

Annex III

Amendments to relevant sections of the product information

Note:

These amendments to the relevant sections of the product information are the outcome of the referral procedure.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

Amendments to relevant sections of the product information

The existing product information shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the agreed wording as provided below.

Intravenous gadoteric acid, gadobutrol, gadoteridol

Summary of product characteristics

- Section 4.1 Therapeutic indications

<Product name> should be used only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI).

- Section 4.2 Posology and method of administration

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 detailed in this section.

Intra-articular gadoteric acid

Summary of product characteristics

- Section 4.1 Therapeutic indications

<Product name> should be used only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI).

- Section 4.2 Posology and method of administration

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

Intra-articular gadopentetic acid

Summary of Product Characteristics

- Section 4.1 Therapeutic indications

<Product name> should be used only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI) and when another authorised product cannot be used.

- Section 4.2 Posology and method of administration

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

- Section 4.4 Special warnings and precautions for use

After intravenous administration of <active substance name (INN)> gadolinium can be retained in the brain and in other tissues of the body (bones, liver, kidneys, skin) and can cause dose-dependent increases in T1-weighted signal intensity in the brain, particularly in the dentate nucleus, globus pallidus, and thalamus. Clinical consequences are unknown. Retention of gadolinium in the brain has not been identified for intra-articular administration. The possible diagnostic advantages of using <active substance name (INN)> in patients who will require repeated scans should be weighed against the potential for deposition of gadolinium in the brain and other tissues.

- 5.2 Pharmacokinetic properties

<Active substance name (INN)> is a linear GdCA. Studies have shown that after exposure to GdCAs given intravenously at significantly higher doses than intra-articular products gadolinium is retained in the body. This includes retention in the brain and in other tissues and organs. With the linear GdCAs this can cause dose-dependent increases in T1-weighted signal intensity in the brain, particularly in the dentate nucleus, globus pallidus, and thalamus. Signal intensity increases and non-clinical data show that gadolinium is released from linear GdCAs.

Package leaflet

- Section 2: What you need to know before you are given <product name>
 - Accumulation in the body

<Product name> works because it contains a metal called gadolinium. Studies have shown that small amounts of gadolinium can remain in the body, including the brain.

This has not been seen following the small amounts given with injections into the joint.

Intravenous gadoxetic acid

Summary of Product Characteristics

- Section 4.1 Therapeutic indications

<Product name> is indicated for the detection of focal liver lesions and provides information on the character of lesions in T1-weighted magnetic resonance imaging (MRI).

<Product name> should be used only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI) and when delayed phase imaging is required.

This medicinal product is for diagnostic use by intravenous administration only.

- Section 4.2 Posology and method of administration

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 detailed in this section.

- Section 4.4 Special warnings and precautions for use

After administration of <active substance name (INN)> gadolinium can be retained in the brain and in other tissues of the body (bones, liver, kidneys, skin) and can cause dose-dependent increases in T1-weighted signal intensity in the brain, particularly in the dentate nucleus, globus pallidus, and thalamus. Clinical consequences are unknown. The possible diagnostic advantages of using <active

substance name (INN) > in patients who will require repeated scans should be weighed against the potential for deposition of gadolinium in the brain and other tissues.

- 5.2 Pharmacokinetic properties

<Active substance name (INN) > is a linear GdCA. Studies have shown that after exposure to GdCAs gadolinium is retained in the body. This includes retention in the brain and in other tissues and organs. With the linear GdCAs this can cause dose-dependent increases in T1-weighted signal intensity in the brain, particularly in the dentate nucleus, globus pallidus, and thalamus. Signal intensity increases and non-clinical data show that gadolinium is released from linear GdCAs.

Package leaflet

- Section 2: What you need to know before you are given <product name>
 - Accumulation in the body

<Product name> works because it contains a metal called gadolinium. Studies have shown that small amounts of gadolinium can remain in the body, including the brain. No side effects have been seen due to gadolinium remaining in the brain.

Intravenous gadobenic acid (restriction of the indication – all references to other indications should be removed across the Product Information)

Summary of Product Characteristics

Section 4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

<Product name> is a paramagnetic contrast agent for use in diagnostic magnetic resonance imaging (MRI) indicated for: of the liver in adults and children (above the age of 2 years)

~~• MRI of the brain and spine in adults and children above the age of 2 years, where it improves the detection of lesions and provides diagnostic information additional to that obtained with unenhanced MRI (see section 5.1).~~

~~• MR imaging of the whole body in adults and children (above the age of 2 years) including head and neck region, thoracic space (including the heart and female breast), abdomen (pancreas and liver), abdomen (gastrointestinal tract), retroperitoneal space (kidney, adrenal glands), pelvis (prostate, bladder and uterus) and musculoskeletal system where it facilitates identification of abnormal structures or lesions and helps in differentiating normal from pathological tissues (see sections 4.2 and 5.1).~~

~~• Magnetic Resonance Angiography (MRA) for the assessment of stenoses, occlusions and collaterals in adults and children (above the age of 2 years).~~

~~• Specific applications in the heart include measurement of myocardial perfusion under pharmacological stress conditions and viability diagnostics ("delayed enhancement").~~

<Product name> should be used only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI) and when delayed phase imaging is required

• Section 4.2 Posology and method of administration

| Target organ | Recommended dose |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Brain and spine | 0.1 mmol/kg body weight (0.2 mL/kg of the 0.5 M solution) |
| Liver, kidneys, urinary tract, adrenal glands | 0.05 mmol/kg body weight (0.1 mL/kg of the 0.5 M solution) |
| Magnetic resonance angiography | 0.1 mmol/kg body weight (0.2 mL/kg of the 0.5 M solution) |
| Head and neck region, thoracic space (including the heart and female breast), abdomen (gastrointestinal tract including pancreas), pelvis (prostate, bladder and uterus) and musculoskeletal system | 0.1 mmol/kg body weight (0.2 mL/kg of the 0.5 M solution) |
| Cardiac MRI <ul style="list-style-type: none"> • Assessment of cardiac masses or myocardial viability • Assessment of myocardial perfusion | - 0.1 mmol/kg body weight, administered as a single bolus of 0.2 mL/kg of the 0.5 M solution. Two separate injections of 0.05 mmol/kg body weight (each corresponding to 0.1 mL/kg of the 0.5 M solution) during rest and stress imaging. |

The recommended dose of <active substance name (INN)> in adult patients and children is 0.05 mmol/kg body weight (0.1 mL/kg of the 0.5 M solution). 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 detailed in this section.

(...)

Post-contrast imaging acquisition:

| | | |
|-------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| Liver | <u>Dynamic imaging:</u> | <u>Immediately following bolus injection.</u> |
| | <u>Delayed imaging:</u> | between 40 and 120 minutes following the injection, depending on the individual imaging needs. |
| <u>Brain and Spine</u> | up to 60 minutes after the administration. | |
| <u>MRA</u> | immediately after the administration, with scan delay calculated on the basis of test bolus or automatic bolus detection technique. If an automatic contrast detection pulse sequence is not used for bolus timing, then a test bolus injection ≤ 2 mL of the agent should be used to calculate the appropriate scan delay. | |
| <u>Breast</u> | A T1-weighted, gradient-echo sequence with a time resolution of 2 minutes or less should be acquired before contrast injection and repeated several times over a period of 5 to 8 min after a rapid intravenous contrast bolus injection. | |
| <u>Other body areas</u> | T1-weighted sequences to be acquired as either dynamic or static delayed imaging. | |

Special Populations

Impaired renal function

(...)

If use of <Product name> cannot be avoided, the dose should not exceed 0.1 mmol/kg body weight when used for MR of the brain and spine, MR angiography, breast MRI or whole body MRI and should not exceed 0.05 mmol/kg body weight when used for MR of the liver, kidneys, urinary tract, or adrenal glands. More than one dose should not be used during a scan except for MR cardiac perfusion imaging where two separate doses of 0.05 mmol/kg body weight can be administered in the course of a

~~single examination.~~ Because of the lack of information on repeated administration, <Product name> injections should not be repeated unless the interval between injections is at least 7 days.

- Section 4.4 Special warnings and precautions for use

After administration of <active substance name (INN)> gadolinium can be retained in the brain and in other tissues of the body (bones, liver, kidneys, skin) and can cause dose-dependent increases in T1-weighted signal intensity in the brain, particularly in the dentate nucleus, globus pallidus, and thalamus. Clinical consequences are unknown. The possible diagnostic advantages of using <active substance name (INN)> in patients who will require repeated scans should be weighed against the potential for deposition of gadolinium in the brain and other tissues.

- 5.2 Pharmacokinetic properties

<Active substance name (INN)> is a linear GdCA. Studies have shown that after exposure to GdCAs gadolinium is retained in the body. This includes retention in the brain and in other tissues and organs. With the linear GdCAs this can cause dose-dependent increases in T1-weighted signal intensity in the brain, particularly in the dentate nucleus, globus pallidus, and thalamus. Signal intensity increases and non-clinical data show that gadolinium is released from linear GdCAs.

Package leaflet

- Section 1 What <Product name> is and what it is used for

<Product name> is a special dye (or contrast agent) which contains the rare earth metal gadolinium and improves images of the liver ~~brain/spine, arteries and other body areas~~ during MRI scans. It helps your doctor to identify any abnormalities of your liver ~~brain/spine, arteries or other parts of your body~~. This medicine is for diagnostic use only.

<Product name> is approved for use in children above two years of age.

- Section 2: What you need to know before you are given <product name>
 - Accumulation in the body

<Product name> works because it contains a metal called gadolinium. Studies have shown that small amounts of gadolinium can remain in the body, including the brain. No side effects have been seen due to gadolinium remaining in the brain.

- Section 3 How to use <Product name>

<Product name> is injected into a vein, usually in your arm just before the MRI scan. The amount in millilitre you will be injected depends on how much you weigh in kilogram of body weight.

The recommended dose is:

~~**MRI of brain/spine:** 0.2 ml per kilogram of body weight~~

~~**MRI of arteries:** 0.2 ml per kilogram of body weight~~

~~**MRI of the liver, the kidney, urinary tract or adrenal glands:** 0.1 ml per kilogram of body weight~~

~~**MRI of the breast, heart or other body areas:** 0.2 ml per kilogram of body weight~~

- part for healthcare professionals:

Post-contrast imaging acquisition:

| | | |
|-------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| | <u>Dynamic</u> | <u>Immediately following bolus injection.</u> |
| <u>Liver</u> | <u>Delayed imaging:</u> | <u>between 40 and 120 minutes following the injection, depending on the individual imaging needs.</u> |
| <u>Brain</u> | <u>up to 60 minutes after the administration.</u> | |
| <u>MRA</u> | <u>immediately after the administration, with scan delay calculated on the basis of test bolus or automatic bolus detection technique. If an automatic contrast detection pulse sequence is not used for bolus timing, then a test bolus injection ≤ 2 mL of the agent should be used to calculate the appropriate scan delay.</u> | |
| <u>Breast</u> | <u>A T1-weighted, gradient-echo sequence with a time resolution of 2 minutes or less should be acquired before contrast injection and repeated several times over a period of</u> | |
| <u>Other body areas</u> | <u>T1-weighted sequences to be acquired as either dynamic or static delayed imaging.</u> | |

Prior to administration of <Product name>, 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 < 30ml/min /1.73 m²). 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 <Product name>, it should therefore be avoided in patients with severe renal impairment and in patients in the perioperative liver transplantation period unless the diagnostic information is essential and not available with non-contrast enhanced MRI. If use of <Product name> cannot be avoided, the dose should not exceed 0.1 mmol/kg body weight when used for MR of the brain and spine, MR angiography breast MRI or whole body MRI and should not exceed 0.05 mmol/kg body weight. when used for MR of the liver, kidneys, urinary tract or adrenal glands More than one dose should not be used during a scan except for MR cardiac perfusion imaging where two separate doses of 0.05 mmol/kg body weight can be administered in the course of a single examination. Because of the lack of information on repeated administration, <Product name> injections should not be repeated unless the interval between injections is at least 7 days.