver transplantation, it should only be used after a careful risk-benefit assessment, and only if the diagnostic information is necessary and cannot be obtained with a non-contrast-enhanced MRI.

Haemodialysis shortly after administration of ELUCIREM® may be useful to remove the contrast agent from the body. There is no evidence that the initiation of haemodialysis for the prevention or treatment of NSF is suitable for patients not already on dialysis.

Elderly patients

Since renal elimination of ELUCIREM® may decrease in age, careful evaluation of renal dysfunction is particularly important in patients over 65 years of age.

Lack of long-term experience

ELUCIREM® has been studied in clinical trials in patients at a maximum single dose. There are no data on repeated administration of ELUCIREM® and no long-term experience with ELUCIREM®.

Restricted patient population

ELUCIREM® has been studied in two phase III studies (CNS: GDX-44-010, other body regions: GDX-44-011). Patients with decreased renal function (eGFR < 30 mL/min/1.73 m^2) and patients with congestive heart failure class III/IV (NYHA) were excluded from both studies. Patients with inflammatory diseases of the CNS (e.g. patients with an acute flare-up of multiple sclerosis etc.) were excluded from the GDX-44-010 study. Patients with inflammatory diseases or inflammation (e.g. pancreatitis) were excluded from study GDX-44-011. To study other areas of the body, the patient populations are too small for individual body regions and organ systems to make statistically robust statements (see Properties/Effects).

CNS seizures

As with other gadolinium-containing contrast agents, special caution should be taken in patients with a reduced seizure threshold. Precautions such as close monitoring should be taken. All measures to treat a seizure should be ready for use.

Extravasation

Care should be taken to inject intravenously when administering the drug. In case of extravasation, the injection should be stopped immediately. Local intolerance reactions may occur requiring local treatment and follow-up.

Gadolinium retention

After administration of gadolinium-containing contrast agents, gadolinium is still detectable for months or years in the brain, bones, skin and other organs. There are insufficient data (no long-term data, no data after repeated administration of ELUCIREM, few data in patients with renal insufficiency with administration of ELUCIREM), on whether there are comparable or different gadolinium retention values at the recommended doses of ELUCIREM® compared to other approved macrocyclic gadolinium-containing contrast agents.

Risks related to intrathecal administration

The intrathecal administration of gadolinium-based contrast agents (GBCAs) can lead to serious adverse reactions such as death, coma, encephalopathy and seizures. The safety and efficacy of ELUCIREM® has not been demonstrated following intrathecal administration. ELUCIREM® is not approved for intrathecal use.

Sodium content:

ELUCIREM® contains less than 1 mmol sodium (23 mg) per dose (calculated on the basis of a 70 kg person), i.e. it is essentially “sodium-free”.

Interactions

No interaction studies have been conducted with other medicinal products.
In view of the possibility of allergic or allergoid intolerance reactions, the intake of preparations that may affect emergency treatment and cardiovascular compensation must be taken into account: e.g. beta receptor blockers, vasoactive substances, ACE inhibitors, AT2 blockers

Pregnancy, lactation

There is no experience of the use of ELUCIREM® in pregnant women. Animal studies showed placental passage but did not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section “*Preclinical data”*).
ELUCIREM® should not be used during pregnancy unless use is necessary because of the woman’s clinical condition.

Lactation

Gadolinium-containing contrast agents are excreted in very small amounts into breast milk. At clinical doses, no effects on the infant are expected because of this and because of the low absorption from the intestine. Breast-feeding should be discontinued for 24 hours after ELUCIREM® administration.

Fertility

Animal studies do not indicate impairment of fertility (see *Preclinical Data* section).

Effects on ability to drive and use machines

No clinical trials have been conducted concerning this matter.

Undesirable effects

The adverse reactions that occurred in ELUCIREM® clinical trials were usually mild to moderate and transient in terms of intensity. Injection site reactions, headache, nausea, fatigue and diarrhoea were most commonly observed. Adverse reactions are listed by system organ class and frequency as follows: 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), not known (cannot be estimated from the available data). The following data are based on clinical studies in a total of 1 047 individuals receiving ELUCIREM® in a dose range of 0.025 mmol/kg to 0.3 mmol/kg body weight:

System Organ Class	**Frequency**		
	Uncommon:	**Rare**	**Unknown**
Immune system disorders	Maculopapular rash	Hypersensitivity*	Anaphylactic-anaphylactoid reactions
Renal and urinary disorders	Increase in creatinine levels, decrease in eGFR		Acute kidney failure
Vascular disorders	Increased blood pressure		
Nervous system disorders	Headache	Taste disturbance	
Gastrointestinal disorders	-	Diarrhoea, nausea, abdominal pain, vomiting	
General disorders and administration site conditions	Injection site reactions**	Fatigue, heat	

* See supplementary description below

** Injection site reactions include the following terms: pain at the injection site, oedema at the injection site, cold at the injection site, warmth at the injection site, haematoma at the injection site and erythema at the injection site.

Description of selected adverse effects

Hypersensitivity

A hypersensitivity reaction is a commonly known side effect of gadolinium-based contrast media (see section “Warnings and precautions”). One or more symptoms may occur simultaneously or sequentially. Most of the time, these are skin, respiratory, gastrointestinal, inflammatory, neurological and/or cardiovascular reactions. First adverse drug reactions can be a warning sign of incipient shock, but rarely lead to death. Non-serious adverse reactions assessed as signs of hypersensitivity have been reported during clinical trials, including immediate (allergic dermatitis, erythema, dyspnoea, throat tightness) and late reactions (periorbital oedema, rash, maculopapular rash and itching).

Nephrogenic systemic fibrosis

After administration of gadolinium-containing contrast agents, gadolinium is still detectable for months or years in the brain, bones, skin and other organs. It is unclear (no long-term data, no data after repeated administration of ELUCIREM®, few data in patients with renal insufficiency with administration of ELUCIREM®) whether there are comparable or different gadolinium retention values at the recommended doses of ELUCIREM® compared to other approved macrocyclic gadolinium-containing contrast agents.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

The maximum daily dose tested in humans was 0.3 mmol/kg body weight, which corresponds to six times the recommended dose. In clinical use, no symptoms of poisoning due to overdose have been observed so far. At higher doses, worsening of renal function has been observed.

ELUCIREM® can be removed by haemodialysis. However, there is no evidence that haemodialysis is suitable for prevention of nephrogenic systemic fibrosis (NSF).

Properties/Effects

ATC code

ELUCIREM®: V08CA12

Mechanism of action

The contrast enhancement effect is mediated by gadopiclenol, a macrocyclic non-ionic gadolinium complex, whose active proportion (paramagnetic) accelerates relaxation rates of water protons in its environment in the body, resulting in an increase in signal intensity (brightness) of tissues in T1-weighted MRI imaging. This increase in signal intensity may at the same time lead to an increase in image contrast. Sequences weighted on T2/T2* may result in a decrease in signal strength.

Pharmacodynamics

In MRI, visualisation of normal and pathological tissue is partly dependent on small fluctuations in radio frequency signal intensity caused by

- Differences in proton density
- Differences in spin-lattice or longitudinal relaxation time (T1)
- Differences in spin-spin or transverse relaxation time (T2)

When gadopiclenol is brought into an external magnetic field (in the patient in the MRI machine), gadopiclenol shortens both T1 and T2 relaxation times in the target tissue. The extent to which a contrast agent may influence the relaxation rate of tissue water (1/T1 or 1/T2) is referred to as relaxivity (r1 or r2).
Gadopiclenol has high molecular relaxivity in water due to its chemical structure. Gadopiclenol can exchange more spin-lattice energy owing to two water molecules closely connected to the gadolinium.
Due to its high relaxivity, gadopiclenol can be administered at half the dose of gadolinium compared to other non-specific gadolinium-containing contrast agents, achieving the same contrast enhancement. The high relaxivity of gadopiclenol is achieved without in vivo protein interactions, since relaxivity in

physiological medium is comparable to water and has little dependence on magnetic field strength (0.47 T to 3.0 T, at 37 °C).

	r_1 [L/(mmol*s)]			r_2 [L/(mmol*s)]		
Magnetic field strength	**0.47 T**	**1.5 T**	**3 T**	**0.47 T**	**1.5 T**	**3 T**
Molecular relaxivity in water	12.5	12.2	11.3	14.6	15.0	13.5
Molecular relaxivity in biological media	13.2	12.8	11.6	15.1	15.1	14.7

Due to its macrocyclic structure, gadopiclenol has both high thermodynamic and kinetic stability. In fact, in the in vitro experiment it takes longer to a 50% decomplexation or release at a pH of 1.2 and 37 °C (the half-life is about 20 days).

Cardiac electrophysiology

Even in a 6-fold gadopiclenol overdose (i.e. 0.3 mmol/kg), no clinically relevant QT prolongation was observed in adult patients.

Clinical efficacy

In two pivotal phase III studies (GDX-44-010, GDX-44-011), adult patients undergoing an MRI with gadopiclenol (0.05 mmol/kg body weight) and an MRI with gadobutrol (0.1 mmol/kg body weight) were examined after a definitive pathological finding in the area of the CNS or other body regions was determined by means of an MRI or CT scan prior to study inclusion. No patients with symptoms were included in the two studies in whom no previous imaging diagnostics had been performed (MRI or CT naïve patients). Patients with decreased renal function eGFR (< 30 mL/min/1.73 m^2) and patients with congestive heart failure class III/IV (NYHA) were excluded from both studies.
The GDX-44-010 study (n = 256 patients) was used to investigate the CNS. This included 5 (n = 2.1%) patients with a disease of the spinal CNS. Patients with inflammatory diseases of the CNS (e.g. patients with an acute flare-up of multiple sclerosis etc.) were excluded from the study.
The GDX-44-011 study (n = 304 patients) was designed to examine other areas of the body (head and neck, chest, abdomen, pelvis and musculoskeletal system). Patients with inflammatory diseases or inflammation (e.g. pancreatitis) were excluded from the study. The test strength of the GDX-44-011 study was designed to provide a statistically meaningful result for all body regions together in the total number of 304 patients. The test strength of the GDX-44-011 study was not sufficient to demonstrate

a statistically robust outcome for the various areas of the body (head and neck, chest, abdomen, pelvis and musculoskeletal system) or for individual organs.

Lesion visualisation

The primary endpoint was the assessment of lesion visualisation using three criteria (border delineation, internal morphology and degree of contrast enhancement) by three independent, blinded evaluators using a 4-point scale. The mean score for each of the three lesion representation criteria was calculated as the sum of the scores for up to three most representative lesions divided by the number of all lesions.

Both studies showed:

- the superiority of combined native/contrast enhanced MRI (paired) with ELUCIREM® versus native MRI for all three lesion visualisation criteria ($p < 0.0001$ for all three evaluators (n = 3 readers, paired t-testing for matching lesions).
- the non-inferiority of gadopiclenol at a dose of 0.05 mmol/kg compared to gadobutrol at 0.1 mmol/kg ($p < 0.0001$ for all three evaluators, paired t-testing for matching lesions).

Table GDX-44-010 Study: CNS lesion visualisation per patient depending on reader: Comparison of the native examination versus IV administration of ELUCIREM 0.05 mmol/kg with the native data (paired)

	n	LS mean (SE)			95% CI difference
		Paired	Native	Difference*	
Border demarcation					
Reader 1	227	3.90 (0.02)	2.08 (0.02)	1.82 (0.03)	(1.76, 1.88)
Reader 2	229	3.64 (0.04)	1.74 (0.04)	1.90 (0.05)	(1.81, 2.00)
Reader 3	202	3.97 (0.03)	2.61 (0.03)	1.36 (0.04)	(1.29, 1.44)
Internal morphology					
Reader 1	227	3.92 (0.03)	1.66 (0.03)	2.26 (0.03)	(2.20, 2.33)
Reader 2	229	3.65 (0.03)	1.88 (0.03)	1.77 (0.04)	(1.69, 1.85)
Reader 3	202	3.97 (0.04)	2.01 (0.04)	1.96 (0.05)	(1.85, 2.06)
Extent of contrast enhancement					
Reader 1	227	3.77 (0.03)	1.00 (0.03)	2.77 (0.04)	(2.69, 2.85)
Reader 2	229	3.58 (0.03)	1.00 (0.03)	2.58 (0.05)	(2.49, 2.67)
Reader 3	202	3.90 (0.02)	1.00 (0.02)	2.90 (0.03)	(2.84, 2.95)

LS: Least squares; SE: Standard error; CI: Confidence interval.
Only matching lesions will be considered. The mixed models based on the full analysis set t (n = 239) include the factor lesion visualisation as a dependent variable, MRI modality (Native vs KM-assisted MRI) as a fixed variable, and the patient as a random variable.
*$p < 0.0001$ results for all comparisons

Table GDX-44-010 Study: CNS lesion visualisation per patient depending on reader: Contrast agent comparison: IV ELUCIREM 0.05 mmol/kg vs IV Gadobutrol 0.1 mmol/kg

	n	LS mean (SE)			95% CI difference
		Gadopiclenol	Gadobutrol	Difference*	
Border demarcation					
Reader 1	227	3.91 (0.02)	3.93 (0.02)	-0.02 (0.02)	[-0.06; 0.02]
Reader 2	231	3.64 (0.04)	3.60 (0.04)	0.03 (0.04)	[-0.04; 0.11]
Reader 3	220	3.97 (0.01)	3.95 (0.01)	0.02 (0.02)	[-0.01; 0.05]
Internal morphology					
Reader 1	227	3.93 (0.02)	3.93 (0.02)	-0.01 (0.02)	[-0.04; 0.03]

Reader 2	231	3.64 (0.04)	3.62 (0.04)	0.02 (0.03)	[-0.05; 0.09]
Reader 3	220	3.97 (0.02)	3.92 (0.02)	0.05 (0.02)	[0.01; 0.08]
Extent of contrast enhancement					
Reader 1	227	3.78 (0.04)	3.77 (0.04)	0.01 (0.03)	[-0.04; 0.07]
Reader 2	231	3.57 (0.04)	3.52 (0.04)	0.05 (0.04)	[-0.03; 0.12]
Reader 3	220	3.89 (0.03)	3.81 (0.03)	0.09 (0.03)	[0.03; 0.15]

LS: Least squares; SE: Standard error; CI: Confidence interval.
Only matching lesions will be considered. The models based on the per-protocol set (n = 236) include the lesion visualisation factor as a dependent variable, contrast medium and time interval (MRI 1 or MRI 2) as fixed variable, the patient as random variable.
Non-inferiority margin: -0.35
*p < 0.0001 results for all comparisons

Table GDX-44-011 Study: Visualisation of body lesions per patient depending on the reader: comparison of the native examination versus IV ELUCIREM 0.05 mmol/kg with native data (paired)

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

CI: Confidence interval; LS: Least squares; SE: Standard error.
Only matching lesions will be considered. The models based on the full set of analyses (n = 278) include the factor lesion visualisation as a dependent variable, the MRI modality (native versus KM-assisted MRI) as fixed variable, and the patien as random variable.
*p < 0.0001 results for all comparisons

Table GDX-44-011 Study: Visualisation of body lesions per patient and reader: Contrast agent comparison: IV ELUCIREM 0.05 mmol/kg vs IV Gadobutrol 0.1 mmol/kg

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

LS: Least squares; SE: Standard error; CI: Confidence interval.
Only matching lesions will be considered.
The models based on the per-protocol set (n = 260) include the lesion visualisation factor as a dependent variable, contrast medium and time interval (MRI 1 or MRI 2) as fixed variable, and the patient as random variable.
Non-inferiority margin: -0.35
*p < 0.0001 results for all comparisons

Paediatric population

Insufficient clinical data are available in children and adolescents.

Pharmacokinetics

Absorption

There are no human data on oral absorption.

Distribution

After intravenous administration, gadopiclenol is rapidly distributed in the extracellular compartments. The in vitro binding of ^{153}Gd-gadopiclenol to human plasma proteins is negligible and independent of the gadopiclenol concentration, since ^{153}Gd-gadopiclenol binds only to 0.0-1.8% to human plasma proteins. The mean maximum concentration (Cmax) 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 mmol/kg body weight, the mean (%CV) Cmax was 525 (13%) µg/mL, the mean AUCinf was 569 (15%) µg*h/mL, and the mean volume of distribution Vd was 12.9 (13%) litres.

Metabolism

Detectable biotransformation or degradation of gadopiclenol could not be observed.

Elimination

GadoPiclenol is rapidly excreted via the kidneys in unchanged form by passive glomerular filtration. After a dose of 0.05 mmol/kg, the mean plasma elimination half-life in healthy subjects with normal renal function was 1.5 hours, and the clearance was 100 ± 10 mL/min. Urinary excretion is the main route of excretion, with approximately 98% of the dose excreted in the urine after 48 hours in kidney healthy subjects, regardless of the dose administered.

Kinetics in specific patient groups

Patients with renal impairment, dialysis patients

In patients with mild or moderate renal impairment, more than 90% of the administered dose was excreted in urine within 48 hours. In patients with severe renal impairment, approximately 84% of the administered dose was excreted in urine within 5 days.

In end-stage renal disease (ESRD) patients, gadopiclenol was effectively removed from plasma by haemodialysis because the percent decrease in blood concentrations at the end of the first haemodialysis session was 95-98% and 100% after the third haemodialysis session.

Table: Effect of renal insufficiency on the pharmacokinetics of gadopiclenol[a, b]

	Normal (eGFR ≥ 90 mL/min)	Mild (eGFR 60 to < 90 mL/min)	Moderate (eGFR 30 to < 60 mL/min)	Serious (eGFR 15 to < 30 mL/min)
AUC_{inf} (µg·h/mL)	1 113 (24%)	1 711 (31%)	2 759 (28%)	9 671 (18%)
CL_r (mL/min)	96 (10%)	76 (23%)	44 (25%)	14 (26%)
$t_{1/2}$ (hr)	1.9	3.3	3.8	11.7

[a] Following administration of a single gadopiclenol 0.1 mmol/kg dose (equivalent to 2 times the recommended dose).
[b] eGFR: estimated GFR value based on an estimate formula and expressed in mL/min. To convert mL/min/1.73 m^2 to mL/min, multiply by the individual body surface area and divide this value by 1.73.

Patients with hepatic impairment

The pharmacokinetic profile has not been studied in this population.

Other demographic factors

No differences in the pharmacokinetics of gadopiclenol were observed between men and women.

Preclinical data

Based on experimental studies on safety pharmacology, repeated dose toxicity, genotoxicity and reproductive and developmental toxicity, the preclinical studies do not indicate any particular hazards to humans.
Carcinogenicity studies have not been conducted with gadopiclenol.
Single and repeated toxicity studies in neonatal and juvenile rats (before and after breastfeeding) have shown that gadopiclenol was well tolerated at all doses tested (up to eight times the maximum recommended human exposure dose) and had no effect on growth, development during breastfeeding, general behaviour or sexual maturation.

Other information

Incompatibilities

None known.
Due to the lack of studies, ELUCIREM® must not be mixed with other medicinal products.

Shelf life

After opening, the contrast medium should be used up immediately as non-preserved solution for injection and any remaining content should be discarded. When opening vials using a trocar containing a sterile filter, its contents may be stored at room temperature and used in clinical administration for up to 24 hours after opening.
Do not use the preparation after the expiry date which is stated as “EXP” on the packing.

Special precautions for storage

Keep out of the reach of children.
Store at room temperature (15 to 25 °C).
Pre-filled syringes should not be exposed to frost.

Hygiene warnings

General hygiene requirements for sterile solutions always need to be observed when using contrast media. Since the solutions are not preserved, the residual quantities not used in a test run should be discarded.
In addition, the following hygiene measures should be followed in connection with injectors or infusomas: The contrast medium may only be removed by means of a closed system which has at least a trocar with a protective cap, an air filter and a luer connection with a direct tubing connection. The vials may only be pierced once. The instructions for use provided by the manufacturer of the collection and filling sets as well as the injectors should be taken into account. Tubing connections leading to the patient should have hygiene-tested backflow valves and be replaced each time. At least at the end of the daily program, the residual quantities in the vials, pre-filled syringes and the supply lines must be discarded.

Patient documentation

The peel-off label located on the vials or pre-filled syringes should be affixed to the patient's medical record for better traceability. Ensure documentation of the gadolinium-containing contrast agent and the dose used.

Authorisation number

69037, 68791 (Swissmedic)

Packs

Type I glass vials with rubber stopper.

Elucirem solution for injection in vials of 3 mL: 1 [B]

Elucirem solution for injection in vials of 7.5 mL: 1 [B]

Elucirem solution for injection in vials of 10 mL: 1 [B]

Elucirem solution for injection in vials of 15 mL: 1 [B]

Elucirem solution for injection in vials of 30 mL: 1 [B]

Polypropylene plastic pre-filled syringes (latex-free) closed with an elastomer plunger stopper and an elastomer syringe.

Elucirem solution for injection in pre-filled syringes of 7.5 mL: 1 [B]

Elucirem solution for injection in pre-filled syringes of 10 mL: 1 [B]

Marketing authorisation holder

Guerbet AG, Zürich

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