

## **ANNEX I**

### **SUMMARY OF PRODUCT CHARACTERISTICS**

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Elucirem 0.5 mmol/mL solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL of solution contains 485.1 mg gadopiclesol (equivalent to 0.5 mmol of gadopiclesol and to 78.6 mg of gadolinium).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection

Clear, colourless to pale yellow solution

|                          |                              |
|--------------------------|------------------------------|
| Mean osmolality at 37 °C | 850 mOsm/kg H <sub>2</sub> O |
| pH                       | 7.0-7.8                      |
| Viscosity at 20 °C       | 12.5 mPa s                   |
| Viscosity at 37 °C       | 7.7 mPa s                    |

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Elucirem is indicated in adults and children from birth for contrast-enhanced magnetic resonance imaging (MRI) to improve detection and visualization of pathologies with disruption of the blood-brain-barrier (BBB) and/or abnormal vascularity of:

- the brain, spine, and associated tissues of the central nervous system (CNS);
- the liver, kidney, pancreas, breast, lung, prostate, and musculoskeletal system.

It should be used only when diagnostic information is essential and not available with unenhanced MRI.

### 4.2 Posology and method of administration

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

#### Posology

The recommended dose of Elucirem is 0.1 mL/kg body weight (BW) (equivalent to 0.05 mmol/kg BW) to provide diagnostically adequate contrast for all indications.

The dose should be calculated based on the patient's BW and should not exceed the recommended dose per kilogram of BW detailed in this section.

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

**Table 1: Volume of Elucirem to be administered per BW**

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

#### *Elderly*

No dose adjustment is necessary. Caution should be exercised in elderly patients (see section 4.4 and 5.2).

#### *Renal impairment*

No dose adjustment is necessary for patients with any level of renal impairment. Gadopichlenol should only be used in patients with severe renal impairment ( $\text{GFR} < 30 \text{ mL/min/1.73 m}^2$ ) and in patients in the perioperative liver transplantation period after careful risk/benefit assessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI (see section 4.4). If it is necessary to use gadopichlenol, the dose should not exceed 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW). More than one dose should not be used during a scan. Because of the lack of information on repeated administration, gadopichlenol injections should not be repeated unless the interval between injections is at least 7 days.

#### *Hepatic impairment*

No dose adjustment is considered necessary for patients with hepatic impairment. Caution is recommended, especially in the case of perioperative liver transplantation period (see above "renal impairment").

#### *Paediatric population (from birth)*

The recommended and maximum dose of Elucirem is 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW) for all indications. More than one dose should not be used during a scan.

Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, Elucirem should only be used in these patients after careful consideration, at a dose not exceeding 0.05 mmol/kg body weight. Because of the lack of information on repeated administration, Elucirem injections should not be repeated unless the interval between injections is at least 7 days.

#### Method of administration

The medicinal product is for intravenous use only.

The recommended dose is administered intravenously as a bolus injection at approximately 2 mL/sec followed by a flush of sodium chloride 9 mg/ml (0.9%), solution for injection via manual injection or power injector.

Intravenous administration of contrast agent should, if possible, be done with the patient lying down. Since experience shows that most undesirable effects occur within minutes after administration, the patient should be kept under observation during and following administration for at least half an hour (see section 4.4).

For instructions on the medicinal product before administration, see section 6.6.

#### *Paediatric population*

In children, Elucirem in vials with a single use syringe of a volume adapted to the amount to be injected should be used in order to have better precision of the injected volume.

#### Image acquisition

Contrast-enhanced MRI can start after the injection depending on the pulse sequences used and the protocol for the examination. Optimal signal enhancement is generally observed during arterial phase and within a period of about 15 minutes after injection. Longitudinal relaxation times (T1)-weighted sequences are particularly suitable for contrast-enhanced examinations.

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

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

The usual precautions for MRI examination should be applied, such as exclusion of patients with pacemakers, ferromagnetic vascular clips, infusion pumps, nerve stimulators, cochlear implants, or suspected intracorporal metallic foreign bodies, particularly in the eye.

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

There are no or limited clinical data investigating the performance of gadopichlenol for CNS imaging in patients with inflammatory, infectious, autoimmune or demyelinating disorders (such as multiple sclerosis), patients with acute or chronic infarct, or patients with intramedullary spine lesions. There are also no or limited clinical data investigating the performance of gadopichlenol for body imaging in patients with inflammatory, infectious and autoimmune conditions, including acute/chronic pancreatitis, inflammatory bowel disease, inflammatory diseases of head and neck region and endometriosis.

#### Potential for hypersensitivity or anaphylactic reactions

- As with other gadolinium-containing contrast agents, hypersensitivity reactions can occur, including life-threatening. Hypersensitivity reactions may be either allergic (described as anaphylactic reactions when serious) or non-allergic. They can occur either immediately (less than 60 minutes) after injection or delayed (up to 7 days). Anaphylactic reactions occur immediately and can be fatal. They are independent of the dose, can occur after even the first dose of the product, and are often unpredictable.

- During the examination, supervision by a physician is necessary. If hypersensitivity reactions occur, administration of the contrast agent must be discontinued immediately and – if necessary – a specific therapy must be instituted. A venous access should thus be kept during the entire examination. To permit immediate emergency countermeasures, appropriate drugs (e.g. epinephrine and antihistamines), an endotracheal tube and a respirator should be ready at hand.
- The risk of hypersensitivity reaction may be higher in patients with a history of previous reaction to gadolinium-containing contrast agents, bronchial asthma or allergy.

### Renal impairment and nephrogenic systemic fibrosis (NSF)

Prior to administration of gadopichlenol, it is recommended that all patients are screened for renal dysfunction by obtaining laboratory tests.

There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of some gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR < 30 mL/min/1.73 m<sup>2</sup>). Patients undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. As there is a possibility that NSF may occur with gadopichlenol, it should only be used in patients with severe renal impairment and in patients in the perioperative liver transplantation period after careful benefit/risk assessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI.

Haemodialysis shortly after gadopichlenol administration may be useful at removing it from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.

### Elderly

As the renal clearance of gadopichlenol may be impaired in the elderly, it is particularly important to screen patients aged 65 years and older for renal dysfunction. Caution should be exercised in patients with renal impairment (see section 4.2).

### Paediatric population

#### *Neonates and infants*

Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, Elucirem should only be used in these patients after careful consideration.

There are no clinical data investigating the performance of gadopichlenol in preterm neonates.

### Seizures

As with other gadolinium-containing contrast agents, special caution is necessary in patients with a lowered threshold for seizures. All equipment and drugs necessary to counter convulsions occurring during the MRI examination must be made ready for use beforehand.

### Extravasation

Caution during administration is necessary to avoid any extravasation. In case of extravasation, the injection must be stopped immediately. In case of local reactions, evaluation and treatment should be carried out as necessary.

### Cardiovascular disease

In patients with severe cardiovascular disease gadopichlenol should only be administered after careful risk benefit assessment because no data are available so far.

## Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per 15 mL, that is to say essentially 'sodium-free'.

## **4.5 Interaction with other medicinal products and other forms of interaction**

No interaction studies have been performed.

### Concomitant medicinal products to be taken into account

Beta-blockers, vasoactive substances, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists decrease the efficacy of the mechanisms of cardiovascular compensation for blood pressure disorders. The physician must obtain information before injection of gadopiclesol about the concomitant intake of those medicinal products.

## **4.6 Fertility, pregnancy and lactation**

### Pregnancy

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

### Breast-feeding

Gadolinium-containing contrast agents are excreted into breast milk in very small amounts. At clinical doses, no effects on the infant are anticipated due to the small amount excreted in milk and poor absorption from the gut. Continuing or discontinuing breast feeding for a period of 24 hours after administration of Elucirem, should be at the discretion of the doctor and breast-feeding mother.

### Fertility

Animal studies do not indicate impairment of fertility (see section 5.3).

## **4.7 Effects on ability to drive and use machines**

Elucirem has no or negligible influence on the ability to drive and use machines.

## **4.8 Undesirable effects**

### Summary of the safety profile

The most frequent adverse reactions were injection site pain, headache, nausea, injection site coldness, fatigue and diarrhoea.

### Tabulated list of adverse reactions

Table 2 below presents adverse reactions based on clinical trials including 1083 subjects exposed to gadopiclesol ranging from 0.05 mL/kg BW (equivalent to 0.025 mmol/kg BW) to 0.6 mL/kg BW (equivalent to 0.3 mmol/kg BW).

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

**Table 2: Adverse reactions reported following gadopiclesol administration**

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

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

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

#### Description of selected adverse reactions

##### *Hypersensitivity*

Immediate reactions include one or more effects, which appear simultaneously or sequentially, which are most often cutaneous, respiratory and/or vascular reactions. Each sign may be a warning sign of a starting shock and go very rarely to death.

##### *Nephrogenic systemic fibrosis (NSF)*

Isolated cases of NSF have been reported with other gadolinium-containing contrast agents (see section 4.4).

#### Paediatric population

A total of 80 paediatric patients aged 2 years and older and 36 paediatric patients aged less than 2 years received an injection of gadopiclesol at the dose of 0.1 mL/kg BW (0.05 mmol/kg BW) in two clinical trials.

As compared to adults, the safety profile of gadopiclesol in the paediatric population did not show any specific safety concern.

Overall, 69 Treatment Emergent Adverse Events (TEAEs) occurred during and/or after gadopiclesol administration for 33 patients out of 116 (28.4%).

Among these TEAEs, 2 events in 2 patients (1.7%), one under 2 years old and one 9 years old, were considered related to gadopiclesol (erythema and maculopapular rash).

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## **4.9 Overdose**

The maximum daily single dose tested in humans was 0.6 mL/kg BW (equivalent to 0.3 mmol/kg BW), which corresponds to 6 times the recommended dose.

No signs of intoxication from an overdose have so far been reported.

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: paramagnetic contrast media, ATC code: V08CA12.

Gadopiclenol is a paramagnetic agent for Magnetic Resonance Imaging (MRI).

#### Mechanism of action

The contrast-enhancing effect is mediated by gadopiclenol which is a macrocyclic non-ionic complex of gadolinium, the active moiety which enhances the relaxation rates of water protons in its vicinity in the body, leading to an increase in signal intensity (brightness) of tissues.

When placed in a magnetic field (patient in MRI machine), gadopiclenol shortens the  $T_1$  and  $T_2$  relaxation times in targeted tissues. The extent to which a contrast agent can affect the relaxation rate of tissue water ( $1/T_1$  or  $1/T_2$ ) is termed relaxivity ( $r_1$  or  $r_2$ ).

Gadopiclenol presents a high relaxivity in water (see Table 3) due to its chemical structure, because it can exchange two water molecules, which are linked to the gadolinium to complete its coordination number in addition to the four nitrogens and the three oxygens of the carboxylate functions of the gadopiclenol chelate. This explains that, gadopiclenol given at half dose of gadolinium compared to other non-specific gadolinium-containing contrast agents, may provide the same contrast enhancement.

**Table 3: Relaxivity at 37 °C for gadopiclenol**

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

#### Clinical efficacy and safety

Two pivotal studies included adult patients undergoing MRI with gadopiclenol at 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW) and MRI with gadobutrol at 0.1 mL/kg BW (equivalent to 0.1 mmol/kg BW). One study (Study GDX-44-010; PICTURE) included 256 patients presenting with known or highly suspected CNS lesions with focal areas of disrupted BBB (e.g. primary and secondary tumors). The majority of patients (72%) presented with brain tumors, 20% had brain or spine metastases and 8% presented with other pathologies.

The other study (Study GDX-44-011; PROMISE) included 304 patients with known or suspected abnormalities or lesions in other body regions (8% in head and neck, 28% in thorax, 35% in abdomen, 22% in pelvis and 7% in musculo-skeletal system) both based on results of a previous imaging procedure such as CT or MRI. The most frequent pathologies were breast tumors (23%) and liver tumors (21%).

The primary endpoint was the evaluation of lesion visualization, based on 3 co-criteria (border delineation, internal morphology and degree of contrast enhancement) by three independent blinded readers, using a 4-point scale. The mean of scores for each of the 3 lesion visualization co-criteria was calculated as the sum of scores for up to 3 most representative lesions divided by the number of lesions.

Both studies demonstrated:

- Superiority of the combined unenhanced/contrast-enhanced MRI (Paired) with gadopiclesol over unenhanced MRI (Pre) for all 3 lesion visualization criteria ( $p < 0.0001$  for all three readers, paired t-tests on matching lesions).
- Non-inferiority of gadopiclesol at 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW) to gadobutrol at 0.1 mL/kg BW (equivalent to 0.1 mmol/kg BW) ( $p < 0.0001$  for all three readers, paired t-tests on matching lesions).

The pooled analysis of the primary outcome over the three readers, and for each lesion visualization criterion also demonstrated the non-inferiority of gadopiclesol at 0.05 mmol/kg to gadobutrol at 0.1 mmol/kg in both studies, as shown in table 4 below.

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

| Table 4: Erosion visualization – On-site Readings – Full analysis set |            |              |              |               |                   |         |
|-----------------------------------------------------------------------|------------|--------------|--------------|---------------|-------------------|---------|
|                                                                       | n patients | LS Mean (SE) |              |               | 95% CI difference | p-value |
|                                                                       |            | Gadopiclenol | Gadobutrol   | Difference    |                   |         |
| Study GDX-44-010 (PICTURE)                                            |            |              |              |               |                   |         |
| Border delineation                                                    | 239        | 3.83 ( 0.02) | 3.82 ( 0.02) | 0.01 ( 0.02)  | [ -0.02 ; 0.05]   | 0.5025  |
| Internal morphology                                                   | 239        | 3.83 ( 0.02) | 3.81 ( 0.02) | 0.02 ( 0.02)  | [ -0.01 ; 0.05]   | 0.2006  |
| Degree of contrast enhancement                                        | 239        | 3.73 ( 0.03) | 3.68 ( 0.03) | 0.05 ( 0.02)  | [ 0.01 ; 0.09]    | 0.0172  |
| Study GDX-44-011 (PROMISE)                                            |            |              |              |               |                   |         |
| Border delineation                                                    | 273        | 3.60 ( 0.03) | 3.60 ( 0.03) | -0.00 ( 0.02) | [ -0.05 ; 0.04]   | 0.8987  |
| Internal morphology                                                   | 273        | 3.75 ( 0.02) | 3.76 ( 0.02) | -0.01 ( 0.02) | [ -0.05 ; 0.03]   | 0.6822  |
| Degree of contrast enhancement                                        | 273        | 3.30 ( 0.04) | 3.29 ( 0.04) | 0.01 ( 0.03)  | [ -0.05 ; 0.07]   | 0.8546  |
| CI: Confidence Interval ; LS: Least Squares ; SE: Standard Error      |            |              |              |               |                   |         |

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

The secondary criteria evaluated included quantitative evaluations (Contrast to Noise Ratio, Lesion to Brain (background) Ratio and percentage of lesion enhancement), overall diagnostic preference and impact on patient management.

In Study GDX-44-010, Lesion to Brain Ratio, and percentage of lesion enhancement were statistically significantly higher with gadopiclesol at 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW) compared to gadobutrol at 0.1 mL/kg BW (equivalent to 0.1 mmol/kg BW) for all 3 readers. Contrast to Noise Ratio was statistically significantly higher for 2 readers. In Study GDX-44-011, percentage of lesion enhancement was significantly higher with gadopiclesol at 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW) compared to gadobutrol at 0.1 mL/kg BW (equivalent to 0.1 mmol/kg BW) and no statistically significant difference was observed for Lesion to Background Ratio.

Lesion visualisation parameters (e.g., co-primary endpoints and quantitative assessments, such as, Contrast to Noise Ratio, Lesion to Brain (background) Ratio and percentage of lesion enhancement) were assessed in all the lesions identified by the blinded readers, independently of their size, in more than 86% of patients in CNS study and in more than 81% of patients in Body study, who had no more than 3 lesions. In the remaining patients with more than 3 lesions visible, a subset of 3 most representative lesions were selected for assessment of the co-primary endpoints. Therefore, in those patients, the additional lesions were not assessed. Consequently, the technical capability of lesion visualisation for both contrast agents cannot be extrapolated for those non-selected lesions.

The overall diagnostic preference was assessed in a global matched-pairs fashion (reading of images from both MRI assessed side by side) by three additional blinded readers in each study. The results are summarized in the Table 5 below. In Study GDX-44-010, in majority, the readers expressed a preference for images acquired with gadopiclesol. In Study GDX-44-011, in majority, the readers expressed no diagnostic preference between images acquired with gadopiclesol and with gadobutrol.

**Table 5: Results on overall diagnostic preference for Study GDX-44-010 (CNS) and Study GDX-44-011 (Body)**

|                         | Reader | N   | gadopiclenol preferred | No preference | gadobutrol preferred | p-value* |
|-------------------------|--------|-----|------------------------|---------------|----------------------|----------|
| Study GDX-44-010 (CNS)  | 4      | 241 | 108 (44.8 %)           | 98 (40.7 %)   | 35 (14.5 %)          | < 0.0001 |
|                         | 5      | 241 | 131 (54.4 %)           | 52 (21.6 %)   | 58 (24.1 %)          | < 0.0001 |
|                         | 6      | 241 | 138 (57.3 %)           | 56 (23.2 %)   | 47 (19.5 %)          | < 0.0001 |
| Study GDX-44-011 (Body) | 4      | 276 | 36 (13.0 %)            | 216 (78.3 %)  | 24 (8.7 %)           | 0.1223   |
|                         | 5      | 276 | 40 (14.5 %)            | 206 (74.6 %)  | 30 (10.9 %)          | 0.2346   |
|                         | 6      | 276 | 33 (12.0 %)            | 228 (82.6 %)  | 15 (5.4 %)           | 0.0079   |

\* Wilcoxon signed-rank test.

A change in patient treatment plan was reported after administration of gadopiclenol at 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW) in 23.3 % and 30.1 % of patients in Study GDX-44-010 and Study GDX-44-011, respectively.

Analysis per subgroups in Study GDX-44-010 revealed that treatment plan could be changed for 64 % of the 22 patients for whom the investigator considered that diagnosis was not assessable (or grade of glial tumor could not be determined) based on unenhanced MRI, 28 % of 81 patients with malignant diagnosis and about 12 % of 111 patients with non-malignant diagnosis.

In Study GDX-44-011, treatment plan could be changed after MRI with gadopiclenol for 41 % of the 22 patients with non-assessable diagnosis based on unenhanced MRI, 32 % of 165 patients with malignant diagnosis and 14 % of 64 patients with non-malignant diagnosis.

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

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

|                                 | Perfect match at lesion level* | Perfect match at patient level* |
|---------------------------------|--------------------------------|---------------------------------|
| Study GDX-44-010 (CNS)          | 88.0% to 89.8%                 | 84.3% to 86.0%                  |
| Study GDX-44-011 (Body) overall | 92.3% to 95.5%                 | 81.3% to 85.0%                  |
| Head & Neck                     | 89.5% to 100%                  | 70.6% to 94.1%                  |
| Thorax                          | 88.3% to 93.2%                 | 69.8% to 73.2%                  |
| Pelvis                          | 91.7% to 100%                  | 87.5% to 94.6%                  |
| Abdomen                         | 94.6% to 95.2%                 | 84.0% to 87.2%                  |
| Musculoskeletal                 | 100%                           | 100%                            |

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

#### *Paediatric population*

Two studies (Study GDX-44-007 and GDX-44-015) included 80 paediatric patients aged 2 to 17 years old and 36 neonates and infants less than 2 years old, who were administered a single dose of gadopiclenol (0.1 mL/kg BW, equivalent to 0.05 mmol/kg BW). Pre- and post-contrast-enhanced images were assessed for 78 patients undergoing MRI for CNS imaging, 34 patients for body imaging and 3 for blood vessels imaging.

Diagnostic efficacy was evaluated and there was no difference among the paediatric age groups.

## 5.2 Pharmacokinetic properties

### Absorption

The absolute bioavailability of gadopiclesol (in humans) is 100%, as it is only administered via the intravenous route.

After an intravenous dose of 0.1 to 0.2 mL/kg BW (equivalent respectively to 0.05 and 0.1 mmol/kg BW), the  $C_{\max}$  was  $525 \pm 70$  mcg/mL and  $992 \pm 233$  mcg/mL, respectively.

The  $C_{\max}$  increased 1.1-fold, 1.1-fold and 1.4-fold and the  $AUC_{\inf}$  increased 1.5-fold, 2.5-fold and 8.7-fold in patients with mild, moderate and severe renal impairment, respectively after a dose of 0.2 mL/kg BW (equivalent to 0.1 mmol/kg BW).

In addition, the increase in  $C_{\max}$  and  $AUC_{\inf}$  is expected to be similar with a dose of 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW) based on the results of population pharmacokinetic simulations.

### Distribution

After intravenous administration gadopiclesol is rapidly distributed in the extracellular fluids.

After a dose of 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW) the distribution volume  $V_d$  was  $12.9 \pm 1.7$  L.

The *in vitro* binding of  $^{153}\text{Gd}$ -gadopiclesol to human plasma proteins is negligible and independent of the gadopiclesol concentration, as  $^{153}\text{Gd}$ -gadopiclesol bound 0.0–1.8% to human plasma proteins and 0.0–0.1% to human red blood cells.

### Biotransformation

Gadopiclesol is not metabolised.

The lack of metabolism is confirmed by *in vitro* data using pooled human liver microsomes incubated with  $^{153}\text{Gd}$ -gadopiclesol. After 120 minutes  $\geq 95\%$  of the  $^{153}\text{Gd}$ -gadopiclesol remained in unchanged form. The results were similar when heat inactivated pooled human liver microsomes (negative controls) were incubated with  $^{153}\text{Gd}$ -gadopiclesol, indicating that  $^{153}\text{Gd}$ -gadopiclesol is not metabolised.

### Elimination

Gadopiclesol is eliminated rapidly in unchanged form through the kidneys by glomerular filtration. After a dose of 0.1 to 0.2 mL/kg BW (equivalent respectively to 0.05 and 0.1 mmol/kg BW), the mean plasma elimination half-life ( $t_{1/2}$ ) in healthy volunteers with a normal renal function was 1.5 and 1.7 hour, respectively, and the clearance was  $100 \pm 10$  mL/min and  $96 \pm 12$  mL/min, respectively. Urinary excretion is the major route of elimination of gadopiclesol, with approximately 98 % of the dose excreted in urine after 48 hours regardless of the dose administered.

### Linearity/non-linearity

The pharmacokinetic profile of gadopiclesol is linear in the studied dose range (0.05 to 0.6 mL/kg BW equivalent to 0.025 to 0.3 mmol/kg BW), without difference between males and females. Mean maximum concentration ( $C_{\max}$ ) and Area Under the Curve ( $AUC_{\inf}$ ) increased proportionally to the dose.

### Paediatric population

Two phase 2 studies (GDX-44-007 and GDX-44-015) included 80 paediatric patients aged 2 to 17 years old (60 in the CNS cohort were included in the PK analysis) and 36 aged less than 2 years. They all received a single dose of gadopiclesol at 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW).

Individual parameters predicted from the latest population pharmacokinetic model and normalised by BW were similar between adults and children. The median clearance ranged from 0.08 L/h/kg (for age group 12-17 years old) to 0.12 L/h/kg (for age group 3-23 months old).

The median terminal half-life was 1.78 hour for age group 12-17 years old, 1.61 hour for age group 7-11 years old, 1.75 hour for age group 2-6 years old, 1.45 hour for age group 3-23 months old and 2.10 for age group less than 3 months old. .

The pharmacokinetics of gadopichlenol in children are comparable to the pharmacokinetics in adults.

#### Renal impairment and dialysability

The elimination half-life ( $t_{1/2}$ ) is prolonged in subjects with renal impairment, increasing with the degree of renal impairment. In patients with mild ( $60 \leq \text{eGFR} < 90 \text{ mL/min}$ ), moderate ( $30 \leq \text{eGFR} < 60 \text{ mL/min}$ ) and severe ( $15 \leq \text{eGFR} < 30 \text{ mL/min}$ ) renal impairment, the mean  $t_{1/2}$  was 3.3, 3.8 and 11.7 hours, respectively and the clearance was 1.02, 0.62 and 0.17 mL/min/kg, respectively.

The  $C_{\text{max}}$  increased 1.1-fold, 1.1-fold and 1.4-fold and the  $\text{AUC}_{\text{inf}}$  increased 1.5-fold, 2.5-fold and 8.7-fold in patients with mild, moderate and severe renal impairment, respectively after a dose of 0.2 mL/kg BW (equivalent to 0.1 mmol/kg BW).

In addition, the increase in  $C_{\text{max}}$  and  $\text{AUC}_{\text{inf}}$  is expected to be similar with a dose of 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW) based on the results of population pharmacokinetic simulations.

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

In patients with End Stage Renal Disease (ESRD), 4 hour haemodialysis effectively removed gadopichlenol from plasma as the percentage of decrease in blood concentrations was 95 to 98 % at the end of the first haemodialysis session.

#### Weight

The effect of weight was investigated with population pharmacokinetic simulations of patients with a BW ranging from 40 kg to 150 kg receiving a gadopichlenol dose of 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW). The ratios of median  $\text{AUC}_{\text{inf}}$  of gadopichlenol between a typical healthy subject of 70 kg and subjects weighing 40 kg and 150 kg was 0.86 and 2.06, respectively. The ratios of the plasma concentrations 10, 20 and 30 minutes after administration between a typical healthy subject of 70 kg and subjects weighing 40 kg and 150 kg ranged from 0.93 to 1.26.

### **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development.

Juvenile animal toxicity studies have not revealed any relevant findings.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Tetraxetan  
Trometamol

Hydrochloric acid (for pH adjustment)  
Sodium hydroxide (for pH adjustment)  
Water for injections

## **6.2 Incompatibilities**

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

## **6.3 Shelf life**

3 years.

### For vials

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

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless the opening has taken place in controlled and validated aseptic conditions.

## **6.4 Special precautions for storage**

### For vials

This medicinal product does not require any special storage conditions.

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

### For pre-filled syringes

Do not freeze.

## **6.5 Nature and contents of container**

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

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

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

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

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

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

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

7.5 mL, 10 mL or 15 mL of solution for injection in a 15 mL plastic (polypropylene) pre-filled syringe, graduated every 0.5 mL, without a needle, with an elastomeric (bromobutyl) plunger stopper and capped

with an elastomeric (bromobutyl) tip cap. Pack size of 1 or a multipack containing 10 (10 packs of 1) pre-filled syringes.

7.5 mL, 10 mL or 15 mL of solution for injection in 15 mL plastic (polypropylene) pre-filled syringe, graduated every 0.5 mL, with an elastomeric (bromobutyl) plunger stopper and capped with an elastomeric (bromobutyl) tip cap with administration set for manual injection (one extension line and one catheter) in pack size of 1.

7.5 mL, 10 mL or 15 mL of solution for injection in 15 mL plastic (polypropylene) pre-filled syringe, graduated every 0.5 mL, with an elastomeric (bromobutyl) plunger stopper and capped with an elastomeric (bromobutyl) tip cap with administration set for Optistar Elite injector (one extension line, one catheter and one empty 60 mL plastic syringe) in pack size of 1.

7.5 mL, 10 mL or 15 mL of solution for injection in 15 mL plastic (polypropylene) pre-filled syringe, graduated every 0.5 mL, with an elastomeric (bromobutyl) plunger stopper and capped with an elastomeric (bromobutyl) tip cap with administration set for Medrad Spectris Solaris EP injector (one extension line, one catheter and one empty 115 mL plastic syringe) in pack size of 1.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal and other handling**

Do not use if the medicinal product including packaging is opened or damaged.

The solution for injection should be inspected visually prior to use.

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

Before and during the use of the product, follow the safety, hygiene and asepsis rules.

### For vials

The vial stopper should be pierced only once.

### For pre-filled syringes

Do not use the pre-filled syringe if there are any signs of leakage.

The pre-filled syringe is for single use only. Do not attempt to re-use even after cleaning or sterilizing the single use pre-filled syringe.

Screw the push rod into the syringe plunger. It is important to rotate and push the push rod an additional ½ turn so that the plunger can rotate freely.

Before using the pre-filled syringe, remove the tip cap by spinning it.

Connection is compatible with luer 6%.

All luer connections should be gently hand tightened without over tightening to ensure secure connection and to prevent damage to the device.

Before connecting to the patient, prime completely the intravenous line and check the absence of air: hold the syringe erect and push plunger forward until all of the air is evacuated and fluid either appears at the tip of the needle or the tubing is filled.

The dose volume accuracy has been checked and is conform to ISO 7886-1.

The delivered dose accuracy for 15 mL syringes, graduated every 0.5 mL, depends on the injected volume. For a volume range of 5 to 15 mL, it may vary up to  $\pm 0.6$  mL.

When used with a power injector, follow injector instructions for use.

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

The peel-off tracking label available on the vial or the pre-filled syringe should be stuck onto the patient record to enable accurate recording of the gadolinium contrast agent used. The dose used should also be recorded. If electronic patient records are used, the name of the product, the batch number and the dose should be entered into the patient record.

Any unused portions and waste material derived from disposal and items which come into contact with the product when administering this product with an automatic application system should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Guerbet  
15 rue des Vanesses  
93420 Villepinte  
France

## **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/23/1772/001-025

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 07/12/2023

## **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>

## **ANNEX II**

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## **A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer(s) responsible for batch release

Guerbet  
16 rue Jean Chaptal  
93600 Aulnay-sous-Bois  
France

BIPSO GmbH  
Robert-Gerwig-Strasse 4  
Singen (Hohentwiel)  
78224  
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to restricted medical prescription (see annex I: Summary of Product Characteristics, section 4.2).

## **C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## **D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**Text for the carton box (outer packaging) of 3 mL, 7.5 mL, 10 mL, 15 mL, 30 mL, 50 mL and 100 mL vial for all pack sizes.**

**The outer label contains Blue box.**

**Text for the inner label (immediate packaging) of 15 mL, 30 mL, 50 mL and 100 mL vial.**

**No Blue box is included in the inner label.**

**1. NAME OF THE MEDICINAL PRODUCT**

Elucirem 0.5 mmol/mL solution for injection  
gadopichlenol

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

1 mL of solution contains 485.1 mg gadopichlenol (equivalent to 0.5 mmol of gadopichlenol and to 78.6 mg of gadolinium).

**3. LIST OF EXCIPIENTS**

Excipients: tetraxetan, trometamol, hydrochloric acid, sodium hydroxide, water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection

**On the outer carton:**

Single pack:

1 vial of 3 mL

1 vial of 7.5 mL

1 vial of 10 mL

1 vial of 15 mL

1 vial of 30 mL

1 vial of 50 mL

1 vial of 100 mL

Other pack:

25 vials of 7.5 mL

25 vials of 10 mL

25 vials of 15 mL

**On the inner label:**

15 mL

30 mL

50 mL

100 mL

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Intravenous use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Not applicable.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Not applicable.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Not applicable.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Guerbet  
15 rue des Vanesses  
93420 Villepinte  
France

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/23/1772/001 1 vial of 3 mL  
EU/1/23/1772/002 1 vial of 7.5 mL  
EU/1/23/1772/003 25 vials of 7.5 mL  
EU/1/23/1772/004 1 vial of 10 mL  
EU/1/23/1772/005 25 vials of 10 mL  
EU/1/23/1772/006 1 vial of 15 mL  
EU/1/23/1772/007 25 vials of 15 mL  
EU/1/23/1772/008 1 vial of 30 mL  
EU/1/23/1772/009 1 vial of 50 mL  
EU/1/23/1772/010 1 vial of 100 mL

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| <b>13. BATCH NUMBER</b> |
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Lot

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| <b>14. GENERAL CLASSIFICATION FOR SUPPLY</b> |
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| <b>15. INSTRUCTIONS ON USE</b> |
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|-----------------------------------|
| <b>16. INFORMATION IN BRAILLE</b> |
|-----------------------------------|

Not applicable.

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|-------------------------------------------|
| <b>17. UNIQUE IDENTIFIER – 2D BARCODE</b> |
|-------------------------------------------|

Not applicable.

|                                                    |
|----------------------------------------------------|
| <b>18. UNIQUE IDENTIFIER - HUMAN READABLE DATA</b> |
|----------------------------------------------------|

Not applicable.

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

Text for the inner label (immediate packaging) of 3 mL, 7.5 mL and 10 mL vial.

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Elucirem 0.5 mmol/mL Injection  
gadopiclenol  
Intravenous use

**2. METHOD OF ADMINISTRATION**

Not applicable.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

3 mL  
7.5 mL  
10 mL

**6. OTHER**

Not applicable.

## **PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**Text for the carton box (outer packaging) of 7.5 mL, 10 mL and 15 mL pre-filled syringe for single pack and multipack.**

**The outer label contains Blue box.**

**Text for the inner label (immediate packaging) of 15 mL pre-filled syringe.**

**No Blue box is included in the inner label.**

### **1. NAME OF THE MEDICINAL PRODUCT**

Elucirem 0.5 mmol/mL solution for injection  
gadopiclesol

### **2. STATEMENT OF ACTIVE SUBSTANCE(S)**

1 mL of solution contains 485.1 mg gadopiclesol (equivalent to 0.5 mmol of gadopiclesol and to 78.6 mg of gadolinium).

### **3. LIST OF EXCIPIENTS**

Excipients: tetraxetan, trometamol, hydrochloric acid, sodium hydroxide, water for injections.

### **4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection

#### **On the outer carton:**

##### Single pack:

1 pre-filled syringe of 7.5 mL

1 pre-filled syringe of 10 mL

1 pre-filled syringe of 15 mL

1 pre-filled syringe of 7.5 mL with administration set for manual injection (extension line + catheter)

1 pre-filled syringe of 10 mL with administration set for manual injection (extension line + catheter)

1 pre-filled syringe of 15 mL with administration set for manual injection (extension line + catheter)

1 pre-filled syringe of 7.5 mL with administration set for Optistar Elite injector (extension line + catheter + empty 60-mL syringe)

1 pre-filled syringe of 10 mL with administration set for Optistar Elite injector (extension line + catheter + empty 60-mL syringe)

1 pre-filled syringe of 15 mL with administration set for Optistar Elite injector (extension line + catheter + empty 60-mL syringe)

1 pre-filled syringe of 7.5 mL with administration set for Medrad Spectris Solaris EP injector (extension line + catheter + empty 115-mL syringe)

1 pre-filled syringe of 10 mL with administration set for Medrad Spectris Solaris EP injector (extension line + catheter + empty 115-mL syringe)

1 pre-filled syringe of 15 mL with administration set for Medrad Spectris Solaris EP injector (extension line + catheter + empty 115-mL syringe)

**Multipack:**

10 pre-filled syringes of 7.5 mL

10 pre-filled syringes of 10 mL

10 pre-filled syringes of 15 mL

**On the inner label:**

15 mL

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

Intravenous use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Not applicable.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not freeze.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Not applicable.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Guerbet  
15 rue des Vanesses  
93420 Villepinte  
France

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/23/1772/011 1 pre-filled syringe of 7.5 mL

EU/1/23/1772/012 10 (10 x 1) pre-filled syringes of 7.5 mL (multipack)

EU/1/23/1772/013 1 pre-filled syringe of 7.5 mL + administration set for manual injection (1 extension line + 1 catheter)

EU/1/23/1772/014 1 pre-filled syringe of 7.5 mL + administration set for Optistar Elite injector (1 extension line + 1 catheter +1 syringe of 60 ml)

EU/1/23/1772/015 1 pre-filled syringe of 7.5 mL + administration set for Medrad Spectris Solaris EP injector (1 extension line + 1 catheter +1 syringe of 115 ml)

EU/1/23/1772/016 1 pre-filled syringe of 10 mL

EU/1/23/1772/017 10 (10 x 1) pre-filled syringes of 10 mL (multipack)

EU/1/23/1772/018 1 pre-filled syringe of 10 mL + administration set for manual injection (1 extension line + 1 catheter)

EU/1/23/1772/019 1 pre-filled syringe of 10 mL + administration set for Optistar Elite injector (1 extension line + 1 catheter +1 syringe of 60 ml)

EU/1/23/1772/020 1 pre-filled syringe of 10 mL + administration set for Medrad Spectris Solaris EP injector (1 extension line + 1 catheter + 1 syringe of 115 ml)

EU/1/23/1772/021 1 pre-filled syringe of 15 mL

EU/1/23/1772/022 10 (10 x 1) pre-filled syringes of 15 mL (multipack)

EU/1/23/1772/023 1 pre-filled syringe of 15 mL + administration set for manual injection (1 extension line + 1 catheter)

EU/1/23/1772/024 1 pre-filled syringe of 15 mL + administration set for Optistar Elite injector (1 extension line + 1 catheter +1 syringe of 60 ml)

EU/1/23/1772/025 1 pre-filled syringe of 15 mL + administration set for Medrad Spectris Solaris EP injector (1 extension line + 1 catheter +1 syringe of 115 ml)

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| <b>13. BATCH NUMBER</b> |
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Lot

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| <b>14. GENERAL CLASSIFICATION FOR SUPPLY</b> |
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| <b>15. INSTRUCTIONS ON USE</b> |
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|-----------------------------------|
| <b>16. INFORMATION IN BRAILLE</b> |
|-----------------------------------|

Not applicable.

|                                           |
|-------------------------------------------|
| <b>17. UNIQUE IDENTIFIER – 2D BARCODE</b> |
|-------------------------------------------|

Not applicable.

|                                                    |
|----------------------------------------------------|
| <b>18. UNIQUE IDENTIFIER - HUMAN READABLE DATA</b> |
|----------------------------------------------------|

Not applicable.

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**  
**Text for the inner label (immediate packaging) of 7.5 mL and 10 mL pre-filled syringe.**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Elucirem 0.5 mmol/mL Injection  
gadopiclenol  
Intravenous use

**2. METHOD OF ADMINISTRATION**

Not applicable.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

7.5 mL  
10 mL

**6. OTHER**

Not applicable.

## **B. PACKAGE LEAFLET**

## **Package leaflet: Information for the patient**

### **Elucirem 0.5 mmol/mL solution for injection** gadopichlenol

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you are given this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, radiologist or pharmacist.
- If you get any side effects, talk to your doctor, radiologist or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Elucirem is and what it is used for
2. What you need to know before you are given Elucirem
3. How Elucirem will be given to you
4. Possible side effects
5. How to store Elucirem
6. Contents of the pack and other information

#### **1. What Elucirem is and what it is used for**

Elucirem is a contrast agent which enhances the contrast of the images obtained during magnetic resonance imaging (MRI) examinations. Elucirem contains the active substance gadopichlenol.

It improves the visualisation and delineation of abnormal structures or lesions of certain parts of the body and helps in the differentiation between healthy and diseased tissue.

It is used in adults and children from birth.

It is given as an injection into your vein. This medicine is for diagnostic use only and will only be administered by healthcare professionals experienced in the field of clinical MRI practice.

#### **2. What you need to know before you are given Elucirem**

##### **Elucirem must not be given to you**

- if you are allergic to gadopichlenol or any of the other ingredients of this medicine (listed in section 6).

##### **Warnings and precautions**

Talk to your doctor, radiologist or pharmacist before you are given Elucirem:

- if you had a previous reaction to any contrast agent,
- if you have asthma,
- if you have a history of allergy (such as hay fever, hives),
- if your kidneys do not work properly,
- if you had seizures (fits) or are being treated for epilepsy,
- if you have a disease affecting your heart or your blood vessels.

In all these cases, your doctor will decide whether the intended examination is possible or not. If you are given Elucirem, your doctor or radiologist will take the necessary precautions and the administration of it will be carefully monitored.

Your doctor or radiologist may decide to take a blood test to check how well your kidneys are working before making the decision to use Elucirem, especially if you are 65 years of age or older.

### **Children**

As kidney function is immature in babies up to 4 weeks of age and infants up to 1 year of age, Elucirem will only be used in these patients after careful consideration by the doctor.

### **Other medicines and Elucirem**

Tell your doctor, radiologist or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, please inform your doctor, radiologist or pharmacist if you are taking or have recently taken medicines for heart and blood pressure disorders such as beta-blocking agents, vasoactive substances, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists.

### **Pregnancy and breast-feeding**

#### **Pregnancy**

Gadopicolenol can cross the placenta. It is not known whether it affects the baby. Tell your doctor or radiologist if you think you are, or might become pregnant as Elucirem should not be used during pregnancy unless strictly necessary.

#### **Breast-feeding**

Tell your doctor or radiologist if you are breast-feeding or about to start breast-feeding.

Your doctor will discuss whether you should continue or interrupt breast-feeding for a period of 24 hours after you receive Elucirem.

### **Driving and using machines**

Elucirem has no or negligible effect on the ability to drive and use machines. However, if you feel unwell after the examination, you should not drive or use machines.

### **Elucirem contains sodium**

This medicine contains less than 1 mmol sodium (23 mg) per 15 mL vial, that is to say essentially 'sodium-free'.

## **3. How Elucirem will be given to you**

Elucirem will be injected into your vein using a small needle by a specialised healthcare professional. It can be administered by hand or by an automatic injector.

Your doctor or radiologist will determine the dose you will receive and supervise the injection. The usual dose of 0.1 mL/kg body weight is the same in adults and children.

In children, your doctor or radiologist will use Elucirem in vials with a single use syringe to be able to have a better precision of the injected volume.

After the injection, you will be kept under supervision for at least 30 minutes. This is the time where most undesired reactions (such as allergic reactions) may occur. However, in rare cases, reactions may occur after hours or days.

### **Use in patients with severe kidney problems**

The use of Elucirem is not recommended in patients with severe kidney problems. However, if it is required you should only receive one dose of Elucirem during a scan and you should not receive a second injection for at least 7 days.

### Use in children

As kidney function is immature in babies up to 4 weeks of age and infants up to 1 year of age, Elucirem will only be used in these patients after careful consideration by the doctor. Children should only receive one dose of Elucirem during a scan and should not receive a second injection for at least 7 days.

### Use in elderly

It is not necessary to adjust your dose if you are 65 years of age or older, but you may have a blood test to check how well your kidneys are working.

### If you receive more Elucirem than you should

It is highly unlikely that you will receive an overdose of Elucirem, as it will be given to you by a trained healthcare professional. If it does happen, Elucirem can be removed from the body by haemodialysis (blood cleaning).

If you have any further questions on the use of this medicine, ask your doctor, radiologist or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

After the administration of Elucirem, you will be kept under observation. Most side effects occur within minutes. There is a small risk that you may have an allergic reaction to it. These effects can occur immediately and up to seven days after the injection. Such reactions can be severe and result in shock (case of allergic reaction that could put your life in danger).

**Tell your doctor, radiologist or health professional immediately if you get any of the following side effects as it may be the first signs of a shock:**

- swelling of the face, lips, tongue or throat
- lightheadedness (low blood pressure)
- breathing difficulties
- skin rash
- coughing, sneezing or runny nose

Possible side effects which have been observed during clinical trials with Elucirem are listed below by how likely they are:

| Frequency                                             | Possible side effects                                                                                                                                                          |
|-------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Common</b> (may affect up to 1 in 10 people)       | Injection site reaction*<br>Headache                                                                                                                                           |
| <b>Uncommon</b><br>(may affect up to 1 in 100 people) | Allergic reaction**<br>Diarrhoea<br>Nausea (feeling sick)<br>Fatigue (tiredness)<br>Abdominal pain<br>Unusual taste in the mouth<br>Feeling of warmth<br>Vomiting (being sick) |

\*Injection site reaction includes: pain, swelling, cold feeling, warm feeling, bruising or redness.

\*\*Allergic reaction may include: inflammation of the skin, reddening of the skin, breathing difficulties, voice impairment, throat tightness, throat irritation, abnormal sensation in the mouth, transient reddening of the face (early reactions) and puffy eyes, swelling, rash and itching (late reactions).

There have been reports of nephrogenic systemic fibrosis (NSF) (which causes hardening of the skin and may affect also soft tissue and internal organs) with other contrast agent containing gadolinium however no NSF case has been reported with Elucirem during the clinical trials.

### **Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store Elucirem**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial or pre-filled syringe label and the carton box after “EXP”. The expiry date refers to the last day of that month.

This medicine is a clear, colorless to pale yellow solution.

Do not use this medicine if the solution is not clear or if it contains visible particles.

For vials: This medicine does not require any special storage conditions.

Chemical and physical in-use stability has been demonstrated for 24 hours at up to 25 °C. From a microbiological point of view, the product should be used immediately after opening.

For pre-filled syringes: Do not freeze.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What Elucirem contains**

- The active substance is gadopichlenol. Each mL of solution contains 485.1 mg gadopichlenol (equivalent to 0.5 mmol of gadopichlenol and to 78.6 mg of gadolinium).
- The other ingredients are tetraxetan, trometamol, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections. See section 2 “Elucirem contains sodium”

### **What Elucirem looks like and contents of the pack**

It is a clear, colourless to pale yellow solution for injection.

It is available in packs including:

- 1 vial containing 3, 7.5, 10, 15, 30, 50 or 100 mL of solution for injection.
- 25 vials containing 7.5, 10 or 15 mL of solution for injection.
- 1 or 10 (10 x 1) pre-filled syringes containing 7.5, 10 or 15 mL of solution for injection.
- 1 pre-filled syringe containing 7.5, 10 or 15 mL of solution for injection with administration set for manual injection (one extension line and one catheter).
- 1 pre-filled syringe containing 7.5, 10 or 15 mL of solution for injection with administration set for Optistar Elite injector (one extension line, one catheter and one empty 60 mL-plastic syringe).
- 1 pre-filled syringe containing 7.5, 10 or 15 mL of solution for injection with administration set for Medrad Spectris Solaris EP injector (one extension line, one catheter and one empty 115 mL-plastic syringe).

Not all pack sizes may be marketed.

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BIPSO GmbH  
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**This leaflet was last revised in**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>.

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**The following information is intended for healthcare professionals only:**

For details on how to use the product, please refer to the section 6.6 Special precautions for disposal and other handling of the Summary of Product Characteristics of this product.

#### **Annex IV**

#### **Conclusions on the request for one-year marketing protection presented by the European Medicines Agency**

**Conclusions presented by the European Medicines Agency on:**

- **one-year marketing protection**

The CHMP reviewed the data submitted by the marketing authorisation holder, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies as further explained in the European Public Assessment Report.