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Pharmacovigilance Risk Assessment Committee (PRAC)

## Assessment report

Referral under Article 31 of Directive 2001/83/EC resulting from  
pharmacovigilance data

Gadolinium containing contrast agents

Procedure number(s): EMEA/H/A-31/1437

Optimark EMEA/H/A-31/1437/C/000745/0034

Note:

Assessment report as adopted by the PRAC and considered by the CHMP with all  
information of a commercially confidential nature deleted.



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# 1. Information on the procedure

Gadolinium containing contrast agents (GdCAs) are complexes of gadolinium (III) with different types of organic chelators. They are used for contrast enhancement in magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA). Intra-articular GdCA formulations are also used in arthrography for MR of joints. Within the class, they can be differentiated in linear or macrocyclic compounds and whether they are ionic or non-ionic.

In a previous referral under Article 31 of Directive 2001/83/EC finalised in 2010, the Committee for Medicinal Products for Human Use (CHMP) concluded that the use of GdCAs is associated with the risk of nephrogenic systemic fibrosis (NSF), a serious and life-threatening syndrome involving fibrosis of the skin, joints and internal organs in patients with renal impairment. The CHMP concluded that the risk of NSF is different for the different GdCAs, which were then categorised into three groups for NSF risk (high risk, medium risk and low risk).

In addition, since the finalisation of the previous referral, data in animals and humans indicates the accumulation of gadolinium following administration of GdCAs in other tissues, including the liver, kidney, muscle, skin and bone. Furthermore, recent publications indicated the accumulation of gadolinium in the brain, which was initially found in unenhanced MRI scans in patients that had received GdCAs in the past.

In January 2016, in the framework of a PSUSA procedure, the PRAC reviewed all available literature and data related to the accumulation of gadolinium in the brain and recommended the removal of statements from the product information of all GdCAs that the products do not pass the intact blood brain barrier. The MAHs were also requested to update the safety specifications in the Risk Management Plans for these products to reflect these findings. However, the PRAC considered that the knowledge about brain accumulation and its clinical consequences needed to be further investigated in the appropriate framework, requiring therefore a review at EU level.

On 9 March 2016, the European Commission triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of gadolinium containing medicinal products and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

## 2. Scientific discussion

### 2.1. Introduction

Gadolinium-containing contrast agents (GdCAs) consist of a gadolinium ion that is bound to a carrier molecule (a chelator or chelating agent). Interactions between the gadolinium ion and water molecules alter the relaxation time of protons in the water molecules within a magnetic field, which increases the signal intensity on T1-weighted magnetic resonance (MR) imaging. GdCAs are used to provide image enhancement of magnetic resonance imaging (MRI), magnetic resonance angiography (MRA) and MR arthrography.

The eight GdCAs authorised in the EU have different carrier molecules with different physicochemical properties. The GdCAs may be categorised by their structure: whether they are linear or macrocyclic, and whether the molecule is ionic or non-ionic. The carrier molecules of the authorised GdCAs include examples of all combinations of these two properties. The GdCAs are generally injected into a vein and are cleared from the body by the kidneys.

Most products are indicated for whole body MRI or have specific organs or areas of the body indications for enhancement of MRI. There are two GdCAs that undergo hepatic uptake, and can therefore provide delayed-phase enhancement of hepatic MRI; these are Primovist (gadoteric acid) and Multihance (gadobenic acid). Primovist only has a liver imaging indication. Multihance has also other indications. Two GdCAs products, gadopentetic acid (Magnevist 2mmol/l) and gadoteric acid (Artirem), are authorised at lower doses for intra-articular administration for magnetic resonance arthrography.

Generics of some of the GdCAs products are authorised in some EU Members States.

The following table provides an overview of the EU authorised Gd containing agents and their classification into linear and ionic/non-ionic:

<b>INN</b>	<b>Structure and ionicity</b>
Gadodiamide	Linear Non-Ionic
Gadoversetamide	Linear Non-Ionic
Gadopentetic acid	Linear Ionic
Gadobenic acid	Linear Ionic
Gadoxetic acid	Linear Ionic
Gadoteridol	Macrocyclic Non-Ionic
Gadobutrol	Macrocyclic Non-Ionic
Gadoteric acid	Macrocyclic Ionic

An overview of the relevant information for the discussion is presented hereinafter, including non-clinical and clinical data submitted by marketing authorisation holders (MAHs) and the results of consultations with experts and the Pharmacovigilance Risk Assessment Committee (PRAC).

## **2.2. Non-clinical aspects**

### **2.2.1. Non-chelated gadolinium toxicity**

Early studies investigating the toxicity of gadolinium (Gd) showed that when injected directly into the CNS, gadolinium contrast agents have a neurotoxic potential (Ray et al. 1996 and 1998) with dose dependent morphologic and behavioural changes. (Ray et al. 1998) showed that gadodiamide introduced into the lateral ventricle of rats at high doses produced predominately acute cerebellar changes.

Gadolinium has also been shown to be toxic in non-clinical studies, with effect including cellular necrosis, fibrosis, and lesions related to mineral deposition (Spencer et al. 1997; Rees et al. 1997), and an in vitro study in rat neurons, gadolinium-induced cytotoxicity via oxidative injury was reported (Xia et al. 2011).

### **2.2.2. Deposition in the brain**

When more recent findings came to light that GdCAs could cause NSF, MAHs and other academic groups initiated further toxicology studies of GdCAs in non-clinical models such as the rat and mouse species in order to try to better characterise the general safety risks. Recently published non-clinical studies in rats following repeated exposure with GdCAs have demonstrated persistent T1-weighted signal hyperintensity in MRI scans and gadolinium presence in the brain (Robert et al. 2015; Robert et al. 2016; Jost et al. 2016a; Lohrke et al. 2015 & 2016). In addition, data from ongoing non-clinical studies extending these published findings have been provided by the MAHs during the procedure on:

- the pathway(s) by which Gd enters the brain;
- the extent, location and time course of Gd deposition in the brain;
- the molecular form(s) of Gd present in the brain;
- the potential for GdCA deposition resulting in neurological or histopathological changes after repeated administrations of linear and macrocyclic contrast agents.

To date the non-clinical studies have overall demonstrated several observations, as discussed below.

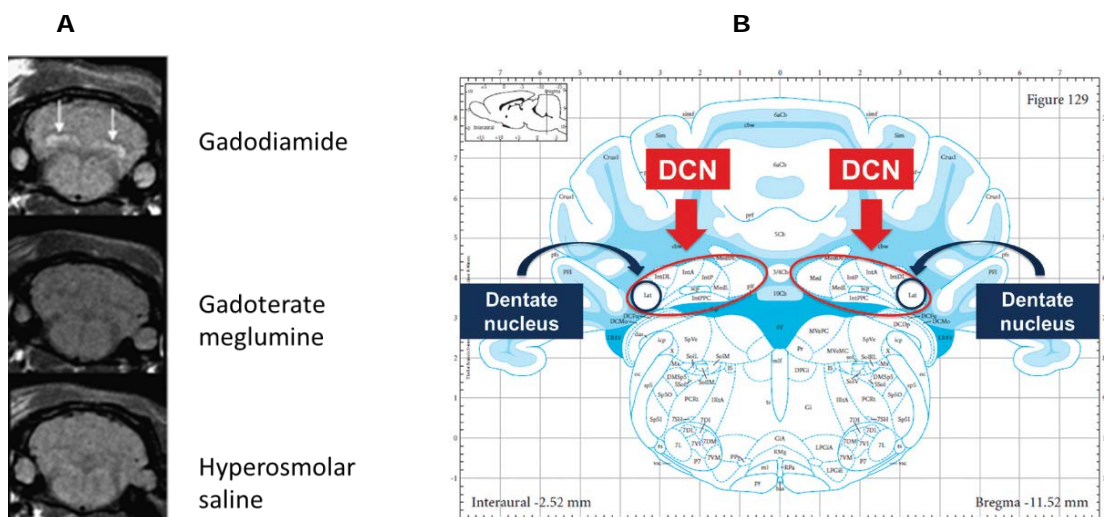
#### **2.2.2.1. Entry of GdCAs to the brain**

A possible route of entry for GdCAs into brain tissue is via the CSF (Jost et al. 2015). Jost et al. 2016 demonstrated that all GdCAs tested may circumvent the blood brain barrier (BBB) and enter the brain as parent compound. Appearance in the CSF occurs at an early time point (within 10 minutes) and there is clearance from the CSF 4 hours later.

In an unpublished study by the MAH Guerbet, that was made available during the procedure, repetitive administration of gadodiamide in rats with renal failure was associated with an increase of a T1 hypersignal in the choroid plexus of the 4th ventricle at 6 weeks consistent with the hypothesis of entry of GdCAs via the blood/CSF barrier in the choroid plexus.

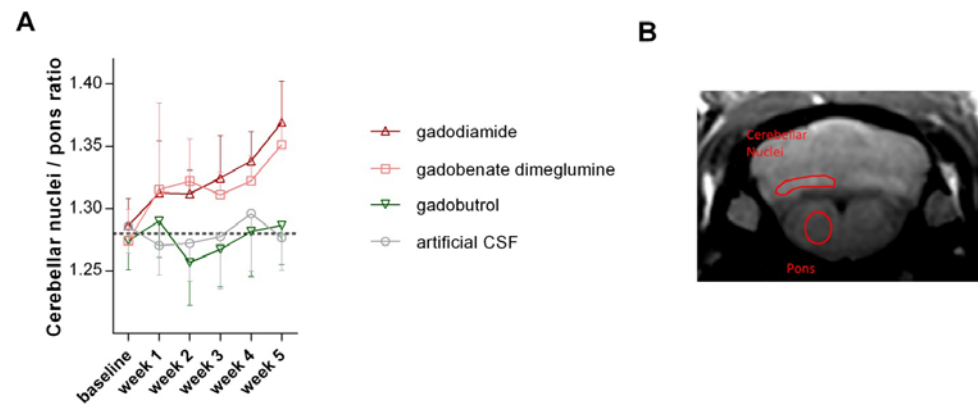
#### **2.2.2.2. Deposition of gadolinium in the brain – MRI and biochemical data**

Significant and persistent T1 signal hyperintensity (SI) in deep cerebellar nuclei (DCN) which includes the dentate nucleus, is observed after repetitive high dose administrations of linear GdCAs (gadodiamide, gadopentetic acid, gadobenic acid). Such finding was not shown for the macrocyclic agents (gadoteridol, gadobutrol and gadoteric acid) (Robert et al. 2015) (see Figure 1).



**Figure 1:** A) Example of T1w MRI at week 10 (completion of the 5 week treatment-free period). B) Anatomy of rat brain: localization of the deep cerebellar nuclei (DCN) and dentate nucleus (Reproduced and adapted from Robert et al. 2015)

Administration of the linear GdCAs gadodiamide and gadobenic acid directly into the CSF resulted in increased signal intensity in the DCN in rats up to 5 weeks after administration. Such finding was not shown for the macrocyclic agent gadobutrol (MAH Bayer report, see Figure 2).

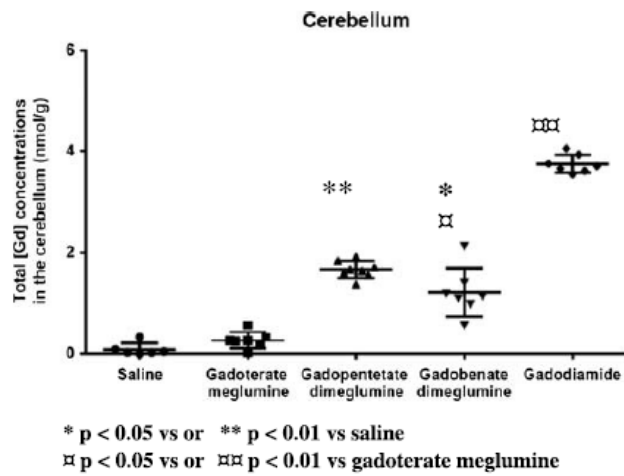


**Figure 2:** Signal intensity after direct injection into the CSF (A) Time course of SI ratio between cerebellar nuclei and pons after application of Omniscan (gadodiamide), Multihance (gadobenate dimeglumine), Gadovist (gadobutrol) and artificial CSF. (B) Representative image 5 weeks after application of gadodiamide with exemplary region of Neurological effects of gadolinium in the brain

Rapid T1 hyperintensity between DCN and the surrounding cerebellum was observed after gadodiamide (Omniscan) administration. Enhancement after gadobenate dimeglumine (Multihance) or gadopentetate dimeglumine (Magnevist) appeared more progressively during the 10 weeks of imaging compared with gadodiamide (Omniscan). No such enhancement was observed with gadoteric acid (Dotarem) or saline, which remained at baseline levels.

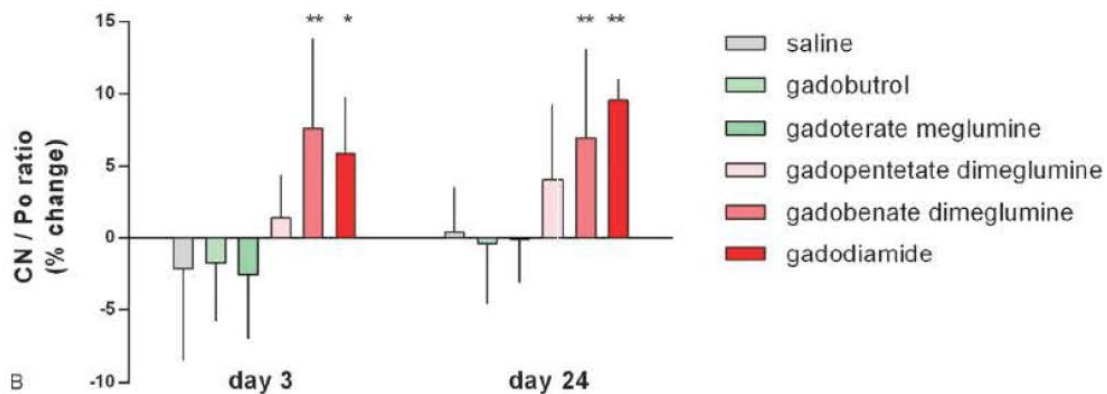
Robert et al. 2016 showed that Gd presence in brain measured by inductively coupled plasma mass spectrometry (ICP-MS) is detected in all brain tissue, not just the DCN, with all GdCAs tested. While the presence of Gd was observed with gadoteric acid, no statistically significant difference could be

found in the concentration of Gd in the cerebellum compared with saline (see Figure 3 below). In contrast to the gadoteric acid finding, the presence of Gd was detected with gadodiamide, gadobenamic acid and gadopentetic acid.



**Figure 3:** Total gadolinium concentration in nanomole Gd per gram of tissue for cerebellum and nmol/mL of plasma. Individual values, mean, and SD are given (reproduced directly from Robert et al. 2016)

In a further study by Jost et al. (2015) increased SI in the deep cerebellar nuclei was found up to 24 days after multiple, extended doses of linear GdCAs, confirming the clinical experience and previous rat studies (Robert et al. 2015; Robert et al. 2016). The signal enhancement in the globus pallidus (GP) could not be seen in rats (Figure 4).



**Figure 4:** Percent change of CN/Po for day 3 and day 24 p.i. compared with baseline after injection of saline, gadobutrol, gadoterate meglumine, gadopentetate dimeglumine, gadobenate dimeglumine, and gadodiamide \*P < 0.05 and \*\*P < 0.01 indicate significance of GdCA group compared with saline (reproduced directly from Jost et al. 2016)

A potential effect on metabolism in the brain in regions of Gd deposition has been detected with a significant increase of the creatine/phosphocreatine in the Guerbet study ER-15-00019. No significant modification is observed for the others metabolites.



### 2.2.2.3. Dose-accumulation and persistence of gadolinium in the brain and other tissues

Studies have shown that there is a dose-dependent level of Gd in the brain for linear agents and this is likely to be related to cumulative dose (Robert et al. 2016) rather than single large or repeat small dose regimens.

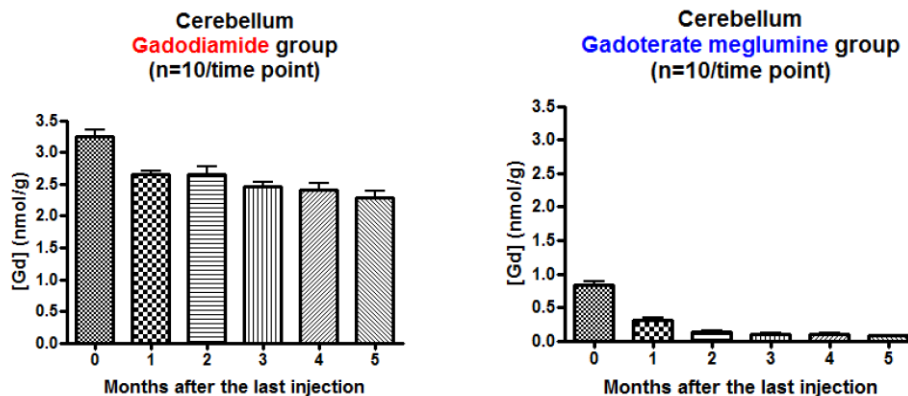
Dose-dependent low levels of Gd were detected in the brain.  $2.49 \pm 0.29$  nmol/g or 0.00023% of the injected dose (% ID) at 1 week post-dosing with gadodiamide. At week 50, the Gd levels were  $1.56 \pm 0.29$  nmol/g and demonstrated no reduction from the 20 week time point ( $1.38$  nmol/g  $\pm 0.10$ ) (Study B041015; Smith et al. 2016).

Rasschaert et al. (2016) reported levels of retained Gd of 12.3 nmol/g in pooled DCN, after a cumulative dose of 20 times the human dose of gadodiamide, when adjusted for body surface area. A recent study (MacDonald et al 2017 in press) also reports a Gd level of around 44nmol/g, in the dentate nucleus after 7 days wash-out following a cumulative dose of 80x the human dose of gadodiamide when adjusted for body surface area.

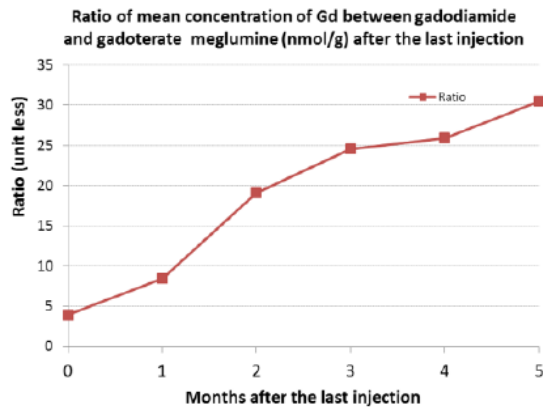
Fretellier et al. (2011) reported skin Gd concentrations of  $490.5 \pm 223.2$  nmol/g following 5 daily injections of 2.5 mmol/kg of gadodiamide. The highest Gd levels found in the brain of rats exposed to 20 doses of 0.6 mmol/kg of gadodiamide was  $3.75 \pm 0.18$  nmol/g (cerebellum – Robert et al. 2016).

A biodistribution study (Study FRCG-03-1530) from the MAH Bracco indicated that the brain tissue Gd concentrations for gadoteridol were similar to the previously published studies for the two macrocyclic GdCAs, gadobutrol, and gadoteric acid.

Gd levels in the brain following the administration of macrocyclic agents are consistently several fold lower than for linear agents. At 5 months, Gd levels are over 30 fold higher in the brain following gadodiamide administration; compared to gadoteric acid a macrocyclic agent, based on a study presented by the MAH Guerbet:

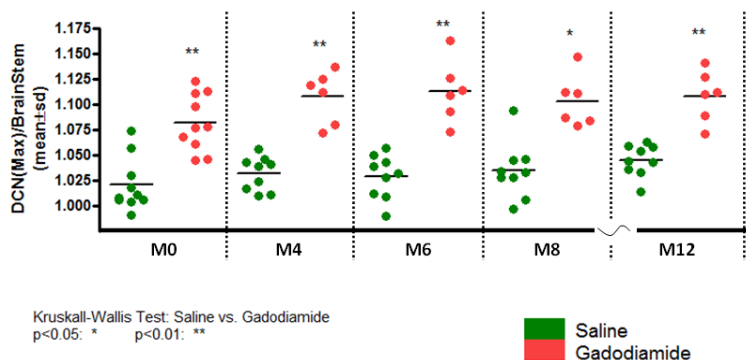


**Figure 5:** Time courses of the Gd concentrations in rat cerebella after repeated intravenous injections of either Omniscan (gadodiamide) or Dotarem (gadoterate meglumine).



**Figure 6: Time course of the Gd concentration ratio over time in the cerebellum following repeated administration of Omniscan and Dotarem**

For the linear agents evaluated (gadodiamide, gadopentetic acid, and gadobenic acid) the T1 signal intensity in the DCN has been shown to persist for at least 1 year without any reduction in intensity. A study presented by the MAH Guerbet (ER-15-00019) showed a persistent T1 signal enhancement of the DCN in healthy rats, lasting at least 1 year following the last injection of gadodiamide (Figure 7).



**Figure 7: 12-month follow-up of DCN/brain stem signal ratio after repeated administration of Omniscan (gadodiamide)**

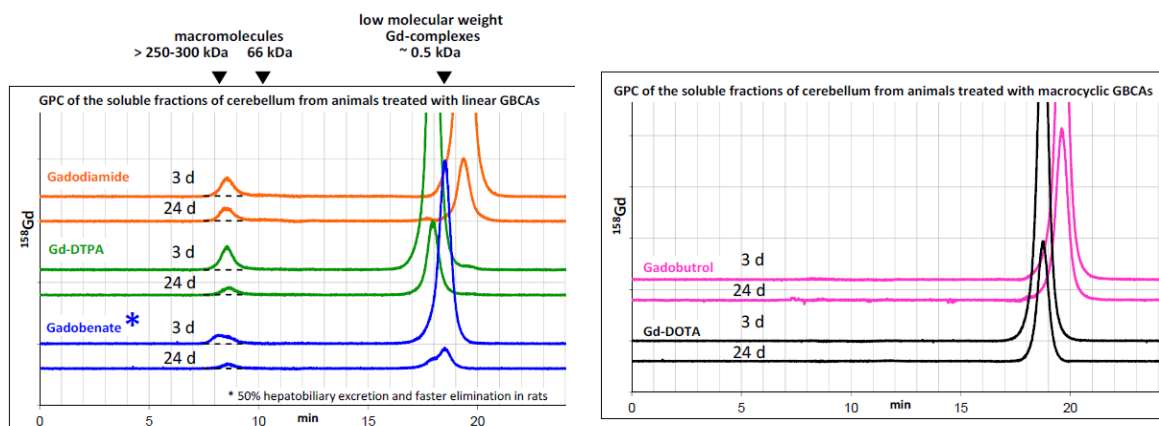
Also, a study presented by the MAH Bayer reported increased signal intensity in the DCN of rats persisted for up to 1 year after multiple administrations of the linear GdCAs gadobenic acid and gadopentetic acid. The ICP-MS Gd measurements revealed no clearance over time between 5 weeks and one year after the last administration, suggesting a long term persistence and retention for the linear GdCAs without clearance over the time. In the group treated with the macrocyclic GdCA gadobutrol, there was low Gd concentration in the cerebellum and the concentration of Gd decreased considerably between 5 weeks and 26 weeks and then further slightly between 26 and 52 weeks. This indicates a slow but progressive elimination process for the macrocyclic Gadovist (gadobutrol).

#### 2.2.2.4. Molecular form of Gd in the brain

Initial findings suggest the residual Gd found in the rat brain after repeated administration of linear GdCAs is present in at least 3 distinctive forms — in a solubilised fraction which may contain the presumably intact GdCA, as soluble macromolecules complexes and present in an insoluble fraction

(Frenzel et al 2017). The study found that brain soluble fractions from animals receiving linear agents contained a proportion of Gd bound to macromolecules while for macrocyclic agents these molecules are not detected, as shown in Figure 8 below. The following additional observations were made in this study:

- In view of total brain gadolinium concentrations a clear decrease in the tissue concentrations between day 3 and day 24 p.i. was observed for all GdCAs for the macrocyclic agents (–62% to –72%) , for the linear agents (–23% to –47%).
- The soluble fractions from animals receiving macrocyclic GdCAs contained only small Gd-containing molecules, which the authors considered to be most probably the intact GdCA.
- The Gd concentration of the soluble fractions from all agents (linear and macrocyclic agents) showed a clear washout between days 3 and 24 post administration indicating that the elimination from brain was still ongoing, but occurred at a much slower rate than from other tissues. The washout of the soluble fraction from day 3 to day 24 was in the range from –60% to –73%, which was similar for all investigated GBCAs and for the 3 brain sections.
- The Gd concentrations in the insoluble fractions of the cerebellum were considerably low for the macrocyclic GdCAs (0.3–0.5 nmol Gd/g tissue), for linear GdCAs (2.5 to 4.4 nmol Gd/g tissue).
- Minimal change was observed in the Gd concentrations in the insoluble fraction between day 3 and 24 post administration for all substances tested. The nature of the insoluble forms has not been determined.
- The GPC separation did not allow identification of the chemical nature of the macromolecule and whether it had bound the intact GdCA or the transmetallated Gd<sup>3+</sup> ion. The authors considered that it is very unlikely that the intact GdCA were bound to a macromolecule as their binding to plasma proteins is very low or negligible.
- In addition, the authors spiked brain homogenate with each of the GdCAs tested. In these samples, with the exception of gadodiamide, all linear and macrocyclic GdCAs could be fully recovered.



**Figure 8: Examples of Gd-specific GPC chromatograms of cerebellum homogenates from animals 3 and 24 days after injection with (A) linear GdCAs Omniscan, Magnevist and Multihance and (B) macrocyclic GdCAs Dotarem and Gadovist. The chromatograms show the intensity \* Smaller peak area likely due to faster elimination of Multihance because of relevant hepatobiliary excretion which is about 50% in rats but only 3-5% in humans**

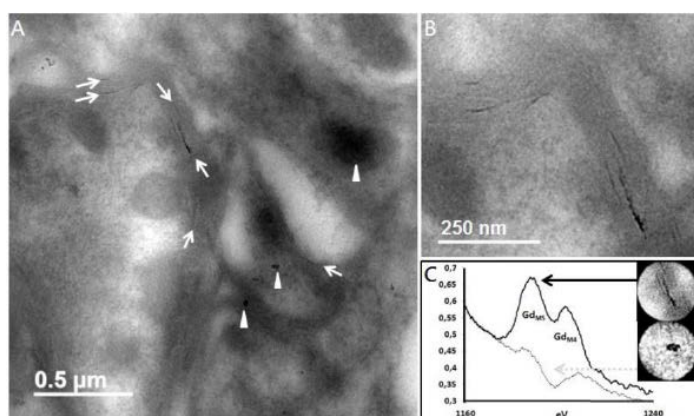
A previous *in vitro* study (Frenzel et al. 2008) showed that when GdCAs are incubated in human serum, the rates of gadolinium release seen were much lower for macrocyclic GdCAs than for linear GdCAs.

Gd levels found in the brain of the treated animals were found to be in much lower concentrations compared to levels found in other organs, such as skin (Lohrke (2015 & 2016)). In these studies, laser ablation coupled with ICP-MS was used to visualize the tissue distribution pattern of gadolinium. Measurements made in the brain revealed a local presence of Gd in the DCN (including the lateral cerebellar nucleus which is equivalent to the dentate nucleus in humans) only for gadopentetate dimeglumine but not for gadobutrol. These studies also indicated that the Gd concentrations in the skin correlated with concentrations found in the brain but concentrations in the skin were found to be higher.

#### **2.2.2.5. Neurological or histopathological findings after repeated administrations of linear and macrocyclic contrast agents**

Thus far, no studies have reported any clinical signs of neurotoxicity associated with retained Gd up to 50 weeks post-dosing. Furthermore, no histopathology findings have been reported with Gd levels up to approximately 4-13 nmol/g brain tissue (Smith et al. 2017). In another study, histopathological sections were made from the brain tissue of treated animals and stained with haematoxylin and eosin to visualise the tissue architecture (Lohrke 2016). There were no morphological changes in the brain detected by light microscopy examination in animals treated with any of the GdCAs. In 4 gadodiamide treated animals, macroscopic and microscopic pathologies were observed in the skin and reported to be similar in many aspects to lesions of human nephrogenic systemic fibrosis (NSF).

A study from the MAH Guerbet (ER-15-00002), using gadodiamide in rats found singular Gd deposits in gadodiamide-treated rats while no Gd deposits were found in one saline-treated rat. These filamentous gadolinium deposits were superimposed to neuropile regions: either in the cytosol or superimposed to cell membranes (Figure 9).



**Figure 9: Transmission electron microscopy of deep cerebellar nuclei in a gadodiamide-treated rat, and EELS spectrum. Presence of filamentous electron-dense Gd deposits interest in one hemisphere**

In two separate juvenile toxicity studies submitted by the MAHs with gadopentetic acid (Bayer study PH-36510) and gadobenic acid (Bracco study AB21194), results showed that brain Gd level were consistent those in previously reported repeat dose studies in adult rats. Treatment did not appear to induce any behavioural or neurological effects or any histological lesions in the brain in these studies.

### 2.2.3. Impact of renal impairment on brain accumulation

Renal impairment is known to increase the long term accumulation of Gd in rats in line with the propensity of GdCAs to release Gd in vivo (Pietsch 2009). Repetitive administration of gadodiamide in rats with renal failure was associated with an increase in the T1 hypersignal in the DCN relative to controls with normal renal function (Rasschaert et al. 2016). A study by Guerbet (ER-15-00020) supported this finding and found that renal failure increased the concentration of circulating free gadolinium (dissociated form from the carrier).

Kartamihardja et al. 2016 recently published a study evaluating the impact of impaired renal function on Gd deposition in various organs of mice after repeated intravenous administrations. They found that although renal impairment increased short-term Gd retention after gadodiamide administration, long-term Gd retention for Gd-based contrast agents was almost unaffected by renal function, suggesting that the chemical structures of retained Gd may not be consistent and some Gd is slowly eliminated after initially being retained.

### 2.2.4. Discussion on non-clinical data

The initial studies reported by Robert et al. (2015), Robert et al. (2016) and Jost et al. (2016a) have provided a model that replicates the Gd brain accumulation and cerebellum T1 signal intensity. Significant and persistent T1 signal hyperintensity in DCN is observed after repetitive high dose administrations of linear GdCAs (gadodiamide, gadopentetic acid, gadobenic acid); such was not observed with macrocyclic agents (gadobutrol, gadoteric acid). Recent data provided by the MAHs has evaluated the long term persistence of the T1 signal intensity and shown that for the linear GdCAs gadodiamide, gadopentetic acid, gadobenic acid the hyperintensity signal in the DCN persists for up to a year in rats without any significant decreases (MAHs Bayer and Guerbet). Gadolinium is distributed throughout the brain but higher concentrations have been detected in the regions associated with increased SI such as the DCN. The levels of Gd in the brain appear to be dose-dependent for linear agents and this is likely to be related to cumulative dose (Robert et al. 2016). The Gd concentration for two macrocyclic GdCAs (gadobutrol) and (gadoteric acid) does not show any dose clear dependent increase.

The data for Gd retention in tissues such as skin, bone and brain are consistent with the proven relative kinetic stability of macrocyclic agents. There is a correlation between the increased Gd levels in the brain after 4-5 weeks of wash-out and the stability of linear agents. Kinetic stability appears to correlate with lower brain retention for the macrocyclic agents. This data highlights the importance of the greater kinetic stability of macrocyclic agents which prevents their dissociation in vivo.

Recent studies have provided important insights into the molecular form of Gd present in the brain and highlights a clear difference in the fate of Gd in the brain following administration of either linear or macrocyclic agents with 3 separate and distinctive forms (Frenzel et al 2107). The soluble fractions from linear agents contained a proportion of Gd bound to macromolecules; the soluble fractions from animals receiving macrocyclic GdCAs contained only small Gd-containing molecules, most probably the intact GdCA. The Gd concentrations in the insoluble fractions of the cerebellum were 5-15 fold lower for the macrocyclic GdCAs than for linear GdCAs. The Gd concentration of the soluble fractions from all agents showed a clear washout between days 3 and 24 post administration indicating that the elimination from brain occurred at a much slower rate than from other tissues. Minimal Gd elimination was observed in the insoluble fraction between day 3 and 24 post administration. Therefore, there is a correlation between clearance from this insoluble fraction and the persistence of SI in the brain for up to one year following the administration of linear agents. The nature of the insoluble forms has not been determined. It is thought that the precise molecular forms of the Gd in the soluble

macromolecular complexes are not known but the most plausible explanation based on the results of the studies is that the macromolecules are bound to a dechelated Gd<sup>3+</sup> ion. Gadolinium bound to macromolecules is expected to have a higher relaxivity and would be capable of generating a T1-weighted signal at low concentration.

Renal impairment is known to increase the long term retention of Gd in rats in line with the propensity of GdCAs to release Gd in vivo (Pietsch 2009). Renal failure in rats potentiated the gadodiamide-induced increase in the T1 hypersignal. It also increased the concentration of circulating gadolinium, which was almost completely in the dissociated form. It is acknowledged that to date no adverse consequences of Gd accumulation in the brain in the non-clinical studies following intravenous dosing have been reported. Although the cumulative doses in non-clinical studies represent up to 80 times a single clinical i.v. GdCA dose, they have not achieved retained Gd concentrations higher than those observed in clinical samples. Thus the retained Gd brain levels detected in the non-clinical studies are in the same range and in some cases lower than those obtained in post-mortem human brain and do not provide a margin of safety. There have been no studies that have reported any clinical signs of neurotoxicity at either 1 week post-dosing or at 20 weeks post-dosing. Gadolinium levels found in the brain of the treated animals are lower than compared to levels found in other organs, such as skin. However, it is important to recognise that using healthy animals does not represent the variability of pathologies such as Multiple Sclerosis and tumours that may be found in humans. There is concern that Gd retention in the brain may, for example, exacerbate chronic diseases such as Multiple Sclerosis or diseases normally associated with aging, such as dementia or Parkinson's disease.

There is evidence from electron microscopy (EM) studies that Gd deposits are found predominately in the capillary walls in the dentate nucleus but no histological changes have been reported. In studies where histopathology has been performed, no findings of note have been reported associated with brain Gd levels of 13.1 nmol/g at 8 weeks (Lohrke et al. 2015) and 1.56 nmol/g at 50 weeks (Smith et al. 2016; MAH GE update). Of note, in studies where Gd was injected directly into the brain, dose dependent morphologic and behavioural changes were observed. However, the doses used in these studies were considered high and not relevant the normal clinical use of GdCAs. Given the probable lifetime persistence of a fraction of Gd in the brain, the potential for effects emerging after longer term Gd brain retention have not been adequately addressed as effects such as inflammation, degeneration or proliferation may take time to develop.

### **2.2.5. Non-clinical conclusions**

In summary, Gd presence in brain regions was observed with all GdCA tested with a 4 to 14 fold increase in levels for linear agents (Robert et al. 2016; MAH unpublished studies). Data on stability, as well as in vitro and non-clinical studies, strongly suggest that linear gadolinium-containing contrast agents (GdCAs) release gadolinium from the ligand molecules. Based on non-clinical data, both linear and macrocyclic agents have the ability to distribute to the brain. Linear agents are retained and persist for up to one year or longer. Macrocyclic agents show only a transient increase in Gd in the brain and undergo early washout.

Gadolinium has been measured in the brain, both indirectly by studies showing signal intensity increases, and directly by studies measuring gadolinium concentrations with mass spectrometry, including methods that allow localisation in the brain (LA-ICP-MS) and separation of Gd species (GPC-MS). Gd levels found in the brain of the treated animals are low, and much lower compared to levels in other organs, such as skin, observed in previous animal studies.

No studies have reported any clinical signs of neurotoxicity associated with retained Gd up to 50 weeks post-dosing. No histopathology findings have been reported with Gd levels up to approximately 4

nmol/g brain tissue. Although no adverse neurological effects, such as cognitive or movement disorders, have yet been demonstrated to be caused by gadolinium accumulation in the brain, long-term safety data are limited.

### 2.3. Clinical Data on efficacy

GdCAs derive their ability to enhance MRI scan from the interaction between water molecules and the gadolinium ion bound to the chelating ligand. Relaxivity is a measure of the strength of the effect on the MRI signal. Specifically, relaxivity is a measure of how the relaxation rates of a solution change as a function of concentration. Higher relaxivity indicates higher contrast enhancing efficacy of the contrast agent. Table 1 below presents the  $r_1$ -relaxivity values at 1.5 tesla in plasma at 37°C. A field strength of 1.5 tesla is standard in current clinical practice. At higher field strengths, for example 3.0 tesla, the  $r_1$ -relaxivity of the GdCAs authorised in the EU are decreased (Thomsen HS. Contrast agents for Magnetic Resonance Imaging. In: Saba L (ed.) Image Principles, Neck and the Brain. Boca Raton; CRC Press, 2016:61-72 (chap 3)).

**Table 1: Relaxivity of GdCAs at 1.5 tesla (after Rohrer et al. 2005)**

	<b>Gd-chelate</b>	<b><math>r_1</math> (L·mmol<sup>-1</sup>·s<sup>-1</sup>)</b>
<b>Macrocyclic</b>	Gadovist	5.2
	Dotarem	3.6
	Prohance	4.1
<b>Linear</b>	MultiHance	6.3
	Primovist	6.9
	Vasovist	16
	Optimark	4.7
	Omniscan	4.3
	Magnevist	4.1

$r_1$  relaxivity in plasma at 37°C

Please note that Vasovist (gadofosveset) is no longer authorised in the EU

The MAHs provided information on the relaxivities of their product during the procedure as outlined in Table 2.

**Table 2: Relaxivity of the different products approved in the EU**

<b>Brand leader product name</b>	<b>INN</b>	<b>Structure and iconicity</b>	<b><math>r_1</math>-relaxivity at 1.5T (mM<sup>-1</sup>s<sup>-1</sup>)</b>
Omniscan	gadodiamide	Linear Non-Ionic	4.3 (4.0 – 4.6)
Optimark	gadoversetamide	Linear Non-Ionic	4.7 (4.4 – 5.0)
Magnevist	gadopentetic acid	Linear Ionic	4.1 (3.9 – 4.3)
Multihance	gadobenic acid	Linear Ionic	6.3 (6.0 – 6.6)
Primovist	gadoxetic acid	Linear Ionic	6.9 (6.5 – 7.3)
Prohance	gadoteridol	Macrocyclic Non-Ionic	4.1 (3.9 – 4.3)
Gadovist	gadobutrol	Macrocyclic Non-Ionic	5.2 (4.9 – 5.5)
Dotarem , Artirem	gadoteric acid	Macrocyclic Ionic	3.6 (3.4 – 3.8)



A description of the structure, therapeutic action, indications, and NSF risk categories for GdCAs authorised in the EU is shown in Table 3.

**Table 3: Active substance, pharmacotherapeutic action, approved indication(s) and NSF risk**

Brand leader product name (MAH)	Active substance	NSF risk category	Structure	Indications (brand leader)
Magnevist (Bayer)	gadopentetic acid	High	Linear ionic	Magnevist i.v.: Cranial and spinal MRI in adults and children Whole body MRI in adults and children  Magnevist 2 mmol/l (intra-articular presentation): MR arthrography in adults
Omniscan (GE Healthcare)	gadodiamide	High	Linear non-ionic	The approved indication/posology texts throughout EU constitute the following general areas and wording: 1. General MRI of the body 2. Cranial and spinal MRI 3. Cardiac MRI
Optimark (Mallinkrodt)	Gadoversetamide	High	Linear non-ionic	Optimark is indicated for use with magnetic resonance imaging (MRI) of the central nervous system (CNS) and liver (use in dynamic phase imaging). It provides contrast enhancement and facilitates visualization and helps with the characterization of focal lesions and abnormal structures in the CNS and liver (dynamic phase) in adult patients and in children of two years and older with known or highly suspected pathology.
Multihance (Bracco)	gadobenic acid	Medium	Linear ionic	Multihance is a paramagnetic contrast agent for use in diagnostic magnetic resonance imaging (MRI) indicated for: - MRI of the liver (use in dynamic and delayed phase imaging) - MRI of the brain and spine - MRI of the whole body (all organs and systems) - Cardiac MRI (including myocardial perfusion) - Contrast-enhanced MR-angiography (all arterial territories, supra-aortic and coronary arteries included) - MRI of the breast.



Brand leader product name (MAH)	Active substance	NSF risk category	Structure	Indications (brand leader)
Primovist (Bayer)	gadoxetic acid	Medium	Linear ionic	Liver MRI (use in dynamic and delayed phase imaging)
Dotarem, Artirem (Guerbet)	gadoteric acid	Low	Macrocyclic ionic	Dotarem: Central Nervous System (CNS), Contrast-enhanced magnetic resonance angiography (CE-MRA), CE-MRI of the whole body, CE-MRI in children (from neonates to 17 years of age). Artirem: MR Arthrography in adults
Gadovist (Bayer)	gadobutrol	Low	Macrocyclic non-ionic	general indications in adults and children): Contrast-enhanced MRI: - Cranial and spinal - Head and neck, Whole body, Breast, Abdomen (pancreas, liver (use in dynamic phase imaging) and spleen), Pelvis (prostate, bladder and uterus) - Kidney, Musculoskeletal system MR - Angiography Cardiac MRI
Prohance (Bracco)	gadoteridol	Low	Macrocyclic non-ionic	Using Magnetic Resonance Imaging (MRI), ProHance provides contrast enhancement of the brain, spine and surrounding tissues resulting in improved visualization (compared with unenhanced MRI) of lesions with abnormal vascularity or those thought to cause a disruption of the normal blood-brain barrier. ProHance can also be used for whole body MRI including the head, neck, liver (use in dynamic phase imaging), breast, musculoskeletal system and soft tissue pathologies.

Estimated exposure data by active substance for the year 2015 as total numbers of patients exposed in the EU, and, if marketed, in Japan and US is presented in Table 4.

**Table 4: Estimated numbers of patients exposed\* to GdCAs in 2015 (EU, Japan, and USA, based on data provided for the brand leader products and two of the generic MAHs)**

GdCA	Structure and Ionicity	Estimated exposure in the EU 2015	Estimated exposure in Japan 2015	Estimated exposure in the USA 2015
gadodiamide	Linear Non-Ionic	554,292	212,138	867,780
gadoversetamide	Linear Non-Ionic	24,542	-	663,865
gadopentetic acid	Linear Ionic	635,284	459,569	1,560,190
gadobenic acid	Linear Ionic	952,610	-	2,282,040
gadoxetic acid	Linear Ionic	132,586	203,600	133,765
gadoteridol	Macrocyclic Non-Ionic	573,026	303,697	599,725
gadobutrol	Macrocyclic Non-Ionic	2,345,557	134,135	2,714,920
gadoteric acid	Macrocyclic Ionic	4,433,705	273,600	391,769

\*Exposure is calculated from sales data, on the assumption that one vial or pre-filled syringe equates to one patient exposed. The generic MAHs used a different assumption that each 15ml sold equates to one patient exposed because this is the standard dose for a 75kg patient. It also should be noted that there are 14 other MAHs with authorised generic GdCA products that have not provided response for the second round of this referral, and so the figures do not capture all usage in the EU during 2015.

Overall, considering the products for which data were provided, approximately 76% percent of the usage was macrocyclic agents and approximately 24% was linear agents.

For Gadodiamide (Omniscan), the MAH has claimed that their product has a unique indication in myocardial perfusion imaging.

For Gadobenic acid (Multihance), the MAH submitted a number of studies in support of their claim that the higher relaxivity of Multihance leads to significantly improved visualization of lesions. The blinded design and intra-individual comparison of images were reported in well-designed studies. The endpoints used in these studies evaluated technical performance such as lesion contrast enhancement compared with surrounding tissues, degree of delineation of lesion borders, degree of definition of extent of disease, and degree of visualisation of lesion internal morphology as well diagnostic performance.

These studies include ones with a prospective, randomised, double-blind design, where blinded readers compared images obtained with gadobenic acid (Multihance) with images from the same patients obtained with other GdCAs. Studies with this type of design have been conducted in indications of CNS imaging (Maravilla et al. 2006; Rowley et al. 2008; Seidl et al. 2012; Vaneckova et al. 2015), breast MRI (Pediconi et al. 2008; Martincich et al. 2011 Gilbert et al. 2014; Pediconi et al. 2013) and magnetic resonance angiography (Gerretsen et al. 2010; Li et al. 2013; Wang et al. 2013). The CNS imaging studies reported preference of blinded readers for images obtained with Multihance, based on diagnostic information endpoints, percentage of lesion enhancement, and contrast-to-noise ratio. The breast imaging studies reported higher rates of lesion detection with Multihance in two studies, higher sensitivity, accuracy, positive predictive value, and negative predictive value for Multihance in one study, and non-inferiority of Gadovist (gadobutrol) to Multihance in one study.

For gadobutrol (Gadovist), the MAH Bayer, presented a list of 11 studies which compared Gadovist with Multihance (gadobenic acid), in a range of indications including CNS imaging, magnetic resonance angiography, breast imaging, and whole body imaging (Herborn et al. 2003; Thilman et al. 2005; Essig et al. 2006; Attenberger et al. 2008; Achenbach et al. 2010; Pediconni et al. 2012; Seidl et al. 2012; Kramer et al. 2013; Kim et al. 2013; Semelka et al. 2013; Wildgruber et al. 2014).

### ***Liver-specific imaging***

The arterial phase relies on the hepatic portal vein and hepatic arteries bringing blood carrying intravenously administered GdCAs to the liver. This phase of enhancement occurs rapidly following injection of a GdCA. Because the GdCA reaches the liver through the circulation this phase of enhancement is most useful for imaging of highly vascular features, such as hepatic carcinomas. All the authorised GdCAs can provide enhancement of liver imaging in the dynamic phase.

The delayed or hepatic phase relies on selective uptake of a GdCA by functioning hepatocytes. This phase allows hypovascular lesions that do not take up the GdCA to be distinguished from the normal liver parenchyma which is enhanced by this phase. The delayed or hepatic phase occurs following a delay after administering the GdCA, and the length of this delay varies between different GdCAs. Delayed phase imaging has particular clinical utility for the imaging of hypovascular tumours, such as metastases from colorectal cancer, as well as for other aspects of liver imaging such as differentiating between focal nodular hyperplasia and hepatocellular carcinoma.

Acquisition of arterial phase and hepatic phase images of the liver provide different contrast between normal tissue and lesions. The difference is created at different time points because of the GdCA reaching the liver by the circulation or by hepatocyte uptake. Images from these time points can be combined in dynamic contrast-enhanced MRI of the liver. This requires use of a GdCA with hepatic uptake. Dynamic liver imaging of this type can provide greater diagnostic accuracy than other MRI techniques for liver imaging, and is a vital method for investigation of liver pathology (Maniam S and Szklaruk 2010).

Two GdCAs, gadoxetic acid (Primovist) and gadobenic acid (Multihance) undergo hepatic uptake, and can provide delayed phase enhancement of MRI for the liver. For Primovist the extent of this hepatic uptake is approximately 50%. The SmPC states that delayed phase imaging can be performed at 20 minutes post injection with an imaging window lasting at least 120 minutes. The authorised dose for liver imaging is 0.025 mmol/kg.

For gadobenic acid (Multihance), the extent is between 3% and 5% (Spinazzi et al. 1999). The SmPC states that delayed phase imaging can be performed between 40 and 120 minutes following the injection. The authorised dose for liver imaging is 0.05 mmol/kg.

The studies that have been referenced by the MAHs include a small study (n=18) in which both arterial phase and delayed phase (hepatic) MRI images were obtained for patient suspected of having hepatocellular carcinoma (Park et al. 2010). Also submitted was information on a retrospective study in preoperative MRI of living liver donors (n=62) (Lee et al. 2011). These studies did not report significant differences between the two GdCAs.

Some retrospective studies have investigated respiratory motion artefacts with gadoxetic acid (Primovist) and gadobenic acid (Multihance) affecting the dynamic (arterial) phase of liver imaging, and found that:

- dynamic imaging with Primovist may be affected by short-term dyspnea of unknown origin that may cause respiratory motion artefacts and image degradation, especially during the arterial phase of imaging (McClellan et al. 2016).
- crossover comparison studies showed that severe respiratory motion artifacts are common and affect dynamic imaging with Primovist but not with Multihance (Furlan et al. 2016; Motosugi et al. 2016; Davenport et al. 2014).
- transient dyspnea and respiratory motion artifacts observed with Primovist are dose-related and occur significantly more often in patients with chronic obstructive pulmonary disease and in patients with a similar prior episode associated with the agent (Davenport et al. 2014; Bashir et al. 2015).

Two recent prospective studies (McClellan et al. 2016; Shah et al. 2017) reported higher rates of respiratory motion artefacts with Primovist (gadoxetic acid) than with other GdCAs. In particular, the study by McClellan et al. was a double-blinded placebo-controlled trial conducted in healthy volunteers (n=44) who all received Primovist (gadoxetic acid), Dotarem (gadoteric acid), and saline placebo. This study supported the findings of the previous retrospective studies, as it reported that the duration of breath hold was significantly shorter with Primovist than with Dotarem or saline. The study reported more respiratory motion artefacts with Primovist (7%, 3/44) than Dotarem (2%, 1/44) or saline (none), although this result did not reach statistical significance.

### 2.3.1. Discussion on efficacy

PRAC considered the data available related to the efficacy of the technical and diagnostic performance of GdCA and the clinical utility of the use of these products in the different MRI indications, and concluded that GdCAs are effective to enhance MRI images of a range of body parts and tissues. This is supported by the studies of GdCA-enhanced MRI

Although there is a relationship between relaxivity and image quality, differences in relaxivity and resultant image quality have not clearly established a difference in diagnostic performance and an impact on the diagnostic thinking and patient management.

The PRAC accepted that higher relaxivity results in a brighter signal, but a conclusion that this translates into significant and clinically relevant differences in diagnostic performance needs to be supported by robust evidence from clinical studies.

Gadodiamide is indicated for general MRI of the body, and its indication statement specifically mentions cranial and spinal MRI and evaluation of coronary artery disease by myocardial perfusion imaging. The PRAC considered that the whole body MRI encompasses imaging of the heart, including myocardial perfusion imaging.

For the liver imaging, the delayed or hepatic phase occurs following a delay after administering the GdCA with hepatic uptake. Delayed phase imaging has particular clinical utility for the imaging of hypovascular tumours, such as metastases from colorectal cancer, as well as for other aspects of liver imaging such as differentiating between focal nodular hyperplasia and hepatocellular carcinoma.

Primovist (gadoxetic acid) has clinical utility in imaging of the liver, based on the very significant hepatic uptake, low dose (0.025 mmol/kg body weight) and relative ease of use in terms of time to delayed phase scanning (20 min).

Multihance (gadobenic acid) also has shown to have clinical utility in the liver and undergoes hepatic uptake but to a lesser extent, requires a high dose (0.05 mmol/kg body weight), and a long time to the onset of delayed phase imaging (40 mins).

The PRAC further considered that overall the rate of occurrence of respiratory motion artefacts in liver imaging studies does not appear to be a major factor in determining the utility of GdCAs for arterial phase liver imaging. No data have been presented to suggest that respiratory motion artefacts have a major impact on clinical utility in delayed imaging and such an effect seems unlikely given the wider time window that exists compared with arterial phase imaging.

It can be argued that since these are all measurements of how a GdCA has affected the image produced by an MRI scan these all potentially have an impact on patient-relevant outcomes such as the ability to make a diagnosis, and an impact on subsequent choice and timing of treatment and management of disease. However, the impact on diagnostic thinking and patient management is not directly captured by these. This is a limitation of all studies of this type, and one that has been acknowledged by the authors of published studies.

There is the possibility that studies using a blinded comparison of MRI images obtained with two GdCAs side by side might produce results favouring one of the GdCAs on the basis of brighter appearance of the images, but not reflecting any difference in the diagnostic information available or the impact on patient management. It should also be noted that in Seidl et al. the blinded readers' reasons for preferring gadobenic acid (Multihance) for the global diagnostic preference criterion were provided. The most common reason was "superior contrast enhancement" (in ~ 89% of cases). "Better delineation of at least 1 lesion" (~ 45% of cases) and "Better visualisation of internal lesion structure" (~ 26% of cases) were the next most common reasons. However reasons related to number of lesions detected and making a diagnosis were only infrequently given as the reason for preferring the images enhanced with gadobenic acid: "Detection of more lesions" (~ 4% of cases) and "Greater diagnostic confidence" (~ 5% of cases). This supports the conclusion that in studies where reader preference is reported from an intra-individual comparison the extent of contrast enhancement is a stronger driver for overall preference than reasons related to diagnosis. In addition, among the prospective, randomised, double-blind intra-individual comparison studies performed comparing Multihance with other GdCAs most compared Multihance with a GdCA with a relaxivity in the lower range for the class. In the four studies conducted in the CNS indication only Seidl et al. compared Multihance with a higher relaxivity comparator, the macrocyclic agent Gadovist (gadobutrol). This may have contributed to the reader preference for Multihance in these studies, driven by the strength of contrast enhancement.

### **2.3.2. Conclusion on efficacy**

There are no significant uncertainties about whether GdCAs effectively enhance magnetic resonance imaging. There are limitations to the interpretation of the data from studies comparing different GdCAs.

PRAC also considered that two linear agents (gadoxetic acid and gadobenic acid) with hepatic uptake have clinical utility for delayed phase liver imaging.

## **2.4. Data on clinical safety**

### **2.4.1.1. MRI studies**

Evidence that gadolinium can accumulate in brain tissue in humans comes from studies exploring changes in signal intensity in the brain after exposure to GdCAs. These studies have examined the relative strength of the signal from certain regions of the brain, particularly the dentate nucleus and globus pallidus, by defining signal ratios between the region of interest and another part of the brain.

Most of these studies were conducted in populations of patients who underwent repeated GdCA-enhanced MRI scans for investigation of brain malignancies. The studies by Tedeschi et al. and Stojanov et al. were conducted in patients with relapsing-remitting multiple sclerosis. The primary reasons for MRI with Primovist (gadoteric acid) in Kahn et al. were mainly hepatocellular carcinoma, neuroendocrine tumour, and colorectal cancer.

Since the first studies were published in 2014 and 2015 publication of further studies has continued up to the present, and throughout the period of this referral. Table 5 below summarises published studies that have assessed repeated exposure to GdCAs and signal intensity increases in the brain for each agent, according to the most recent search of the literature.

**Table 5: Published studies reporting signal intensity increases for each GdCA**

GdCA	Structure	Repeated exposure and signal intensity changes in the brain	
		Statistically significant association reported	No statistically significant association reported
gadopentetic acid (Magnevist)	Linear non-ionic	Adin et al. 2015, Kanda et al. 2015a, Radbruch et al. 2015a, Cao et al. 2016a, Hu et al. 2016, Radbruch et al. 2016a, Flood et al. 2016, Schlemm et al. 2016, Roberts et al. 2016b, Kuno et al. 2016	-
gadodiamide (Omniscan)	Linear ionic	Errante et al. 2014, Quattrocchi et al. 2015, Ramalho et al. 2015	-
gadoversetamide (Optimark)	Linear non-ionic	-	-
gadobenic acid (Multihance)	Linear ionic	Weberling et al. 2015, Ramalho et al. 2015†	Ramalho et al. 2016*
gadoteric acid (Dotarem)	Linear ionic	Kahn et al. 2016	Ichikawa et al. 2017
gadoterol (Gadovist)	Macrocylic non-ionic	-	Radbruch et al. 2015a, Radbruch et al. 2016a, Eisele et al. 2016
gadoteridol (Prohance)	Macrocylic ionic	Stojanov et al. 2015**	Radbruch et al. 2015b, Cao et al. 2016a, Radbruch et al. 2016a, Schlemm et al. 2016
		-	Kanda et al. 2015a

† Ramalho et al. 2015 reported no statistically significant increase in signal intensity ratio for DN-to-middle cerebellar peduncle ratio or GP-to-thalamus ratio, or statistically significant relative percentage change for GP-to-thalamus. There was a statistically significant increase in percentage change for DN-to-middle cerebellar peduncle ratio ( $p = 0.013$ )

\* Ramalho et al. 2016 reported a non-statistically significantly increase in relative change in signal intensity ratio in patients in group 1 with prior gadodiamide exposure, not those without prior gadodiamide exposure ( $p = 0.0735$ )

\*\* Stojanov et al. could not exclude exposure to linear GdCA prior to study period, and signal intensity increases were not visible on MRI images

In addition to the studies presented in Table 5, there have been published studied cohorts of patients exposed to different linear or macrocyclic GdCAs:

- A study by Bae et al. reported signal intensity increases in six patients who received linear GdCAs, either gadopentetic acid or gadodiamide, and no signal intensity increases in 44 patients who received macrocyclic GdCAs, either gadobutrol or gadoteric acid.
- A study by Cao et al. reported signal intensity increases in the brains of patients on haemodialysis ( $n=25$ ), exposed to linear GdCAs gadodiamide, gadopentetic acid, and gadobenic acid (Cao et al. 2016b). Signal intensity increases did not occur in haemodialysis patients not exposed to GdCAs.
- Zhang et al. reported signal intensity increases in a range of brain areas in 13 patients with 35 or more administrations of linear GdCAs, gadopentetic acid or gadobenic acid (Zhang et al. 2016).
- Tedeschi et al. reported signal intensity increases mainly related to gadopentetic acid in relapsing-remitting multiple sclerosis patients ( $n=74$ ), and a “borderline” effect with gadobutrol and gadoteric acid. However the 35 patients in this study appear to have received both the linear agent gadopentetic acid (Magnevist) and the macrocyclic GdCAs, and the “borderline effect” with macrocyclic agents reported in the multivariate regression analysis was not presented as occurring in an analysis of patients only exposed to the macrocyclic GdCAs.
- Tanaka et al. 2016 and Kanda et al. 2014 both reported increases in the signal intensity of the dentate nucleus in patients exposed only to linear agents, which were either gadopentetic acid or gadodiamide.
- Hinoda et al. 2016 compared patients exposed to GdCAs ( $n=48$ ) with unexposed controls ( $n=48$ ). Most patients in the exposed group ( $n=41$ ) underwent several MRI scans with linear GdCAs (median number of doses 5) and also macrocyclic GdCAs (median number of doses 4). There were 7 patients who received only macrocyclic GdCAs (median number of doses 1). DN-to-cerebellum signal intensity ratios in the GdCA group were significantly higher than in the unexposed group, and were correlated with the number of doses of linear GdCAs. This is consistent with the other studies demonstrating similar correlations between exposure to linear GdCAs and signal intensity ratio increases. The study did not report on this endpoint for patients exposed only to macrocyclic GdCAs.

A number of studies have shown a correlation between the number of exposures to linear GdCAs and the signal intensity changes. (Kanda et al. 2014; Adin et al. 2015; Ramalho et al. 2015; Stojanov et al. 2015; Cao et al. 2016; Tanaka et al. 2016; Tedeschi et al. 2016). This relationship further strengthens the interpretation of the MRI studies as evidence that accumulation of gadolinium in the brain is causally related to exposure to linear GdCAs.

Of the published studies which have investigated the association between macrocyclic GdCAs and signal intensity (SI) changes in the brain seven reported no association between macrocyclic GdCAs and SI increases. One study reported only a borderline effect on signal intensity for gadobutrol (Gadovist) and gadoteric acid (Dotarem) compared with a linear agent gadopentetic acid in a multivariate regression analysis (Tedeschi et al. 2016), and these were not patients who had received only macrocyclic GdCAs. The only study reporting an effect for a macrocyclic agent is Stojanov et al., which reported signal increase in the DN and GP after between 4 and 6 administrations of gadobutrol



in patients with relapsing-remitting multiple sclerosis (n=58). The correlation between DN-to-pons signal intensity increases and the number of administrations of gadobutrol was low in this study (Spearman's correlation coefficient 0.263). Some limitations of this study have been raised in a letter to the European Radiology journal, particularly, that previous exposure to linear GdCAs before the study started could not be excluded, the low correlation coefficient, and that signal hyperintensity was not visible on the images provided in the paper (Agris et al. 2016).

Two studies in particular are significant because they reported signal intensity increases in parts of the brain in which signal hyperintensity had not been previously reported. Zhang et al. reported signal intensity increases after the use of linear agents in a range of brain areas, including the dentate nucleus and globus pallidus, but also the posterior thalamus, substantia nigra, red nucleus, cerebellar peduncle, and colliculi (Zhang et al. 2016). Kuno et al. reported signal intensity increased in the dentate nucleus, globus pallidus, and thalamus, and also in the grey matter of the whole brain (with linear agents (Kuno et al. 2016).

### ***Paediatric population***

There are some studies that have produced particular findings of note, or included particular populations of interest, such as children or patients with severely impaired renal function. Three studies have reported signal intensity changes in paediatric populations (Hu et al. 2016; Flood et al. 2016; Roberts et al. 2016b) after the use of linear agents. The paediatric patients in these studies had a mean age of approximately 7.5 years in Hu et al and Roberts et al., and approximately 10 years in Flood et al. The reasons for MRI included a large number of brain malignancies, but also a range of other conditions and symptoms.

### ***Impact of renal impairment and other factors***

The major route of excretion for GdCAs is renal, and prolonged elimination time due to severely impaired renal function could theoretically increase the potential for accumulation in brain tissue.

Some studies (Kanda et al. 2014; Kanda et al. 2015a; Stojanov et al. 2015; Weberling et al. 2016) assessed the correlation between renal function and signal intensity increases and found no correlation. These studies did not include patients with severe renal impairment, and the majority of the patients had normal renal function. The potential for brain signal intensity increases after exposure to gadodiamide and gadopentetic acid has been compared in patients with haemodialysis and patients with normal renal function (Cao et al. 2016b). This study found that the magnitude of the signal intensity increases was greater in the haemodialysis group.

Regarding the possible influence of brain irradiation or multiple sclerosis (MS), patients with brain malignancies or MS are likely to receive multiple contrast-enhanced MRI scans and it has been suggested that the association between signal intensity in the DN and brain irradiation or progressive MS may in fact be confounded by GdCA exposure (Runge 2015; Stojanov et al. 2016).

The published studies include those which have reported hyperintense appearance of the dentate nucleus that was associated with repeated exposure to GdCAs, but not with previous radiation dose or history of chemotherapy (Adin et al. 2015). Another study reported that signal intensity in the dentate nucleus was increased after repeated exposures to gadobenic acid, but that control variables including age, sex, radiation therapy, liver function, and kidney function did not have a significant effect on signal intensity (Weberling et al. 2016).



### 2.4.1.2. Post mortem tissue studies

Three studies have been published, in which the presence of gadolinium in brain tissue samples was confirmed by qualitative and quantitative tests. These studies are summarised in table 8 below.

*McDonald et al.* 2015 reported that 13 patients exposed to gadodiamide (Omniscan) for brain MRI had detectable gadolinium in brain tissue from the dentate nucleus, pons, globus pallidus, and thalamus (0.3 – 58.8 µg per gram of tissue). Higher concentrations were seen in patients who had more total exposures to gadodiamide. Samples from 10 control patients who had received at least one MRI exam but did not receive GdCAs did not contain detectable levels of gadolinium. Transmission electron microscopy showed gadolinium to be largely deposited in the endothelial walls, although densitometry performed with wider field views suggested that 18%–42% of gadolinium had crossed the blood-brain barrier and reached the neural tissue interstitium. The study also found that changes in signal intensity were strongly correlated with the amount of gadolinium detected by inductively coupled plasma mass spectrometry (ICP-MS). The authors were unable to detect gross histologic changes between GdCAs and control group samples under light microscopy. The authors did not report that histological changes were detected by microscopy although electron microscopy was not used specifically to assess histological changes. The presence of histological changes visible only on electron microscopy does not appear to be excluded by this study.

Kanda et al. reported that gadolinium was detected in post-mortem brain tissue samples by ICP-MS in five patients who had all been exposed to multiple doses of linear GdCAs, for investigation of a range of pathologies (glioblastoma, maxillary cancer, malignant lymphoma, brain infarction, pneumonia) (Kanda et al. 2015b). Samples from 5 control patients who did not receive GdCAs contained levels of gadolinium that were many fold lower, and in 15/25 reported test results appear to have been below the limit of detection.

Murata et al. reported that gadolinium was detected in post-mortem tissue samples from 9 patients who had received MRI scans with GdCA contrast and 9 control patients. Gadolinium was detected in all brain areas tested, the putamen, globus pallidus, caudate nucleus, white matter, and dentate nucleus. The highest levels were in the globus pallidus and dentate nucleus. Gadolinium was also found in bone, at higher levels than in brain. Control subjects showed gadolinium levels at or below limits of measurement in all brain tissue areas. There were four GdCA- exposed patients with samples of both DN and bone, and eight with samples of both GP and cortical bone from a rib. The authors compared the concentrations of gadolinium in GP and bone, and reported a correlation between GP and cortical bone concentrations of  $r = 0.81$  ( $P = 0.022$ ,  $n = 8$ ).

**Table 6: Summary of tissue sample studies**

Reference	GdCAs studied	Tissue samples	Analytic techniques	Findings
Kanda et al. 2015b	gadodiamide (Omniscan), gadopentetic acid (Magnevist), gadoteridol (Prohance)	Post-mortem brain tissue samples, n=10 (5 with GdCA exposure, 5 controls without)	Mass spectrometry	Gadolinium detected in all GdCA group samples. Concentrations were higher in the DN and GP than in cerebellar white matter, and the frontal lobe cortex, and frontal lobe white matter.
McDonald et al. 2015	gadodiamide (Omniscan)	Post-mortem brain tissue samples, n=23 (13 with GdCA exposure, 10 controls)	Electron microscopy, mass spectrometry	Patients in the GdCA group had elevated levels of gadolinium in the DN, pons, GP, and thalamus. None of the patients in the

		without)		control group had detectable levels of gadolinium.
Murata et al. 2016	gadoteridol (Prohance), gadobutrol (Gadovist), gadobenic acid (Multihance), gadoxetic acid (Primovist)	Post-mortem brain, skin, and bone tissue samples from patients exposed to GdCAs n=18	Mass spectrometry	Gadolinium was detected in brain tissue (DN, GP, pons, caudate nucleus, white matter) bone and skin in samples from patients exposed to GdCAs. Control subjects showed gadolinium levels at or below limits of measurement in all brain tissue areas. Gadolinium levels in bone were lower by an order of magnitude or more in controls compared with exposed samples.

The patients exposed to gadodiamide (Omniscan) and gadopentetic acid (Magnevist) in McDonald et al. and Kanda et al. had higher concentrations of gadolinium in the dentate nucleus and globus pallidus than the patients exposed to macrocyclic GdCAs in Murata et al. The three studies included tissue samples from patients with different numbers of exposures to GdCAs, and different lengths of time elapsed between the last GdCA exposure and autopsy, and patient age, sex, and underlying disease also differed. This introduces variation which makes it difficult to reliably compare the concentrations of gadolinium in the tissue samples between studies. In Kanda et al. although some patients were exposed to macrocyclic agents all patients had at least one exposure to gadopentetic acid. Murata et al. included only a single patient exposed to gadobenic acid (Multihance). This patient was given only one dose of gadobenic acid, and the tissue samples had levels of gadolinium higher than some of the samples from patients exposed only to macrocyclic GdCA, but lower than others.

Details of the concentrations of gadolinium in the exposed patients in these three studies are presented in Table 9. Data are presented as nmol of gadolinium per gram of brain tissue, to be consistent with the units of concentration used in the non-clinical studies

**Table 7: Post-mortem brain tissue sample gadolinium concentrations (nmol/g)**

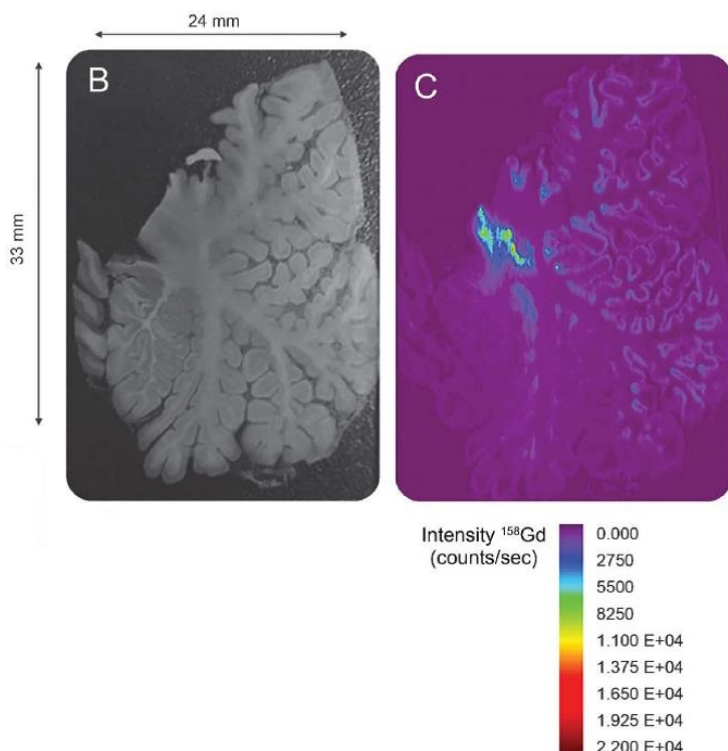
Reference	Case number	GdCAs	Number of GdCA doses	Time between last exposure and post mortem (days)	Concentration of gadolinium (nmol/g)	
					DN	GP
Kanda et al. 2015b	1	gadopentetic acid	4	450	3.2	3.05
	2	gadopentetic acid, gadoteridol	4	60	0.64	0.83
	3	gadopentetic acid	3	15	13.4	4.96
	4	gadopentetic acid	2	120	0.426	0.172
	5	gadopentetic acid, gadodiamide, gadoteridol	3	1170	0.76	0.76
McDonald et al. 2015	1	gadodiamide	4	18	0.6	0.0
	2	gadodiamide	5	13	28.0	3.8

Reference	Case number	GdCAs	Number of GdCA doses	Time between last exposure and post mortem (days)	Concentration of gadolinium (nmol/g)		
					DN	GP	
	3	gadodiamide	6	86	1.9	1.3	
	4	gadodiamide	7	29	13.4	3.8	
	5	gadodiamide	8	511	6.4	22.9	
	6	gadodiamide	9	197	52.1	5.1	
	7	gadodiamide	10	44	24.8	13.4	
	8	gadodiamide	11	523	54.1	8.3	
	9	gadodiamide	11	20	42.0	10.8	
	10	gadodiamide	14	17	74.4	21.0	
	11	gadodiamide	17	53	161.5	33.1	
	12	gadodiamide	28	62	63.6	72.5	
	13	gadodiamide	29	106	373.9	109.4	
	Murata et al. 2016	1	gadobutrol	1	5	6.804	3.975
		2	gadobutrol	2	392	0.706	1.196
3		gadoteridol	1	15	4.96	0.420	
4		gadoteridol	11	19	NA	0.248	
5		gadoteridol	3	53	NA	0.146	
6		gadoteridol	1	118	BRL	0.051	
7		gadoteridol	1	90	BRL	BRL	
8		gadoxetic acid	10	90	NA	0.941	
9		gadobenidic acid	1	83	0.496	0.331	

BRL = below reporting limit

In their original publication Murata et al. did not report that there was histopathological assessment in their study. In a subsequent review article which included details of their post-mortem study (Murata et al. 2016b), they stated that they also performed histologic examination of a subset of tissues from samples from the post-mortem study with the highest levels of gadolinium deposition in the globus pallidus, head of caudate, and putamen. Comparison of these with control samples using haematoxylin-eosin-stained histologic examination together with quantitative counting of glial cells and neurons and found no statistical difference between exposed patients and controls that would suggest reactive changes.

A very recently published article has provided further information of gadolinium present in post-mortem brain tissue sample (Roberts et al. 2017). The authors report on the distribution of gadolinium within the brain of a patient who died aged 17, having been previously healthy and with status epilepticus as the proximal cause of death. The patients had undergone 4 MRI scans with GdCA contrast; two of these were with Magnevist (gadopentetic acid), for the other two scans the GdCA was not documented and the patient may have received either Magnevist or Omniscan (gadodiamide). There was no hyperintensity noted in the dentate nucleus in the last MRI scan conducted before the patient's death. The authors used laser ablation inductively coupled plasma mass spectroscopy (LA-ICP-MS) to assess the presence of gadolinium in the cerebellum, and reported heavy deposition of gadolinium in the dentate nucleus and also throughout the cerebellar cortex. Figure 10, taken from part of the figure within the publication, shows the autopsy section through the cerebellum and the LA-ICP-MS findings.



**Figure 10: Distribution of gadolinium within the cerebellum (Roberts et al. 2017)**

The authors reported that using ICP-MS the total gadolinium concentration within the dentate and peridentate white matter was 1.01  $\mu\text{g/g}$  (6.4 nmol/g). This is within the range of concentrations reported in patients exposed to multiple doses of the linear GdCAs gadopentetic acid (Magnevist) and gadodiamide (Omniscan) in the studies by Kanda et al. and McDonald et al (Kanda et al. 2015b; McDonald et al. 2015). The authors also provided an image of LA-ICP-MS visualisation of gadolinium from the cerebellum of a control patient not exposed to GdCAs, and this image showed no gadolinium in the sample. The form of gadolinium, either as intact GdCA or as gadolinium released from the ligand and bound to other molecules, was not determined by this study.

#### **2.4.1.3. Observational studies**

A publication by Welk et al. reported the results of a large retrospective observational study in several linked administrative databases from Canada (Welk et al. 2016). The study was designed to investigate the potential association between GdCA exposure and Parkinsonism symptoms, on the basis that brain accumulation of gadolinium has been reported in the globus pallidus and that consequences of damage to this part of the brain may include Parkinsonism. Between 2003 and 2013 patients who underwent unenhanced MRI or at least one GdCA-enhanced MRI were identified. Exposure was assessed using fee codes. Patients with an initial MRI of the brain or spinal cord, or with prior Parkinsonism or neurosurgery were excluded. The outcome of Parkinsonism was assessed using diagnosis codes from hospital admissions and physician visits or a dispensed Parkinson's disease-specific medication. Patients in the GdCA-exposed cohort ( $n = 99,739$ ) and non-exposed cohort ( $n = 146,818$ ) were similar with respect to baseline characteristics such as age, sex, comorbidities of dementia, melanoma, seizure, and encephalitis, and use of medication in the previous 6 months. The GdCA-exposed cohort included a greater proportion of patients with bowel, breast, prostate, lung, or rectal cancer (27.8% vs. 12.9%), and with stroke (3.3% vs. 1.8%). The GdCA-exposed cohort also included a greater proportion of patients with one or more previous hospitalisation (47.0% vs. 31.9%),

and with previous computed tomography of the head (11.5% vs. 18.4%). A subset of 38 covariates particularly relevant to Parkinsonism (based on potential associations from the literature) or significantly different at baseline (standardized difference >10%) were included in a multivariable time-dependent extended Cox regression model; the hazard ratio is interpreted as the hazard of Parkinsonism per additional gadolinium exposure.

In the adjusted analysis the relative risk of Parkinsonism was not increased in patients exposed to GdCAs compared with those not exposed; Hazard Ratio 1.04 (95% CI 0.98 – 1.09). Covariates adjusted for in this analysis included demographics, MRI study body part, year of cohort entry, comorbidities and, medications, post-hoc sensitivity analyses based on adjustment for additional covariates or on an outcome definition that did not include dispensing of medicines for Parkinson's disease gave results consistent with the main analysis. The authors considered that strengths of the study included large cohorts with a similar propensity for MRI scans, assessment of more than 100 baseline characteristics, and methodology accounting for the cumulative nature of gadolinium exposure. The authors considered that a study limitation was the potential for differential misclassification of the outcome.

#### **2.4.1.4. Literature case reports and survey data**

A case report (Miller et al. 2015) described a paediatric oncology patient. Treatments included radiotherapy, chemotherapy, and proton beam therapy. The patient was exposed to 35 MRI examinations with gadopentetic acid (Magnevist) between the ages of 8 and 20 years. A progressive increase in signal intensity was seen in the dentate nuclei, the globus pallidus and the thalamus. At the age of 21 years, the patient had no intracranial lesion on MRI, no significant visible treatment-related intracranial structural abnormality, or significant documented medical problems.

Neuropsychological testing suggested difficulties with executive functioning, visual memory and reasoning, reading comprehension, and mathematical abilities. The authors concluded that the dominant variable factor, and most likely cause of the qualitative and quantitative changes in the brain images was the cumulative dose of the linear GdCA gadopentetic acid.

A publication by Barbieri et al. reported hyperintensity in the dentate nucleus in three patients with multiple exposures to GdCAs (Barbieri et al, 2016). The patients had all been exposed to several different GdCAs, both macrocyclic and linear. The article described some neurological symptoms such as aphasia and confusion in these patients, however probable causes for these events such as herpes simplex encephalitis, intracranial haemorrhage, and leukoencephalopathy of likely microangiopathic origin were reported. The authors concluded that further research is needed to determine possible clinical consequences of gadolinium deposits in the brain.

A survey based on information reported by patients to a website has been published which reported chronic symptoms after exposure to GdCAs (Burke et al. 2016). All the patients attributed their current symptoms to gadolinium exposure. Forty-one of the patients who responded reported undergoing at least one form of gadolinium testing, and some had used several testing methods. The authors report a pattern in the types of symptoms reported (n=49), with head and neck symptoms (headache, vision change, and hearing change) and bone or joint pain both described by 78% of the cases, and skin changes were observed in 59% of cases. Other symptoms reported included flu-like symptoms (31%) digestive symptoms (nausea, vomiting, diarrhoea) (47%), chest symptoms (difficulty in breathing) (43%), and generalized whole body symptoms (31%). Other symptoms were reported in 76% of cases.

Another publication from the same research group that published the survey results in Burke et al. reported data on clinical manifestations which the authors attributed to toxicity from exposure to gadolinium (Semelka et al. 2016b). This survey was similar in design to Burke et al.

The symptoms reported included pain at a variety of sites, skin changes musculoskeletal symptoms, and neurological findings. Pain included central pain, peripheral pain, headache, and bone pain, reported as lasting beyond 3 months, and persisted to the time of the survey. The skin changes included skin thickening. In patients with distal leg and arm distribution of pain, 22 also described skin thickening at the site of the pain. In 20 respondents the skin thickening was described as rubbery or spongy skin thickening of the fingers. Clouded mentation was also described in 29 patients, persisting beyond 3 months. All these patients also had headache.

Based on a review of the data the authors of these publications had previously proposed the name “gadolinium deposition disease” to describe disease in patients with normal or near normal renal function who develop persistent symptoms between hours to 2 months after administration of GdCAs (Semelka et al 2016a).

A report of four cases of patients who experienced possibly gadolinium toxicity after exposure to GdCAs was recently published (Semelka et al. 2016c). The patients were identified and included in the publication as they had sought out the senior physician, who has expertise in NSF, to be assessed for possible gadolinium toxicity. These four patients developed new symptoms with an onset time from between hours to 4 weeks after exposure. Two patients presented months after receiving GdCAs and two presented years after first exposure.

The authors noted some consistency in the symptoms that are reported, such as “glove-and-sock” pain occurring in all cases, torso pain in three, skin thickening in two, and cognitive symptoms in two. Pain in the extremities, torso pain, and skin thickening can all occur in NSF. Gadolinium was detected at levels above the normal range in three cases, in one case the urine sample taken 4 years after the last GdCA exposure. In one case very low levels of gadolinium were detected in a sample of a vein 8 years after the last exposure, and in one case gadolinium at concentrations above the reference range was detected in a hair sample taken 4 years after the last exposure.

#### **2.4.1.5. Spontaneous Adverse Drug Reactions data**

Few potentially relevant reports of adverse reactions that could be related to the accumulation of gadolinium in the brain were identified, and many of the reports identified were derived from literature articles reporting increased signal intensity in dentate nucleus, but not reporting any clinical signs or symptoms possibly related to brain accumulation. There were a small number of cases that reported possible cognitive deficits or movement disorders after exposure to GdCAs. This includes reports based on information from websites. There were four cases not reported to the MAH, and not medically confirmed by a reporting healthcare professional or published in a peer-reviewed journal.

#### **2.4.1.6. Use in pregnancy**

An observational study has been published during this referral procedure investigating exposure to MRI scan and to GdCAs (Ray et al. 2016) during pregnancy. The purpose of the study was to evaluate the long-term safety after exposure to MRI in the first trimester of pregnancy or to GdCAs at any time during pregnancy.

The study compared two cohorts, one with exposure to MRI without a GdCAs in the first trimester and one with exposure to MRI with GdCA contrast between the second gestational week and 2 days before the birth date, with a comparator cohort. The study reported that when pregnancies with exposure to a



GdCA (n=397) were compared with unexposed pregnancies with no MRI (n=1,418,451), the hazard ratio for a broad outcome of any rheumatological, inflammatory, or infiltrative skin condition was increased (adjusted HR, 1.36; 95%CI, 1.09 - 1.69). The hazard ratios for NSF-like outcomes (adjusted HR 1.00; 95% CI 0.33 – 3.02) and congenital anomalies (adjusted HR 1.33; 95% CI 0.98 to 1.82) were not increased. Stillbirths and neonatal deaths occurred among 7 GdCA-enhanced MRI-exposed pregnancies vs. 9,844 unexposed pregnancies (adjusted HR, 3.70; 95% CI, 1.55 - 8.85). The type of GdCA to which the pregnancies were exposed is not known. The timing of the onset of rheumatological, inflammatory, or infiltrative skin conditions was in a follow-up period of up to 4 years after birth. Follow up to 4 years was 46% in the GdCA-exposed cohort, with median follow-up 2.4 years. The extent of follow-up to 4 years in the comparator cohort was not stated; the median follow-up was 3.6 years.

#### **2.4.1.7. Gadolinium accumulation in tissues other than brain**

In addition to the accumulation in the brain, clinical data show that gadolinium can be deposited in other tissues. Gadolinium has been found in the skin (Roberts et al. 2016a), in liver, lungs, intestinal wall, kidney, lymph nodes, skeletal muscle, and bone in patients with NSF (Sanyal et al. 2011). There have also been reports of skin manifestations in patients who did not have NSF, in the form of erythematous skin plaques containing sclerotic bodies, known as gadolinium-associated plaques (GAP) (Bhawan et al. 2013; Gathings et al. 2014).

Apart from the cases of GAP, clinical signs or symptoms associated with deposition of gadolinium have not been confirmed in patients who do not have NSF. There is however a concern over the potential for adverse effects as a result of accumulation in the brain and other tissues in patients without NSF.

Semelka et al. and Burke et al. reported “delayed non-NSF” symptoms in individual patients with normal renal function who have been exposed to GdCAs as described above.

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

Release of gadolinium in patients with severe renal impairment can result in nephrogenic systemic fibrosis (NSF), a serious and life-threatening syndrome involving fibrosis of the skin, joints and internal organs. All GdCAs are renally eliminated, the extent of this renal elimination varies from 50% for gadoxetic acid (Primovist) to 100% for most other members of the class. Elimination of GdCAs is therefore reduced in people with renal dysfunction. Prolonged elimination time in patients with renal impairment and release of gadolinium from ligand molecules are the main factors that contribute to the development of NSF.

The risk of NSF with GdCAs has been kept under close regulatory review since the association was first observed in January 2006. The products have been stratified by risk category for NSF, and warnings and restrictions on the use of the higher NSF risk products in patients with impaired renal function are included in the product information, including contraindication of the high NSF risk products in patients with severe renal impairment or acute kidney injury (AKI). Linear GdCAs are associated with a significant risk of NSF. In some countries the usage of the high NSF risk agents has declined since NSF was recognised as a risk and the risk minimisation measures for GdCAs were introduced, while usage of low NSF risk agents has increased. The implemented risk minimisation measures appear to be effective based on annual reviews of spontaneous case reports.

### 2.4.1.9. Hypersensitivity reactions

Hypersensitivity reactions are well known potential adverse effects of all GdCAs. There are a number of studies which have reported the rate of hypersensitivity reactions or immediate adverse reactions across the class. The different rates reported in twelve of these studies are summarised in Table 8.

**Table 8: Rates of hypersensitivity reactions or immediate adverse events associated with GdCAs reported in the literature (number of reactions per 100,000 exposures\*)**

	Gado-diamide (Omniscan)	Gado-versetamide (Opti-mark)	Gado-pentetic acid (Magnevist)	Gado-benic acid (Multi-hance)	Gadoxetic acid (Primovist)	Gadoteridol (Prohance)	Gadobutrol (Gadovist)	Gadoteric acid (Dotarem)	Gadofosveset (Vasovist)***
<b>Murphy et al. 1999</b>	31	-	66	-	-	406	-	-	-
<b>Abujudeh et al. 2010</b>	-	-	140	280	-	-	-	-	-
<b>Morgan et al. 2011</b>	-	-	-	-	-	666	-	-	-
<b>Prince et al. 2011</b>	20	-	50	120	-	330	-	-	-
<b>Jung et al. 2012</b>	13	-	61	220	116	-	99	80	-
<b>Davenport et al. 2013</b>	0	-	80	190	100	200	-	-	2800
<b>Okigawa et al. 2014</b>	-	-	430	-	820	540	-	240	-
<b>Bruder et al. 2015**</b>	50	-	160	420	-	190	100	120	-
<b>Aran et al. 2015</b>	-	-	90	220	310	-	-	-	800
<b>Granata et al. 2016</b>	-	-	18	80	28	-	56	110	-
<b>Prince et al. 2016</b>	-	-	-	-	-	-	900	-	-
<b>Power et al. 2016</b>	-	-	-	-	-	-	320	-	-

\* Some studies reported percentage rates, these have been converted to rate per 100,000 in order to use the same units across all studies presented here

\*\* The earlier study by Bruder et al. in 2011 used the same data source (EuroCMR Registry) at an earlier time point, and is not included in this table

\*\*\* Vasovist (gadofosveset) is no longer authorised in the EU



A study by Davenport et al. (2013) reported a transient increase in the reporting rate of “allergic-type reactions” (hypersensitivity reactions) after switching from gadopentetic acid (Magnevist) to gadobenic acid (Multihance), and that the reporting rate of this type of reaction with gadobenic acid returned to the previous level after 2 years. It should be noted that Murphy et al. was published in 1999, which would be prior to any switching between different GdCAs because of the risk of NSF, but the study did report a lower rate of hypersensitivity reactions with gadodiamide (Omniscan) and gadopentetic acid (Magnevist) compared with gadoteridol (Prohance). In this case the survey design of the study was a significant limitation, and the authors identified one institution that reported 26.2% of the usage of Prohance in this study and 80.7% of the total adverse events with Prohance, which may have skewed the data, raising the rate of adverse events reported for Prohance.

It should be noted that there is considerable variation in the absolute rates of hypersensitivity reactions reported in these studies, and also in the relative differences in the reporting rates when different agents are compared.

It has also been reported that the rate of hypersensitivity reactions varies depending on the underlying condition of the patients and the reasons for the MRI investigation

In addition to the studies summarised in table 8, Raisch et al. 2014 reported on numbers of spontaneous cases and on measures of disproportionality in reporting for different GdCAs, using data from the FDA AERS database. The study included gadodiamide, gadoversetamide, gadopentetic acid, gadobenic acid, gadoxetic acid, gadoteridol, gadobutrol, gadoteric acid, and gadofosveset (which is not authorised in the EU). The study reported the highest proportional reporting ratio (PRR) for gadobenic acid (Multihance), PRR 17.5 (95% CI 15.2 – 20.2), and the lowest for gadoversetamide (Optimark), PRR 0.82 (95% CI 0.31 – 2.2).

## 2.4.2. Discussion on clinical safety

### MRI studies

The PRAC considered that an increase in signal intensity is an indirect indicator of the presence of gadolinium compounds. There are other factors that have the potential to cause signal intensity increases in the brain, such as the presence of metals such as iron or manganese, a history of brain irradiation (Kasahara et al. 2011), or progressive multiple sclerosis (MS) (Roccatagliata et al. 2009). However there is evidence that the signal increases seen after repeated exposure to GdCAs are not caused solely by these factors. One study found that the number of previous GdCA exposures correlated with R1 relaxation rates but not R2\* values (Tedeschi et al. 2016). R2\* values are correlated with concentration of iron in the grey matter. This is evidence that iron concentrations are not increasing as patients receive multiple GdCA administrations and signal intensity increases in the DN become apparent. The authors concluded that the changes in the dentate nuclei T1 signal were therefore not a result of iron accumulation.

All the studies that have included gadopentetic acid (Magnevist) and gadodiamide (Omniscan) have confirmed increases in signal intensity in association with their use. These are both linear GdCAs that have a high potential to release gadolinium from the chelating ligand.

The linear ionic agent gadobenic acid (Multihance) was included in three published studies which included a cohort of patients exposed only to Multihance. Two of these studies reported signal intensity changes with gadobenic acid (Weberling et al. 2015; Ramalho et al. 2016). A study by Ramalho et al. reported no significant changes in signal intensity ratios with gadobenic acid, although it did report a statistically significant increase in percentage change for DN-to-middle cerebellar peduncle ratio ( $p = 0.013$ ) (Ramalho et al. 2015). A second study with Multihance, by Weberling et al., reported signal

hyperintensity increases in the dentate nucleus in a group of patients most of whom had melanoma and were exposed to at least 5 doses of Multihance (Weberling et al. 2015). A third study with Multihance, by Ramalho et al., included two groups of patients. Patients in group 1 had received multiple doses of gadodiamide (Omniscan) before going on to receive multiple doses of gadobenic acid (Multihance). Patients in group 2 had only received multiple doses of Multihance, with no prior exposure to other GdCAs. Patients in group 1 showed a significantly higher DN-to-middle cerebellar peduncle signal intensity ratio at baseline and at follow-up compared with patients in group 2. There was a non-statistically significant trend towards an increase in relative change in signal intensity ratio in patients in group 1 ( $p = 0.0735$ ). A study by Radbruch et al. reported signal intensity increases in the DN-to-pons signal intensity ratio in patients after at least five consecutive exposures to the linear GdCA Magnevist (gadopentetic acid), but no further signal intensity increases in these patients following subsequent exposures to macrocyclic GdCAs (gadobutrol (Gadovist) or gadoteric acid (Dotarem)) (Radbruch et al. 2016b). It is therefore not established that prior exposure to a linear GdCA, such as gadopentetic acid (Magnevist) in Radbruch et al. 2016b or gadodiamide (Omniscan) in Ramalho et al. 2016 can cause further signal intensity increases at a later time when the patients are exposed to a different GdCA.

For the linear ionic agent Primovist (gadoxetic acid) two studies have been published. One study (Kahn et al. 2016) in patients exposed to gadoxetic acid ( $n=91$ ) reported signal intensity increases in the dentate nucleus in a subgroup of patients who received more than 10 exposures to gadoxetic acid ( $n=32$ ). The effect appeared to be dose-related and no statistically significant increase was detected in the patients with fewer than 10 exposures. Ichikawa et al. reported signal intensity increases in the DN-to-pons ratio in patients with 5 or more exposures to Omniscan (gadodiamide) but not in patients with either 5 or more or 1 exposure to gadoxetic acid (Ichikawa et al. 2017). The standard dose of Primovist is 0.025 mmol/kg, which is lower than the dose for other GdCAs, and so less total gadolinium content per dose may have influenced the results. In vitro data suggest potentially less release of gadolinium from the ligand molecules for Primovist than for other linear GdCAs when incubated in human serum (Frenzel et al. 2008), which is another factor which may have influenced these results.

There are currently no data from clinical MRI studies for the other linear agent, gadoversetamide (Optimark).

In view of factors that may have an impact on the SI increase, the PRAC considered that while impaired renal function is not a necessary precondition for signal hyperintensity increases in the brain impaired renal function does increase the extent of brain accumulation and signal hyperintensity.

In addition, chemotherapy, radiation therapy, age, sex, or liver function did not seem to have an impact on SI increase after the use of GdCAs.

A lower potential for brain accumulation with macrocyclic agents might be expected based on the stability of these agents and on the rates of gadolinium release seen in in vitro studies. When GdCAs are incubated in human serum these rates were much lower for macrocyclic GdCAs than for the non-ionic linear GdCAs (Frenzel et al. 2008). This pattern is also consistent with the evidence from non-clinical studies.

#### Post mortem tissue studies

It is not possible to make reliable conclusions about the relative proportions of the dose that become deposited in the brain because of the heterogeneity in the data within and between these studies. Non-clinical studies have reported higher concentrations of gadolinium in brain tissue after exposure to linear agents compared with macrocyclic agents. The heterogeneity in the clinical post-mortem data prevents firm conclusions, but higher concentrations of gadolinium after exposure to linear GdCAs

seems generally consistent with the non-clinical findings. This evidence combined with the known greater potential for dechelation of gadolinium with the linear GdCAs suggests that concentrations in human brain are also likely to be higher tissue after exposure linear agents compared with macrocyclic agents.

These studies confirm that gadolinium is present in brain tissue after exposure to GdCAs, particularly in the dentate nucleus and globus pallidus. Some level of gadolinium deposition has been confirmed in brain tissue for all the GdCAs represented in these studies, both macrocyclic and linear. The only GdCAs to which no patients had been exposed in these studies were the macrocyclic agent gadoteric acid (Dotarem) and the linear agent gadoversetamide (Optimark). The studies also show that gadolinium can persist in brain tissue for extended periods after the last exposure to a GdCA. The study by McDonald et al. 2015 also demonstrated that in patients exposed to gadodiamide (Omniscan) a proportion of the gadolinium crossed the blood-brain barrier. Gadolinium was detected in brain tissue samples taken at autopsy between 0.5 and 39 months after the last exposure to GdCAs (Kanda et al. 2015b), between 5 and 392 days before autopsy (Murata et al. 2016), and between 13 and 623 days (mean 139, median 53) (McDonald et al. 2015). Across these three studies there are five patients where gadolinium was detected in the brain one year or more after the last exposure to a GdCA.

It should be noted that no histopathological changes have been confirmed in the three studies of non-tumour brain tissue. McDonald et al. reviewed slides of the dentate nucleus from the time of autopsy, but were unable to detect gross histologic changes between GdCA-exposed and control groups. Kanda et al. did not include histopathologic analysis in their study.

The results from a 17 year old patient (Roberts et al. 2017) are consistent with the earlier clinical post-mortem studies, showing gadolinium in the dentate nucleus after exposure to linear GdCAs. Although the studies demonstrating signal hyperintensity increases with linear GdCAs have typically included patients with an average of 5 exposures, or even higher average exposure, it is clear that gadolinium is present in the brain after smaller numbers of exposures. If this patient had not died at age 17, it appear probable that this gadolinium would have remained in his cerebellum for an extended period, since the persistent presence of gadolinium after exposure to linear GdCAs has been seen in non-clinical studies and in other clinical post-mortem studies.

The long-term clinical consequences of such gadolinium retention are currently unknown. It is plausible that adverse clinical consequences could be associated with gadolinium retention. These effects might be delayed and subtle, including effects on fine motor skills or cognitive impairment, particularly in those with ongoing neurological disease. There is also the potential that gadolinium deposition could possibly worsen existing inflammatory diseases.

Given the components of the outcome definition, it could be more sensitive and less specific among those with gadolinium exposure. This could lead to a bias where more events of Parkinsonism would be recorded for the exposed cohort which the authors suggested could mean the actual HR might be lower than 1.04. According to the authors other limitations include the small number of patients who received 4 or more doses of gadolinium, the lack of generalizability to younger patients, the possibility of residual confounding from temporal trends in gadolinium usage not captured in the adjustment for year of initial MRI, and the inability to determine the specific type of gadolinium used.

Another limitation not mentioned by the authors is that the study did not distinguish between different GdCAs. There is strong evidence of a differential risk of brain accumulation across the class. Signal intensity increases in the brain have not been reported in good quality studies for the macrocyclic agents, and it is reasonable to suppose that any potential adverse effects would be likely to occur in patients exposed to linear agents with a higher potential to dechelate, releasing gadolinium from the

ligand molecule. The study included adjustment for year of cohort entry, which in the GdCA-exposed cohort was the year of the initial MRI. The authors noted as a limitation the possibility of residual confounding from temporal trends in gadolinium usage not captured in the adjustment for year of initial MRI. The statistical analysis expressed the relative risk in terms of the effect of each additional dose of GdCA, but it should be noted that only 2.5% of patients underwent more than 3 GdCA-enhanced MRI scans. Most of the studies that report signal intensity increases in the brain report these changes in patients with more exposures than this. Therefore this study may only have included a very small proportion of patients likely to be at the highest risk of Parkinsonism, specifically those with large numbers of exposures to linear GdCAs.

The study period was ten years, however the latency period of any potential adverse effects as a consequence of brain accumulation is not known. The study period may not have been long enough to observe adverse effects of brain accumulation if such events have a long latency period. It is notable that cases of NSF have been reported to occur in patients up to several years after the last exposure to a GdCA. Onset of NSF has been reported 8 years after 5 exposures to unspecified GdCAs in a patient with chronic renal failure (Do et al. 2012), and in another case report 10 years after several exposure to GdCAs in a long-term haemodialysis patient (Larson et al. 2015).

The study investigated an endpoint of Parkinsonism. Because many studies have shown that accumulation of gadolinium occurs in the dentate nucleus and globus pallidus, which are involved in the regulation of movement, this is a reasonable endpoint to choose. But it is possible that adverse effects of brain accumulation could include signs and symptoms other than Parkinsonism. It should be noted that the recent study by Zhang et al. has shown signal intensity increases in a range of brain areas, including the dentate nucleus and globus pallidus, but also the posterior thalamus, substantia nigra, red nucleus, cerebellar peduncle, and colliculi (Zhang et al. 2016). Kuno et al. reported signal intensity increased in the dentate nucleus, globus pallidus, and thalamus, and also in the grey matter of the whole brain (Kuno et al. 2016). Although not confirmed as causally related to GdCA exposure, literature case reports in patients exposed to GdCAs have reported other potential neurological effects, such as impaired cognition (Burke et al. 2016; Semelka et al. 2016b; Semelka et al. 2016c).

In view of the case report described in Miller et al. 2015 the authors did not comment on the possibility that the cognitive difficulties detected by neuropsychological testing might also be related to GdCA exposure. The underlying disease and previous treatments are potential explanations for these adverse effects.

In the patient surveys Semelka 2016b et al and Burke et al 2016 the main limitations are selection bias, as the respondents were self-selected from groups of people already interested in the issue of potential gadolinium toxicity. The symptoms reported in this survey are not medically confirmed, and the results of tests to quantify levels of gadolinium in urine and tissue in Burke et al were not available to the authors of the study.

Strengths of the cases reported in Semelka et al. 2016c are that the symptoms are medically confirmed by a physician experienced in NSF, and in one case skin biopsy of the knee confirmed fibrosis. There are some limitations of these cases for assessing causality in relation to GdCA exposure. The patients are self-selected for further investigation of their symptoms. The cognitive symptoms are more subjective than the skin changes, and reporting of cognitive symptoms could perhaps be influenced by publically available information on gadolinium accumulation in the brain. The level of exposure varies in the cases, including two patients who received only one dose. Exposure to GdCAs is as an acute dose accompanying an MRI investigation, and with these acute exposures and reported ongoing symptoms it is not possible to observe reports of positive rechallenge or dechallenge that typically provide information for causality assessment with other medicines and ADRs.

The cases do not provide strong evidence of a causal association between the reported symptoms and exposure to GdCAs, but the confirmation of increased gadolinium levels and the similar symptoms, include skin changes reminiscent of NSF are notable.

The PRAC further noted that cases from MAHs' ADR databases reported from spontaneous reporting have some similar features, such as symptoms of loss of co-ordination or cognitive problems, and the confirmation of prolonged presence of gadolinium in the body by analysis of urine and hair. The presence of gadolinium in urine after two weeks in one case suggests that some of the dose was distributed to locations where the rate of elimination was much slower than the rapid renal elimination of intact GdCA molecules.

However due to the limited information, lack of medical confirmation, and the possibility that there are alternative explanations for the reported signs and symptoms these cases do not provide evidence on the presence or absence of clinical harm associated with brain deposition. Although two cases reported loss of co-ordination, two did not report events such as ataxia, tremors, and other movement disorders which might be expected as likely consequences of adverse effects on the dentate nucleus or globus pallidus.

While the data from case reports do not confirm that adverse effects occur after accumulation of gadolinium in the brain, absent or limited information from case reports is not evidence that such adverse reactions do not occur. Spontaneous reporting of ADRs is not likely to be a sensitive way of detecting possible cases. Many patients who receive multiple MRI scans with GdCA contrast will have underlying diseases such as brain malignancies and MS that could make it less likely that adverse effects would be identified as potentially related to GdCAs exposure and reported. The accumulation of gadolinium is progressive with repeated doses, and if adverse effects occurred only after multiple exposures, and not necessarily in close temporal association with a dose, this would further reduce the likelihood of potential adverse events being reported.

### Pregnancy

In view of the study in pregnant women (Ray et al. 2016) the PRAC highlighted that if the pattern of time to onset of these events in the GdCA-exposed cohort was markedly different from the comparator cohort it could indicate a different aetiology for the events, but it is not known if time to onset differed between affected babies in the exposed and unexposed cohorts.

This study has some limitations. A major limitation is the potential for differences in the rates of the outcomes in the GdCA-exposed cohort and the comparator cohort, because of confounding by indication. Women requiring MRI to investigate a medical issue are expected to have a different, likely higher, risk of adverse pregnancy outcomes due to conditions than other pregnancy women. This rate could potentially be even higher in women for whom the need for diagnostic information is considered great enough to justify the use of a GdCA in pregnancy, considering that such use is not recommended. Residual confounding by unmeasured factors cannot be discounted, since the study lacked data on exposure to specific teratogens in pregnancy, such as prescription medications or alcohol. The association between gadolinium exposed pregnancies and stillbirth or neonatal death is based on seven events in the GdCA-exposed cohort. The high potential for residual confounding could potentially explain the observed association. For the broader outcome of rheumatological, inflammatory, or infiltrative skin conditions, when this was assessed in the GdCA-exposed cohort the power was about 93% to detect a relative risk of 1.5 or higher. The authors noted that since several models with different outcomes were created, heightening the probability of a type 1 statistical error due to multiple comparisons, and that this findings should be considered exploratory. Despite this, the

authors concluded that: “Until further studies are done, these findings suggest that gadolinium contrast should be avoided during pregnancy.”

The GdCAs vary with respect to information in the SPCs about use in pregnancy. The SPCs for gadoteridol (Prohance), gadoteric acid (Dotarem), and gadoversetamide (Optimark) state that there are no data from use in pregnant women and that animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. The SPCs for gadodiamide (Omniscan), gadopentetic acid (Magnevist), gadoxetic acid (Primovist), gadobenic acid (Multihance), and gadobutrol (Gadovist) all state that there are no data from use in pregnant women and that animal studies have shown reproductive toxicity at repeated high doses. On the basis of the results from study by Ray et al. alone there is not provide robust enough evidence of adverse outcomes associated with exposure to GdCAs during pregnancy to warrant changes to the recommendations in the current product information, or to include information about the results from this study in the SPC. It could potentially be possible to perform a similar study using EU datasets. Some consideration of the available data on exposure to GdCAs during pregnancy, whether an appropriate comparator group can be identified, and whether important confounding factors can be adjusted for would be needed to determine the feasibility of such a study. The MAHs for products considered to have a positive benefit-risk balance are requested to make some updates to the RMPs for their products in section 6 (Recommendations), this includes adding “Pregnant or lactating women” as an area of missing information. At the same time the MAHs should make proposals for conducting a further observational study into the effect of GdCA exposure during pregnancy on pregnancy outcomes.

#### Accumulation in other organs

The accumulation of gadolinium in bone is likely due to the chemical similarity of gadolinium to calcium in terms of its similar ionic radius. It has been reported that while levels in bone are much higher than levels in skin and brain, there is a correlation between the levels found in brain tissue and in bone tissues (Murata et al. 2016a).

If gadolinium is incorporated into bone as gadolinium hydroxyapatite the large size of this molecule compared with the calcium hydroxyapatite which is a major constituent of normal bone could lead it changes in the properties of the bone. It is not currently known how much gadolinium content would be required to produce clinically significant changes. Additionally, there is a potential risk that gadolinium retained in bone or other tissues could potentially be released later and redistributed in the body, as a patient ages and bone density decreases or during pregnancy and breast feeding. MAHs of GdCAs are currently carrying out PASS studies focusing on bone accumulation; this study was imposed as a condition to the marketing authorisations following the previous referral.

#### NSF

In view of NSF, during the procedure some of the MAHs have discussed the data on rates of NSF with their products, and questioned the classification of the GdCAs into the risk categories, arguing that some of their products should be in a lower risk category. PRAC considered that no evidence is of nature to change the risk categories established in the previous referral procedure and no change to the risk minimisation measures currently in place is required.

#### Hypersensitivity

In view of the available study data, the PRAC considered that there are some important limitations of these studies: the retrospective or survey design, the reliance on adverse event recording, and potential for under-reporting or reporting stimulated by changes in use of the products.



Rates of reporting may be higher for products recently introduced to the market, or when an institution has recently switched from one product to another. Switching from linear to macrocyclic agents after the risk of NSF was identified may have increased the rate of reporting for macrocyclic agents, and the different times of authorisation of these products may also have affected reporting rates in these studies. It should also be noted that some studies which included both linear and macrocyclic GdCAs have reported that there were no statistically significant differences in the rates of hypersensitivity reactions between the different GdCAs (Jung et al. 2012; Bruder et al. 2015; Granata et al. 2016).

The PRAC also noted that the vast majority of hypersensitivity reactions are non-serious, such as urticarial, flushing, and nausea, tend to occur in patients with a pre-existing history of hypersensitivity reactions or asthma and have an overall very low reporting rate with all GdCAs. The rate of serious adverse reactions is very low, and the studies which have evaluated the rate of hypersensitivity reactions with GdCAs have all reported that a very low proportion of patients experienced a severe hypersensitivity reaction. The risk of hypersensitivity is appropriately addressed in the product information of GdCAs.

### **2.4.3. Conclusions on clinical safety**

PRAC considered that overall, the MRI studies show signal intensity increases in the brain in with linear agents. MRI studies do not show signal intensity increases with macrocyclic GdCAs. The only studies suggesting any changes in signal intensity increases with macrocyclic GdCAs have significant limitations and do not confirm an association.

Post mortem data showed that gadolinium has been measured in the brain, both indirectly by studies showing signal intensity increases, and directly by studies measuring gadolinium concentrations with mass spectrometry, including methods that allow localisation in the brain (LA-ICP-MS).

The long-term clinical consequences of such gadolinium retention are currently unknown. Although no adverse neurological effects have yet been demonstrated to be caused by gadolinium accumulation in the brain, long-term safety data are limited. Harmful effects and potential interaction with disease processes are plausible in view of stability data suggesting dechelation of linear agents in vivo and the known toxicity of unchelated gadolinium. Based on the knowledge of the function of the affected brain areas (including DN and GP), these effects would include effects on fine motor skills or cognitive impairment, particularly in those with ongoing neurological disease which may mask these events. These effects might be delayed and subtle.

Moreover, there is concern that gadolinium deposition could worsen existing inflammatory diseases, as accumulation in inflammatory lesions has been observed. This was discussed with clinical experts within an ad hoc expert group meeting that confirmed a possible association but this has not yet been demonstrated. The experts also stated that it is plausible that adverse clinical consequences could be associated with gadolinium retention in the brain.

In view of the above, PRAC considered that there are reasonable and serious concerns raised as to the potential of neurological harm associated with the accumulation of gadolinium in the brain.

Gadolinium accumulation has also been reported in a range of other tissues including the liver, kidney, muscle, skin and bone in non-clinical and clinical studies. The evidence strongly suggests a correlation between the potential for release of gadolinium from the ligand and the extent of retention in these tissues and organs.

The PRAC considered that there is no evidence to change the categorisation related to the risk of NSF. Current risk minimisation measures appear to be effective based on spontaneous adverse drug reaction reporting.

There is also evidence that other harmful outcomes are associated with exposure to linear GdCAs, in particular gadolinium-associated skin plaques. Both NSF and Skin plaques are considered to be related to release of Gd from the chelate, which adds to the concern that Gd released in the brain may also have a toxic effect.

In view of data on hypersensitivity reactions, considering the limitations of these data there is not strong evidence of a true difference in the rate of hypersensitivity reactions or other acute reactions associated with GdCAs or of a difference in the rate of ADRs with a fatal outcome across the class.

## **Future studies**

PRAC considered potential studies to be conducted in order to fully address the serious concerns of plausible neurological effects, and adequate toxicity studies and clinical data may be necessary to address this. Results from clinical studies are however considered unlikely to be available in a reasonable timeframe in view of the heterogeneity of the patient population that undergoes MRI and the number of patients needed.

Observational clinical studies will have limitations because methods for measuring adverse cognitive or motor neurological outcomes may not be captured by standard methods, or not be measured routinely, and may neither be reliable nor valid.

Furthermore, interventional clinical studies comparing the different products could be considered unethical.

The design of any future clinical study to investigate the long-term safety of GdCAs in patients would require large numbers of patients to have sufficient power to detect small adverse effects on cognition (cognitive disorders) or physical abilities (fine motor skills). Results from such long-term safety studies are unlikely to be available within reasonable period of time.

## **Risk minimisation measures**

In order to minimise the risk of Gd accumulation in the brain and the potential associated harm in relation to linear GdCAs, PRAC considered options for risk minimisation measures such as warnings in the SmPC, contraindications and other additional risk minimisation measures.

Based on the data available, no specific patient group that would not experience Gd retention in the brain could be identified, as both children and adults are expected to show accumulation of Gd in the brain. Also PRAC was not able to define a safe threshold level for exposure to gadolinium and retention of gadolinium in the brain, or to define a period of time during which a potential adverse effect would have time to manifest.

Therefore, PRAC considered that restriction of the use of linear GdCAs to certain indications or to certain groups of patients would not be justified and would still leave patients exposed to the risk of gadolinium brain accumulation and that risk minimisation measures such as warnings in the SmPC or other contraindications would not limit the exposure to linear GdCAs as no safe level of gadolinium brain accumulation has been established.

PRAC also considered limiting the number of doses for patients and concluded that there are practical difficulties for limiting the number of doses as it is not possible to ascertain which contrast agent was



previously administered to patients, and it would not be possible to ensure effective restriction of number of doses administered during the lifetime of a patient.

### 3. Expert consultation

An Ad Hoc Expert Group meeting took place on 05 September 2016. A summary of the conclusions is provided below:

There is clear clinical evidence that brain accumulation occurs with linear GdCAs, but the evidence suggests that brain accumulation does not occur for macrocyclic GdCAs. The difference in deposition between linear and macrocyclic agents is likely linked to the dissociation constants of the complexes in the tissue environment, which are higher for linear agents.

Macrocyclic GdCAs are suitable for nearly all clinical settings, with the exception of liver imaging for which Multihance (gadobenic acid) and Primovist (gadoxetic acid) are specifically indicated. In a post meeting note an expert mentioned a study which showed better morphologic delineation of brain tumours at the same full dose administered of the linear agent gadobenic acid (Multihance) compared with the macrocyclic agent gadoteric acid (Dotarem) and non-inferiority of half dose gadobenic acid compared with full dose gadoteric acid (Dotarem) (Vaneckova et al. 2015).

An increase in T1-weighted signal intensity has been observed following the use of linear agents in subsequent unenhanced scans. This enhancement will impact on the interpretation of future scans and may lead to misdiagnosis. It was noted that such an impact will have been particularly important for patients treated in the past when brain accumulation with the linear agents was not recognised.

The Expert Group considered that fine motor skills and neurocognitive function were areas of possible adverse effects relating to brain accumulation. The Expert Group was not able to advise on the likelihood of adverse outcomes based on current data, although the group considered harmful effects to be plausible.

The issue of heating of gadolinium in brain tissue in a high strength magnetic field was considered easily amenable to experimental investigation but it was not considered to be of importance.

The particular risk groups raised as a concern for brain accumulation were: Any patient group undergoing repeated scans (breast cancer surveillance, inflammatory bowel disease etc.); children; those with inflammatory and/or demyelinating brain diseases. Use in pregnancy and renal impairment already carry warnings but these groups were also mentioned.

The advice from the Expert Group in terms of minimising the risk from brain accumulation is not to use the linear agents (with the exception of Primovist (gadoxetic acid) for liver scans). Risk minimisation in the product information such as a recommendation to use GdCAs only when clearly needed was also considered potentially useful. The expert group did not consider that there was evidence to support the use of reduced doses of macrocyclic GdCAs in particular clinical situations, such as the use of higher strength magnetic fields.

Further clinical research could perhaps take place in breast screening patients, as these patients have many exposures over years and their data are likely to be captured in databases allowing longer term follow up. These patients also in general have brain pathologies that could complicate the assessment of potential adverse effects. Use of registries might also be helpful. Further non-clinical research should look at juvenile animals and mechanisms of brain deposition.

## 4. Benefit-risk balance (initial referral procedure)

### 4.1. Benefit-risk balance assessment

#### 4.1.1. Gadoteridol

Gadoteridol is indicated for MR imaging of the whole body, and its indication statement specifically mentions brain, spine head, neck, liver, breast, musculoskeletal system MRI. The data considered in this referral procedure do not call its efficacy into question and there are no significant uncertainties about the clinical benefits of gadoteridol in its authorised indications.

In relation to NSF the SmPC for gadoteridol includes a warning that gadoteridol should only be used in patients with severe renal impairment ( $GFR < 30 \text{ ml/min/1.73m}^2$ ) 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.

In terms of clinical data on gadolinium accumulation in the brain, a single study evaluated MRI data from patients exposed to gadoteridol, and did not find an association between gadoteridol and increases in signal intensity in the brain. Non-clinical and clinical studies have reported that gadolinium can be detected in brain tissue after exposure to gadoteridol. Published non-clinical data suggest that for macrocyclic GdCAs such as gadoteridol this gadolinium remains bound to the chelating ligand. This is consistent with what is known about the stability of gadoteridol. Based on these data there are no significant concerns in terms of harmful effects of accumulation gadolinium in the brain for gadoteridol.

With regards to hypersensitivity reactions the SmPC includes appropriate warnings and risk minimisation measures.

In view of the above, the benefit-risk balance of gadoteridol is considered to be positive subject to the agreed changes to the product information.

#### 4.1.2. Gadobutrol

Gadobutrol is indicated for MR imaging of the whole body, and its indication statement specifically mentions cranial and spinal, head and neck, breast, abdomen (pancreas, liver and spleen), pelvis (prostate, bladder and uterus) kidney, musculoskeletal MRI, and angiography cardiac MRI. The data considered in this referral procedure do not call its efficacy into question and there are no significant uncertainties about the clinical benefits of gadobutrol in its authorised indications.

In relation to NSF, the SPC includes a warning that gadobutrol should only be used in patients with severe renal impairment ( $GFR < 30 \text{ ml/min/1.73m}^2$ ) 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.

In terms of clinical data on gadolinium accumulation in the brain, five studies evaluated MRI data from patients exposed to gadobutrol, and did not find an association between gadobutrol and increases in signal intensity in the brain. One study reported an association but the correlation between number of doses of gadobutrol and increase in signal intensity was low and no visible hyperintensity was shown in MR images. A fifth study reported a "borderline association" in the multivariate regression analysis, but the patients in this study also received a linear agent and this an association was not presented as occurring in an analysis of patients only exposed to macrocyclic GdCAs. Non-clinical and clinical studies have reported that gadolinium can be detected in brain tissue after exposure to gadobutrol. Published

non-clinical data suggest that for macrocyclic GdCAs such as gadobutrol this gadolinium remains bound to the chelating ligand. This is consistent with what is known about the stability of gadobutrol. Based on these data there are no significant concerns in terms of harmful effects of accumulation of gadolinium in the brain for gadobutrol.

With regards to hypersensitivity reactions the SmPC includes appropriate warnings and risk minimisation measures.

In view of the above, the benefit-risk balance of gadobutrol is considered to be positive subject to the agreed changes to the product information.

#### **4.1.3. Gadoteric acid**

Gadoteric acid is indicated for MR imaging of the whole body, and its indication statement specifically mentions central nervous system MRI and MR angiography. An intra-articular gadoteric acid product (Artirem) is indicated for MR arthrography. The data considered in this referral procedure do not call its efficacy into question and there are no significant uncertainties about the clinical benefits of gadoteric acid in its authorised indications.

In relation to NSF the SPC includes a warning that gadoteric acid should only be used in patients with severe renal impairment ( $\text{GFR} < 30 \text{ ml/min/1.73m}^2$ ) 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.

In terms of clinical data on gadolinium accumulation in the brain, three studies evaluated MRI data from patients exposed to gadoteric acid, and did not find an association between gadoteric acid and increases in signal intensity in the brain. One other study reported a "borderline association" in the multivariate regression analysis, but the patients in this study appear to have also received a linear agent and this association was not presented as occurring in an analysis of patients only exposed to the macrocyclic GdCAs. Non-clinical and clinical studies have reported that gadolinium can be detected in brain tissue after exposure to gadoteric acid. Published non-clinical data suggest that for macrocyclic GdCAs such as gadoteric acid this gadolinium remains bound to the chelating ligand. This is consistent with what is known about the stability of gadoteric acid. Based on these data there are no significant concerns in terms of harmful effects of accumulation of gadolinium in the brain for gadoteric acid.

With regards to hypersensitivity reactions, the SmPC includes appropriate warnings and risk minimisation measures.

In view of the above, the benefit-risk balance of intravenous gadoteric acid is considered to be positive subject to the agreed changes to the product information.

The intra-articular gadoteric acid product (Artirem) contains a concentration of gadolinium that is approximately 200-fold lower than doses used with the intravenous product. Patients usually undergo one exposure, although if multiple joints are affected, then a patient may receive up to 6 injections of an intra-articular GdCA.

In view of the above, the benefit-risk balance of gadoteric acid is considered to be positive subject to the agreed changes to the product information.

#### 4.1.4. Gadopentetic acid

Gadopentetic acid is indicated for MR imaging of the whole body, and its indication statement specifically mentions cranial and spinal MRI. The data considered in this referral procedure do not call its efficacy into question and there are no significant uncertainties about the clinical benefits of gadopentetic acid in its authorised indications.

In relation to NSF the SPC includes contraindications against the use of gadopentetic acid in patients with severe renal impairment (GFR <30 ml/min/1.73m<sup>2</sup>) and/or acute kidney injury, in patients in the perioperative liver transplantation period and in neonates up to 4 weeks of age. Gadopentetic acid should only be used after careful risk-benefit evaluation in patients with moderate renal impairment (GFR 30-59 ml/min/1.73 m<sup>2</sup>). These risk minimisation measures were introduced in the EU in 2010, and since that time there have not been any new confirmed cases of NSF. However, it is important to note that monitoring of NSF is based on spontaneous ADRs and literature case reports

In terms of clinical gadolinium accumulation in the brain, there are 12 published studies have evaluated MRI data including cohorts of patients exposed only to gadopentetic acid, and all these studies reported an association between gadopentetic acid and increases in signal intensity in the brain. A number of other studies reported signal intensity increase in patients exposed to linear GdCAs including gadopentetic acid, but where not all the patients were exposed to gadopentetic acid only.

Non-clinical and clinical studies have reported that gadolinium can be detected in brain tissue after exposure to gadopentetic acid. Published non-clinical data suggest that for linear GdCAs such as gadopentetic acid gadolinium has been released from the chelating ligand molecule and has become bound to macromolecules. This is consistent with what is known about the stability of gadopentetic acid.

In addition to accumulation of gadolinium in the brain, data from non-clinical and clinical studies and case reports have reported the accumulation of gadolinium in other tissues, including the liver, kidney, muscle, skin and bone. There is evidence of this accumulation in other organs and tissues for linear agents. For example, gadolinium was detected in organs and tissues including the liver, kidney, muscle, skin and bone post-mortem in a patient who had NSF after repeated exposures to gadodiamide (Omniscan) (Sanyal et al. 2011), and high levels of gadolinium have been reported in the skin of a patient with normal renal function who did not have NSF but did have joint contractures with an unknown cause after exposure to multiple contrast agents, potentially including gadobenic acid (Multihance), gadopentetic acid (Magnevist), gadodiamide (Omniscan), and (gadoteridol) Prohance (Roberts et al. 2016).

With regards to hypersensitivity reactions, there is a trend in some studies for a lower rate of hypersensitivity reactions with gadopentetic acid than with other GdCAs, however there are important limitations to these studies. PRAC considered the SmPC includes appropriate warnings and risk minimisation measures.

In view of the above, taking into account the serious concerns about the potential neurological harm and the already identified risks associated with the use of linear GdCAs (including the significant risk of NSF and the gadolinium-associated plaques), the PRAC considered that the benefit in enhancement of MR images does not outweigh the known and potential risks of intravenous gadopentetic acid products in their indications.

The intra-articular gadopentetic acid product, which is used only for contrast enhancement in direct magnetic resonance arthrography, contains a concentration of gadolinium that is approximately 200-fold lower than doses used with the intravenous product. Patients usually undergo one exposure. In

view of the very low exposure, the benefit-risk balance of intra-articular gadopentetic acid containing products is considered to be positive.

#### 4.1.5. Gadodiamide

Gadodiamide is indicated for general MRI of the body, and its indication statement specifically mentions cranial and spinal MRI and evaluation of coronary artery disease by myocardial perfusion imaging. The data considered in this referral procedure do not call its efficacy into question. The MAH has presented a claim that gadodiamide (Omniscan) has a unique indication in myocardial perfusion imaging. PRAC considered that the whole body MRI encompasses imaging of the heart, including myocardial perfusion imaging.

In relation to NSF the SPC includes contraindications against the use of gadodiamide in patients with severe renal impairment (GFR <30 ml/min/1.73m<sup>2</sup>) and/or acute kidney injury, in patients in the perioperative liver transplantation period and in neonates up to 4 weeks of age. Gadodiamide should only be used after careful risk-benefit evaluation in patients with moderate renal impairment (GFR 30-59 ml/min/1.73 m<sup>2</sup>). These risk minimisation measures were introduced in the EU in 2010, and since that time there have not been any new confirmed cases of NSF. However, it is important to note that monitoring of NSF is based on spontaneous ADRs and literature case reports.

In terms of gadolinium accumulation in the brain, 6 published studies have evaluated MRI data from patients exposed to gadodiamide. All these studies reported an association between gadodiamide and increases in signal intensity in the brain. A number of other studies reported signal intensity increase in patients exposed to linear GdCAs including gadodiamide, but where not all the patients were exposed to gadodiamide only. Non-clinical and clinical studies have reported that gadolinium can be detected in brain tissue after exposure to gadodiamide. Published non-clinical data suggest that for linear GdCAs such as gadodiamide gadolinium has been released from the chelating ligand molecule and has become bound to macromolecules. This is consistent with what is known about the stability of gadodiamide.

In addition to accumulation of gadolinium in the brain, data from non-clinical and clinical studies and case reports have reported the accumulation of gadolinium in other tissues, including the liver, kidney, muscle, skin and bone. There is evidence of this accumulation in other organs and tissues for linear agents. For example, gadolinium was detected in organs and tissues including the liver, kidney, muscle, skin and bone post-mortem in a patient who had NSF after repeated exposures to gadodiamide (Omniscan) (Sanyal et al. 2011), and high levels of gadolinium have been reported in the skin of a patient with normal renal function who did not have NSF but did have joint contractures with an unknown cause after exposure to multiple contrast agents, potentially including gadobenic acid (Multihance), gadopentetic acid (Magnevist), gadodiamide (Omniscan), and (gadoteridol) Prohance (Roberts et al. 2016).

With regards to hypersensitivity reactions, the SmPC includes appropriate warnings and risk minimisation measures.

In view of the above, taking into account the serious concerns about the potential neurological harm and the already identified risks associated with the use of linear GdCAs (including the significant risk of NSF and the gadolinium-associated plaques), the PRAC considered that the benefit in enhancement of MR does not outweigh the known and potential risks of Gadodiamide containing products.

#### 4.1.6. Gadoversetamide

Gadoversetamide is indicated for MRI of the central nervous system and liver. The data considered in this referral procedure do not call its efficacy into question and there are no significant uncertainties about the clinical benefits of gadoversetamide in its authorised indications.

In relation to NSF SPC includes contraindications against the use of gadoversetamide in patients with severe renal impairment (GFR <30 ml/min/1.73m<sup>2</sup>) and/or acute kidney injury, in patients in the perioperative liver transplantation period and in neonates up to 4 weeks of age. Gadoversetamide should only be used after careful risk-benefit evaluation in patients with moderate renal impairment (GFR 30-59 ml/min/1.73 m<sup>2</sup>). These risk minimisation measures were introduced in the EU in 2010, and since that time there have not been any new confirmed cases of NSF. However, it is important to note that monitoring of NSF is based on spontaneous ADRs and literature case reports.

In terms of gadolinium accumulation in the brain, there are limited data for gadoversetamide. None of the clinical studies of MRI data reported results for gadoversetamide. Published non-clinical data suggest that for linear GdCAs such as gadoversetamide gadolinium has been released from the chelating ligand molecule and has become bound to macromolecules. This is consistent with what is known about the stability of gadoversetamide.

In addition to accumulation of gadolinium in the brain, data from non-clinical and clinical studies and case reports have reported the accumulation of gadolinium in other tissues, including the liver, kidney, muscle, skin and bone. There is evidence of this accumulation in other organs and tissues for linear agents. For example, gadolinium was detected in organs and tissues including the liver, kidney, muscle, skin and bone post-mortem in a patient who had NSF after repeated exposures to gadodiamide (Omniscan) (Sanyal et al. 2011), and high levels of gadolinium have been reported in the skin of a patient with normal renal function who did not have NSF but did have joint contractures with an unknown cause after exposure to multiple contrast agents, potentially including gadobenic acid (Multihance), gadopentetic acid (Magnevist), gadodiamide (Omniscan), and (gadoteridol) Prohance (Roberts et al. 2016).

With regards to hypersensitivity reactions, the SmPC includes appropriate warnings and risk minimisation measures.

In view of the above, taking into account the serious concerns about the potential neurological harm and the already identified risks associated with the use of linear GdCAs (including the significant risk of NSF and the gadolinium-associated plaques), the PRAC considered that the benefit in enhancement of MR does not outweigh the known and potential risks of gadoversetamide containing products.

#### 4.1.7. Gadoxetic acid

Gadoxetic acid is indicated for MRI of the liver. The data considered in this referral procedure do not call its efficacy into question and there are no significant uncertainties about the clinical benefits of gadoxetic acid in its authorised indications.

Gadoxetic acid has a substantial liver uptake, is administered at a low dose (0.025 mmol/kg of body weight) and has a short time to delayed phase scanning (20 mins). It has shown clinical utility in imaging of the liver. Therefore, it is considered that gadoxetic acid brings an additional benefit to patient management with an exposure to gadolinium that is minimised by the low dose administered, the very significant hepatic uptake and the short time to the delayed phase scanning.

In relation to NSF the SPC includes a warning that use of gadoxetic acid should 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. These risk minimisation measures were introduced in the EU in 2010, and since that time there have not been any new confirmed cases of NSF, however it is important to note that monitoring of NSF is based on spontaneous ADRs and literature case reports.

In terms of gadolinium accumulation in the brain, there are limited data for gadoxetic acid. One study reported signal intensity increases in the dentate nucleus in a subgroup of patients who received more than 10 exposures to gadoxetic acid. The effect appeared to be dose-related and no statistically significant increase was detected in the patients with fewer than 10 exposures. Another study reported no signal intensity increases in the DN-to-pons ratio in patients with either 5 or more or 1 exposure to gadoxetic acid. The lower total gadolinium content per dose of gadoxetic acid may have influenced the results.

*In vitro* data suggest potentially less release of gadolinium from the ligand molecules for Primovist (gadoxetic acid) than for other linear GdCAs when incubated in human serum (Frenzel et al. 2008), which is another factor which may have influenced these results. Published non-clinical data suggest that for linear GdCAs such as gadoxetic acid gadolinium has been released from the chelating ligand molecule and has become bound to macromolecules. This is consistent with what is known about the stability of gadoxetic acid.

In addition to accumulation of gadolinium in the brain, data from non-clinical and clinical studies and case reports have reported the accumulation of gadolinium in other tissues, including the liver, kidney, muscle, skin and bone. There is evidence of this accumulation in other organs and tissues for linear agents. For example, gadolinium was detected in organs and tissues including the liver, kidney, muscle, skin and bone post-mortem in a patient who had NSF after repeated exposures to gadodiamide (Omniscan) (Sanyal et al. 2011), and high levels of gadolinium have been reported in the skin of a patient with normal renal function who did not have NSF but did have joint contractures with an unknown cause after exposure to multiple contrast agents, potentially including gadobenic acid (Multihance), gadopentetic acid (Magnevist), gadodiamide (Omniscan), and (gadoteridol) Prohance (Roberts et al. 2016).

For the linear agent gadoxetic acid that has shown clinical utility in liver imaging, in view of its substantial liver uptake, its administration at a low dose (0.025 mmol/kg of body weight) and the short time to the delayed phase scanning (20 mins), the PRAC considered that it provides an additional benefit to patient management with an exposure to gadolinium that is minimised by the low dose administered and the short time to the delayed phase. Therefore the benefit of gadoxetic acid outweighs its risk.

#### **4.1.8. Gadobenic acid**

Gadobenic acid is indicated for MRI of the whole body MRI, and its indication statement specifically mentions liver, brain and spine, and breast MRI, magnetic resonance angiography (including all arterial territories, supra-aortic and coronary arteries included), and cardiac MRI (including measurement of myocardial perfusion).

Gadobenic acid is in the medium risk category for risk of NSF. The SPC includes a warning that use of gadobenic acid should 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. These risk minimisation measures were introduced in the EU in 2010, and since that time there have not been any new confirmed cases of NSF, it is important to note that monitoring of NSF is based on spontaneous ADRs and literature case reports.



In terms of gadolinium accumulation in the brain, 5 published studies have evaluated MRI data from patients exposed to gadobenic acid. Four of these studies reported an association between exposure to gadobenic acid and increases in signal hyperintensity in the brain. It should be noted that one of these studies reported progressive signal intensity increases with multiple exposures to gadobenic acid in patients with prior gadodiamide exposure, and not in those without prior gadodiamide exposure. There was also one study which did not report a statistically significant association between exposure to gadobenic acid and increases in brain signal hyperintensity, although this study did report a trend for an increase which did not reach statistical significance ( $p = 0.13$ ). Preliminary non-clinical data suggest that for linear GdCAs such as gadobenic acid gadolinium has been released from the chelating ligand molecule and has become bound to macromolecules. This is consistent with what is known about the thermodynamic stability of gadobenic acid.

In addition to accumulation of gadolinium in the brain, data from non-clinical and clinical studies and case reports have reported the accumulation of gadolinium in other tissues, including the liver, kidney, muscle, skin and bone. There is evidence of this accumulation in other organs and tissues for linear agents. For example, gadolinium was detected in organs and tissues including the liver, kidney, muscle, skin and bone post-mortem in a patient who had NSF after repeated exposures to gadodiamide (Omniscan) (Sanyal et al. 2011), and high levels of gadolinium have been reported in the skin of a patient with normal renal function who did not have NSF but did have joint contractures with an unknown cause after exposure to multiple contrast agents, potentially including gadobenic acid (Multihance), gadopentetic acid (Magnevist), gadodiamide (Omniscan), and (gadoteridol) Prohance (Roberts et al. 2016a).

With regards to hypersensitivity reactions, the SmPC includes appropriate warnings and risk minimisation measures.

For gadobenic acid, the available studies do not establish differences in relaxivity, image quality and technical performance. Gadobenic acid undergoes hepatic uptake. However, in view of the extent of the hepatic uptake, the high dose (0.05 mmol/kg body weight) required and the long time to the onset of delayed phase imaging (40 mins), the PRAC considered that the benefit of gadobenic acid containing products in all the authorised indication including the liver imaging does not outweigh the potential and identified risks associated to the use of this product.

## **4.2. Benefit risk conclusions ( initial referral procedure)**

### *Linear Gadolinium-containing contrast agents (GdCAs)*

In view of (a) the evidence suggesting that linear GdCAs release Gd from their chelating ligand molecules due to the low kinetic and thermodynamic stability; (b) the known toxicity of unchelated gadolinium; (c) the data supporting the ability of linear GdCAs to distribute and accumulate in the brain; (d) the fact that linear agents are retained and persist for up to one year or longer in the brain; and (e) the deposition in other tissues with related harm; PRAC considered that there are reasonable and serious concerns raised as to the potential of neurological harm associated with the accumulation of gadolinium in the brain. In view of the affected brain areas (including DN and GP), potential neurological effects would include effects on fine motor skills or cognitive impairment, particularly in patients with ongoing neurological disease which may mask these events.

In order to address the serious concerns of the potential neurological effects, PRAC considered the feasibility of clinical safety studies, both observational and interventional, and concluded that these would not be feasible within a reasonable period of time.

Furthermore, as no specific patient group with less risk of accumulation in the brain or a safe threshold level for retention in the brain could be identified, the restriction of the use of linear GdCAs to certain indications or certain groups of patients was considered not appropriate. Also the restriction of the number of doses administered during the lifetime of a patient raises practical difficulties and therefore would not be effective.

Therefore, taking into account the serious concerns about the potential neurological harm and the already identified risks associated with the use of linear GdCAs (including the significant risk of NSF and the gadolinium-associated plaques), the PRAC considered that the benefit in enhancement of MR images does not outweigh the known and potential risks of these products.

PRAC also considered the two linear GdCAs, gadoxetic acid and gadobenic acid in the liver imaging indication. These products have an uptake by hepatocytes and can provide in addition to the dynamic phase imaging a delayed phase imaging for highly vascularised hepatic lesions and to detect lesions that are visible only in the delayed phase.

For gadobenic acid, the available studies do not establish differences in relaxivity, image quality and technical performance. Gadobenic acid undergoes hepatic uptake. However, in view of the extent of the hepatic uptake, the high dose (0.05 mmol/kg body weight) required and the long time to the onset of delayed phase imaging (40 mins), the PRAC considered that the benefit of gadobenic acid containing products in all the authorised indication including the liver imaging does not outweigh the potential and identified risks associated to the use of this product.

For the linear agent gadoxetic acid that has shown clinical utility in liver imaging, in view of its substantial liver uptake, its administration at a low dose (0.025 mmol/kg of body weight) and the short time to the delayed phase scanning (20 mins), the PRAC considered that it provides an additional benefit to patient management with an exposure to gadolinium that is minimised by the low dose administered and the short time to the delayed phase. Therefore the benefit of gadoxetic acid outweighs its risk.

#### *Macrocyclic GdCAs*

Macrocyclic GdCAs have a very low potential for retention of gadolinium in tissues, are very stable and have a low risk of dechelation. While accumulation in terms of T1w signal intensity increases and gadolinium measured in the brain (likely in the form of intact GdCA molecule) has been seen in the short term with these agents, long-term persistence in the brain was not observed. For these products, the PRAC considered that the risk can be managed through restriction of use, in the lowest dose that provides sufficient enhancement for diagnostic purposes and through appropriate warning in the product information in order to minimise the potential for accumulation of gadolinium in the brain and other organs and tissues.

In addition, macrocyclic agents are associated with a low risk of NSF.

In view of the above, the PRAC considered that the benefits of macrocyclic agents outweigh their risks.

#### *Intra-articular GdCA products*

Intra-articular products containing gadopentetic acid and gadoteric acid are administered at very low doses and present a low risk of tissue accumulation. In addition, the repeated use of these products is most unlikely. Therefore, the PRAC considered that the benefits of these products outweigh their risks.

### **4.3. Re-examination procedure**

Following the adoption of the PRAC recommendation in March 2017, a re-examination request was received from two of the MAHs involved in the procedure, Bracco and GE Healthcare on 14 and 16 May 2017, respectively.

The MAHs grounds for re-examination were received by 15 May 2017.

In their grounds for re-examination, the MAHs considered that the proposed suspension for linear agents, including their products Omniscan and Multihance would be disproportionate, discriminatory and inconsistent with prior EMA actions. In addition, the MAHs provided further justifications supporting a positive benefit risk balance of their linear GdCAs Omniscan and Multihance.

The MAHs also expressed concerns over some legal aspects related to this the referral procedure. It is noted that PRAC is a scientific committee and that while it operates within the framework of the Union legislation regulating medicinal products, it cannot discuss the specific merits of procedural and legal aspects of administrative procedures laid down in the legislation. As a result, procedural and legal considerations are outside the remit of PRAC, and therefore the re-examination of the referral procedure under Article 31 of Directive 2001/83/EC focuses only on the scientific grounds for re-examination.

#### **4.3.1. Detailed grounds for re-examination submitted by the MAHs**

##### **Bracco**

The grounds for re-examination of the PRAC recommendation are summarised below:

- Regulatory inconsistencies

In view of claimed regulatory inconsistencies, Bracco refers particularly to the approval of a type II variation (UK/H/0234/001-002/11/038) to include new indications for MultiHance including for the paediatric population above 2 years of age. The procedure was finalised during the course of this Article 31 referral procedure and concluded that the benefit-risk balance of MultiHance was positive in all new indications, including whole body MRI.

Bracco claims that therefore the PRAC recommendation of 9 March 2017 is inconsistent with the regulatory actions and positions taken in the preceding time period (mainly the extension of indication) and not supported by evidence.

- Inconsistencies and inaccuracies in the assessment of scientific information

##### *Diagnostic efficacy aspects*

Bracco claimed inconsistency in the evaluation of validity of endpoints between the PRAC and a NCA, as the nationally approved Type II variation, which describes a higher performance of Multihance based upon study endpoints, has been challenged during the ongoing referral procedure, which has an impact on the benefit-risk evaluation.

Furthermore, Bracco commented on differences in posology between Multihance and doses recommended for other gadolinium-containing products.

##### *Safety aspects*

Additionally, Bracco claimed inconsistencies in the assessment of benefit/risk balance of Primovist and Multihance for the liver indication in particular with regards to the use of Multihance in children and the lower risk of cardiovascular adverse events.

Bracco further highlighted inconsistencies in the assessment of benefit and risk aspects and criticized the approach of grouping of GdCAs in stability classes.

In view of toxicity aspects Bracco challenged PRAC's assessment of neurotoxicity, which focused mainly on gadolinium released from GdCAs.

In terms of clinical aspects, Bracco challenged the PRAC's assessment of the relaxivity of Multihance with regard to its clinical utility as a general-purpose agent in terms of its use in CNS, breast, angiography and liver imaging.

In view of risk related aspects, Bracco claimed inconsistencies in the approach taken for the risk minimisation of the NSF risk whereby the GdCA products were classified according to their related NSF risk and the approach for the potential risk related to the Gd accumulation in the brain; Bracco provided further justification to support a favourable risk profile based on the available data related to the Gd accumulation in the brain.

Bracco did not agree that linear GdCAs cause more marked Gd retention in brain tissues compared to macrocyclic GdCAs, and that Gd complexes retained following injection of macrocyclic GdCAs seem to be cleared from brain tissues more efficiently than following injection of linear GdCAs.

- Incorrect application of the Precautionary Principle

Bracco stated that the precautionary principle was incorrectly applied, as the recommended suspension of the marketing authorisation of Multihance does not comply with the requirements of precautionary measures in terms of proportionality (i.e. tailored to a reasonable level of protection), non-discrimination and consistency with previous similar decisions.

- Disproportionate nature of the recommendations made by the PRAC

The MAH claimed that the recommendation of suspending the marketing authorisation of Multihance is solely based on the assumption that available non-clinical data on the accumulation of Gd are predictive of greater level and long-term retention of the metal in brain tissue in humans, and that the risk of adverse neurological effects is "plausible". However, there is no scientific evidence to support this hypothesis.

In the view of Bracco, a violation of the principle of proportionality is apparent as less onerous and restrictive measures exist and would allow PRAC to minimise the alleged risks associated with the use of the product ensuring, at the same time, that the disadvantages caused by such measures (chiefly, to patients and physicians) would not be beyond what is necessary to attain that risk minimisation objective.

- Failure to consider alternative measures adequate to mitigate risk.

Bracco also claimed that PRAC has not appropriately considered alternative measures adequate to mitigate risk in line with those proposed by the MAH during the procedure e.g.:

- To update the SmPC to make the physician utilising the product aware and to reduce exposure;
- To extend the posology to lower doses in specific applications and clinical settings where the advances in technology have shown that to be appropriate;
- To provide information about changes to the SmPC to healthcare professionals;
- Evidence-based educational programs aimed at providing healthcare professionals.

## GE Healthcare

The grounds for re-examination of the PRAC recommendation are summarised below:

- Failure to apply appropriate scientific standards to this assessment resulting in inappropriate conclusions and recommendations.

GE Healthcare claimed that based on peer reviewed literature, macrocyclic agents do accumulate in the brain following multiple administrations, as do linear agents. Therefore, in view of data that shows no evidence of clinical harm, there would be no scientific basis for proposing suspension for Omniscan unless macrocyclic agents would also be suspended.

Furthermore, GE Healthcare claimed that the Omniscan's myocardial perfusion indication and the consequences of hypersensitivity reactions related to GdCA products were not adequately taken into account in the benefit-risk assessment.

GE Healthcare also claimed that the assessment contained selective use or interpretation of data.

- Inadequate weight given to relevant pre-clinical, prospective clinical and post-market surveillance data relevant to the risk-benefit balance assessment for GdCAs

GE Healthcare claimed that the notion that macrocyclic GdCA products do not accumulate in brain tissue after administration or that they are eliminated quickly is refuted by multiple independent investigations and clinical observations, and therefore has no basis. GE Healthcare supports their position with the analysis of the Mayo Clinic Study of Ageing (McDonald et al. 2017, manuscript in preparation).

- The suspension recommendation is disproportionate given that there are alternative risk minimization measures that would address the theoretical risks of brain gadolinium.

GE Healthcare claimed that making fine distinctions on the value and risk-benefit between individual agents stands on weak foundations, since the process appears to have systematically ignored key data and stated that the PRAC assessment has been selective in their use and interpretation.

Considering an increasing evidence base that demonstrates the absence of tissue toxicity or clinical harm in the short, medium or long term post-exposure, GE Healthcare believes that other measures than suspension would be adequate to reduce exposure to Omniscan and allow emerging data to further inform the benefit- risk assessment.

- Failure to appropriately balance all Omniscan's risks and benefits.

GE Healthcare claimed that PRAC failed to consider extensive scientific evidence about Omniscan's myocardial perfusion indication and about the lower rates of hypersensitivity reactions with Omniscan and other linear agents compared to macrocyclic agents.

- Incorrect application of the precautionary principle

According to GE Healthcare, the PRAC assessment report makes clear that the proposal to suspend the Omniscan marketing authorisation is being taken on a precautionary basis because there are no identified risks associated with Gd in the brain. GE Healthcare also claims that in this case the precautionary measures appear to be based on "purely hypothetical considerations", especially in view of the aspects related to the NSF risk, which has been assessed in the previous referral. Furthermore, as the detection of Gd in the brain is observed with all GdCAs, i.e., both linear and macrocyclic agents, albeit detected levels are higher for linear agents in animal studies, GE Healthcare claims that Gd brain accumulation is not unique to the linear subclass of GdCAs.

### 4.3.2. PRAC discussion on grounds for re-examination

PRAC considered the detailed grounds as submitted by the MAHs within this re-examination procedure and the scientific data underlying these grounds.

#### *Accumulation of Gd in the brain*

With regards to the claim that virtually no Gd becomes liberated from gadodiamide in the body, PRAC noted that at 37°C in human serum Gd rapidly dissociates from its chelator in vitro (Frenzel et al. 2008) PRAC considered that it is highly unlikely that the release of Gd from gadodiamide is slower in vivo than in vitro. A higher in vivo than in vitro stability would require the occurrence of stabilising agents in vivo, but no conclusive evidence confirming increases of the stability of the Gd complex in the body has been provided by the MAH.

Many preparations especially of linear Gd-based contrast agents contain free chelator in surplus in order to rapidly catch liberated Gd. This clearly indicates that potential dechelation in the body is a recognised phenomenon. Spontaneous release of Gd from its chelator, competition of Gd with other metals (e.g. in metal rich areas of the brain), and competition of the chelator with other chelators (e.g. macromolecules) can occur in the body. Particularly zinc, copper and iron (Frenzel et al., 2008) are described as competing metals which can liberate Gd; glycosaminoglycans like heparin may bind Gd and thereby remove it from its pharmacological chelator. These effects can be mimicked in vitro and will further diminish the stability of the GdCA complex in vivo.

Regarding the validity of an ex-vivo distribution study by Frenzel et al (2017), PRAC acknowledged the study does not contribute to the understanding in which form exactly Gd-based contrast agents are stored in the body, however PRAC considered that the study confirms, in line with other studies, that linear chelators lead to a higher amount of stored Gd and that there is a difference between linear and macrocyclic chelators in respect to binding to insoluble macromolecules. Thus, rather weak binding of linear chelators to Gd becomes obvious in various experiments (including Port et al 2009, Sieber et al 2008), and this makes it unlikely that the complex is fully stable in vivo.

With regards to the MAH's claim that linear GdCAs do not cause more marked Gd retention and do not have a slower release from brain tissues compared to macrocyclic GdCAs, PRAC considered that the study of McDonald et al. (2017), confirming T1 hyperintensity in the rat lateral dentate nucleus 1 week after administration of macrocyclic agents (Gadovist and Prohance), has several shortcomings:

- Only a small signal was detected in a brain region which McDonald et al. assumed to be the dentate nucleus (DN), but this assignment is not convincing when regarding the figures shown.
- The shape and size of the T1 signal is markedly different from the signal shape reported in two other recent publications, (Jost et al., 2016, and Robert et al., 2015) and it is not fully clear whether the region of enhanced signal indeed corresponds to the DN, or other regions in the brain.
- Gd retention was studied rather early (one week) after cessation of treatment so that detected Gd may not represent the long-term storage form. Smith et al. 2017 described that stored Gd still decreases after one week so that obviously a transiently stored pool exists which is different from the material that persists long-term.
- The rather high and particularly highly variable Gd tissue level in saline control animals. All animals should have had water from the same source

- Furthermore, dense deposits in various tissues were detected after GdCA administration by TEM which were regarded as Gd deposits. It is not fully clear how reliable the method of Gd quantification in tissue was.
- High Gd levels with high inter-individual variability were detected in saline-treated controls. The authors could not provide a sound explanation for this. It should be noted that McDonald et al. (2017) reported very little Gd deposition. However, they described the electron microscopic (TEM) finding of electron-dense lumps in the tissues of ProHance-treated animals which at first were assumed to be Gd deposits, obviously because they looked like them. Nevertheless, further analysis did not reveal Gd in them so that a low tissue Gd level was assumed, and it was not questioned what otherwise these dense structures could be. Furthermore, the standard deviation of Gd content in the brain was extraordinary high for Gadovist. These observations leave the possibility that the method used for the Gd determination is unreliable under certain circumstances.

With these uncertainties, conclusions on different or similar behaviour of the different contrast agents studied by McDonald et al. are not possible

The PRAC also noted that high GdCAs doses were tested (20x 2.5 mmol) by McDonald et al., and the study duration is comparably short (e.g. the total doses tested in Frenzel et al 2017 was half that of McDonald et al (10x 2.5mmol), while the time period to the last tissue sampling in Frenzel et al 2017 was 24 days instead of 7 days in McDonald 2017.)

Thus, PRAC considered that the McDonald study did not change their previous conclusions and noted that this view is also supported by the ad-hoc expert group held on the 19th of June.

In addition, low concentrations of linear gadolinium agents as well as macrocyclic agents were detected in non-clinical and clinical studies via mass spectrometry. In non-clinical studies (Robert et al. 2016 Lohrke et al. 2015; Lohrke et al. 2016; Kartamihardja et al. 2016a; Kartamihardja et al. 2016b; Smith et al. 2017; Rasschaert et al. 2016; MAH unpublished studies) the levels were typically around 10-fold higher with linear agents.

Data from the clinical post-mortem studies are heterogeneous and it is therefore difficult to compare the levels. However, these data should be considered in the context of the non-clinical studies showing higher levels of gadolinium in brain tissue after exposure to linear GdCAs, compared with exposure to macrocyclic GdCAs. Non-clinical evidence also shows potential for release of gadolinium from the chelating ligand in the brain with linear GdCAs, but not with macrocyclic GdCAs (Frenzel et al. 2017).

According to the current knowledge about gadolinium deposition in the brain, linear compounds have been detected in the brain at a higher magnitude than the macrocyclic compounds and they appear to be stored there in a form that does not allow an early washout. The linear compounds therefore particularly persist in the brain. The clinical finding, (e.g. Radbruch et al.) that macrocyclic agents do not cause brain T1 hyperintensity was replicated by other groups and can therefore be considered to be substantiated.

In summary, the PRAC considered that there are no new arguments which could convincingly challenge its previous views regarding the dechelation of Gd and hence the low stability of linear GdCA complexes playing a major role for its tissue disposition.



### *Toxicity of accumulation of Gd in the brain*

Toxicity of GdCAs has primarily been attributed to the dissociation of Gd from the chelated complexes. This dissociation is believed to be related to differences in the stability of the complexes among the various types of GdCAs (Spencer et al. 1997). Lanthanide ions such as gadolinium can bind to Ca<sup>2+</sup> binding enzymes and interfere with calcium channels, due to competition with Ca<sup>2+</sup> in cellular and biochemical processes, which can lead to adverse biological effects (Sherry et al. 2009)

With regards to non-clinical studies, unchelated gadolinium in the form of gadolinium chloride has been shown to be toxic with effects including cellular necrosis, fibrosis, and lesions related to mineral deposition (Spencer et al. 1997; Rees et al. 1997), and an in vitro study in rat neurons reported gadolinium-induced cytotoxicity via oxidative injury (Xia et al. 2011).

In view of available observational data which did not confirm a risk related to Gd accumulation in the brain so far, the PRAC considered that:

- the significance of the study by Welk et al. (2016) is limited and results do not indicate an association between exposure to GdCAs and the development of Parkinsonism is premature. However, it demonstrates the complexity and difficulties associated with the objective of analysing potential neurological effects.
- the study results from the Mayo Clinic Study of Ageing (MCSA) study (McDonald et al. 2017, manuscript in preparation), are limited by small sample sizes, relatively short follow-up with regard to potential long-term effects, lack of discussion of sensitivity of the envisaged endpoints regarding detection of potential adverse effects, lack of full detailed information on statistical methods and their robustness and that they are overall too limited to provide reassurance about the safety of usage of GdCAs.

In view of the above, and the claim on the lack of clinical evidence of neurotoxicity due to deposited gadolinium, PRAC considered that while the clinical consequences of gadolinium retention in the brain are currently unknown or remain unclear, absent or limited information from case reports cannot be taken as evidence that such toxicity does not occur.

The regions of the brain with the greatest potential for brain accumulation are the dentate nucleus and globus pallidus. These areas are involved in the regulation of voluntary and involuntary movement; adverse events could potentially include events such as ataxia, tremors and other movement disorders. Adverse effects might be delayed and might be subtle, including effect on fine motor skills or cognitive impairment, particularly in those with ongoing neurological disease.

### *Organ-specific indication for Omniscan*

In view of the claim regarding the cardiac indication of Omniscan, the PRAC highlighted that the primary goal of cardiac perfusion imaging is the detection of myocardial ischemia in patients with suspected coronary artery disease or cardiomyopathy. Perfusion imaging in MRI is typically performed both at rest and during pharmacological stress (for example, with adenosine or dipyridamole), and utilizes a dynamic imaging technique in which signal intensity in the myocardium is evaluated during the passage of the contrast bolus. Cardiac MR including perfusion and delayed enhancement imaging provides relevant information in terms of viable tissue in various cardiovascular disorders needed for work up and management of these diseases.

With regards to the claim that gadodiamide (Omniscan) has a unique indication in myocardial perfusion imaging as it PRAC considered that the whole body MRI indication encompasses imaging of the heart, including myocardial perfusion imaging.

These conclusions are in line with the opinion of the experts expressed at the ad hoc expert meeting, i.e. that linear and macrocyclic agents can be used interchangeably for cardiac imaging and that there is no established or perceived difference in their clinical utility.

#### *Population-specific indication for Multihance*

With regards to the use of Multihance in the paediatric population, it was noted that, while hepatocellular carcinoma as well as metastatic lesions are frequent in the adult population, liver diseases in children are rather diffuse than focal and tumours are rare. The PRAC concluded that based on the available data Multihance can continue to be used in paediatric patients for delayed phase liver imaging.

#### *Higher relaxivity of Multihance*

With regards to the claimed higher relaxivity of Multihance resulting in a better image enhancement and diagnostic performance than other GdCAs, it was noted that higher relaxivity which results in a stronger signal and a brighter image does not automatically translate into differences in diagnostic performance. Therefore, a conclusion that there are significant and clinically relevant differences in diagnostic performance between two GdCAs needs to be supported by robust evidence from clinical studies including evidence on a better clinical outcome and patient management, which is currently lacking; the impact on diagnostic thinking and patient management was not proven.

Indeed, PRAC considered the results of two intra-individual, crossover comparisons of 0.1 mmol/kg body weight with Multihance vs 0.1 mmol/kg body weight of two active comparators (gadopentetate dimeglumine and gadodiamide), in patients with known or suspected brain or spine disease undergoing MRI of the central nervous system (CNS) (MH-109, MH-130) and concluded that the studies were using a blinded comparison of MRI images obtained with two GdCAs side by side and have produced results favouring Multihance on the basis of brighter appearance of the images, but not reflecting any difference in the diagnostic information available or the impact on diagnostic thinking, patient management or clinical outcome. Particularly, it was stated that the influence on patient management was not directly demonstrated by the study results.

In addition, with regards to the SmPCs of macrocyclic GdCAs (Dotarem, Prohance, and Gadovist) recommending higher dose in CNS imaging to improve visualisation and angiography but not in whole body imaging, PRAC considered that clinically relevant differences in diagnostic performance between Multihance and macrocyclic agents need to be supported by robust evidence from comparative clinical studies rather than a comparison of the approved SmPCs, which may have limitations.

With regards to the claim of a lower risk of cardiovascular adverse events for Multihance PRAC considered that nonclinical data as well as available clinical data do not indicate a difference in cardiovascular risk (inducing QT prolongation) within the delayed phase liver imaging agents.

#### *Hypersensitivity*

In view of a potential difference in the frequency of hypersensitivity reactions, PRAC pointed out that these are known infrequent reactions for all GdCAs. Despite worldwide use serious adverse reactions

are rare; urticaria is the most common manifestation. Fatalities are extremely rare. Although in patients with a history of drug allergy the reaction risk might be increased, the risk is still very low. Skin prick testing could facilitate the identification of an alternative GdCA. Premedication with antihistamines and corticosteroids could also be applied. In general, appropriate medications, equipment and staff experienced in the management of hypersensitivity reactions can be expected in any radiological practice.

In view of the claimed differences of hypersensitivity reactions with Omniscan versus other GdCAs based on meta-analyses of available epidemiological data, PRAC considered these differences are too subtle to influence the benefit-risk balance, and that extremely large clinical trials would be necessary to confirm a statistical difference in frequency of hypersensitivity reactions. The experts at the ad-hoc expert meeting shared these same views.

#### *NSF*

With regards to the consideration of the risk of NSF, whilst PRAC relied on the previous assessment and classification of the risk of NSF across the GdCAs products, PRAC considered that the NSF risk contributes to the safety profile of GdCAs and is taken into account to conclude on the whole safety profile of these products and the subsequent impact on their benefit-risk balance.

#### *National assessment*

With regards to the reference to previous assessment conducted at national level (type II variation to extend the indication of Multihance, UK/H/0234/001-002/11/038), it should be noted that the variation application assessment had a different scope than the Article 31 referral procedure and consequently these two procedures are based on a different set of data; therefore a different outcome can be justified. Besides, as the variation was concluded in parallel to the PRAC review, the variation conclusions were understood as being without prejudice of the outcome of the ongoing EU review.

#### ***Clinical studies***

PRAC maintained its view that conducting clinical studies to fully address the potential risk associated with Gd accumulation in the brain would not be feasible within a reasonable period of time. In case such studies were however to be carried out, patients would bear the risks as long as ongoing research is not completed.

#### ***Risk minimisation measures***

The MAHs provided several proposals for risk minimization measures with regards the accumulation and retention of GdCA in the brain of patients exposed to these agents during diagnostic procedures:

- To update the SmPC to make the physician aware of the accumulation in the brain and to reduce exposure and communicate about such update
- To complement the information in the SmPC with evidence-based educational programs
- To extend the posology to lower doses in specific applications and clinical settings where the advances in technology have shown that to be appropriate;

Firstly, PRAC noted that accumulation in the brain is an intrinsic property of intravenous linear GdCAs and therefore, information on brain accumulation in the SmPC will not lead to a reduction of potential

risks associated with this accumulation. Neither would the introduction of educational material address this issue.

In addition, PRAC considered that it is not possible to restrict the use of intravenous linear GdCAs to certain indications or certain groups of patients as:

- No specific patient group with less risk of accumulation in the brain can currently be identified. Hence, the potential risk of brain accumulation and retention in the body tissues cannot be minimised by recommendations to contraindicate use in particular groups (e.g. children, pregnant women, those with renal impairment, other groups) or by avoiding use for particular scans or clinical settings, including repeated use or by restricting re-exposure to certain agents or product classes. The PRAC also noted that in contrast, for NSF a specific patient group (renal insufficiency and patients in the perioperative liver transplantation period) could be identified, and avoidance of use in these populations appears to have minimised the risk of NSF.
- The practical implementation of these measures is moreover not deemed feasible in a clinical setting. There are practical difficulties in clinical daily life for implementing an effective restriction of the number of doses administered during the lifetime of a patient. A restriction by number of doses may not be possible in clinical practice, because previous exposures to GdCAs may not have been recorded sufficiently with regard to the type of GdCA used. Furthermore, the frequency and timing of applications may not be completely recorded in radiologist's patient file/and or accessible to future contacted radiologist or general practitioner, because the patient has changed the radiologist/general practitioner several times due to change of residence or due to other reasons.
- The restriction of the use of linear GdCAs will still leave patients in the remaining population exposed to the risk of harm, without knowing safe threshold level for retention in the brain and other tissues of the body to dechelated gadolinium. Additionally, it is not possible to define a period of time during which no potential adverse effect would have time to manifest.

Therefore, in view of the evidence regarding accumulation of Gd in brain and the plausible harmful effects, and accumulation of Gd in other tissues and the identified related risk, and considering that less restrictive risk minimisation measures are not feasible or not sufficient to bring the risk of accumulation of gadolinium in the brain and other tissues to an acceptable level, PRAC considered the suspension of the marketing authorisation of intravenous linear GdCAs is the most appropriate measure to mitigate the risks related to these products.

### **Expert consultation**

The PRAC considered that a 2nd ad-hoc expert meeting was warranted to address some of the aspects that formed part of the detailed grounds submitted by Bracco and GE Healthcare.

Overall, the experts expressed divergent views concerning the risk minimisation measures.

One group of experts (including the patient representative) supported the PRAC recommendation (i.e. suspension of linear agents besides Primovist and intraarticular Magnevist) and its rationale, with the exception of the suspension of Multihance for liver imaging in absence of macrocyclic agents for this indication and lack of availability of Primovist in one Member State. It was also mentioned that there is currently little, if any, concern amongst experts specifically about the use of macrocyclic agents in clinical practice, and the current safety concern laying over all GdCAs arises from the clinical use of linear GdCAs.

Another group of experts supported the view that macrocyclic agents are more stable and are preferable as first line contrast agents. However, they did not favour the suspension of linear agents which could be preferred by some radiologists for their technical characteristics in some conditions (e.g., breast or brain imaging), especially in conditions that do not require frequent imaging procedures, or which could be used as “second line” agents. Also, according to this view, it would be important to complement this strategy by efforts to better inform healthcare professionals, particularly practitioners requesting imaging, on the choice of contrast agents depending on the different conditions and indications; to allow for increased overall awareness of risk benefit analysis.

There was also an intermediate position within the committee that expressed a view that the linear agents should not be suspended but that macrocyclic agents should be used as the first line contrast agent (excepting for the liver), unless the MAHs produced relevant trial data clearly indicating superior patient management outcomes with use of their linear agent compared to macrocyclics.

For all Gd contrast agents, the experts stated that the general “As Low As Reasonably Achievable” (ALARA) principles should be used and that the exposure to all GdCAs should be minimised, either by reducing the dose or using alternative diagnostic methods, if possible.

Detailed conclusions from the meeting can be found in the enclosure 11 to the report.

### **4.3.3. Final benefit-risk balance following re-examination**

#### *Intravenous linear GdCAs products*

Taking into account the evidence of accumulation of GdCAs in the brain, the fact that linear compounds have been detected in the brain to a much higher amount than the macrocyclic compounds and that they persist in the brain for a longer period, and considering the toxicity of Gd shown in non-clinical studies, the serious concerns about potential neurological harm, deposition in other tissues and its potential risks, and the identified risks associated with the use of linear GdCAs (including the risk of NSF and the gadolinium-associated plaques) and in view of the whole safety profile of these agents, PRAC maintained its conclusion that that the benefit in enhancement of MR images of intravenous linear agents does not outweigh the known and potential risks of these products.

PRAC also considered the two linear GdCAs, gadoxetic acid (Primovist) and gadobenic acid (Multihance). These products undergo hepatic uptake, and have therefore a clinical utility for imaging poorly vascularised hepatic lesions, especially in the delayed phase imaging, that cannot be adequately studied with agents without hepatic uptake and thus allowing early diagnosis of potentially life threatening diseases. Therefore, PRAC considered that the benefits of gadobenic acid and gadoxetic acid outweigh their risks in the context of delayed phase liver imaging. However, PRAC considered the clinical utility outweighing the risks related to accumulation of gadolinium is limited to the delayed phase liver imaging and thus PRAC recommended that the indication of gadobenic acid is restricted to this use only. PRAC noted that gadoxetic acid has only the liver imaging indication.

#### *Macrocyclic GdCAs*

In view of the very low potential for retention of gadolinium in tissues, their stability and low risk of dechelation, PRAC maintained its recommendation that the benefits of macrocyclic agents outweigh their risks. PRAC recommended restriction of use, in the lowest dose that provides sufficient enhancement for diagnostic purposes and through appropriate warning in the product information in

order to minimise the potential for accumulation of gadolinium in the brain and other organs and tissues.

#### *Intra-articular GdCA products*

PRAC also maintained its conclusions that benefits of the intra-articular presentation of the linear GdCA Magnevist outweigh their risks (subject to changes to the product information) as they are administered at very low doses and present a low risk of tissue accumulation.

## **5. Risk management**

The Committee, having considered the data submitted in the procedure was of the opinion that the risk management plan (RMP) for products with a positive benefit-risk balance (except the intra-articular formulations of gadopentetic acid (Magnevist) and gadoteric acid (Artirem)) should be revised accordingly:

### **Important potential risks**

- Accumulation and retention of gadolinium in the brain
- Gadolinium accumulation in organs and tissues other than brain tissues

The above mentioned safety concerns should be updated as outlined below:

- Adverse clinical effects of accumulation and retention of gadolinium in the brain
- Adverse clinical effects of accumulation and retention of gadolinium in organs and tissues other than brain tissues

The following safety concerns should be included in the RMP:

### **Missing information**

- Safety in children – [if product is authorised in children]
- Safety in pregnancy and lactation

RMP Part III, V and VI should be updated accordingly as per the above changes impacting Part II.

At the same time the MAHs should make proposals for conducting a further observational study to evaluate the effect of GdCA exposure during pregnancy and pregnancy outcomes.

### **5.1.1. Amendments to the product information**

The PRAC considered that updates to the product information would be necessary in order to minimise the risk(s) associated with the use of intravenous gadoteric acid, gadobutrol, gadoteridol, gadobenic acid, intra-articular gadoteric acid, intra-articular gadopentetic acid, and gadoxetic acid containing medicinal products. These changes include amendments to sections 4.1, 4.2, 4.4 and 5.2 of the SmPC as appropriate:

The indication was amended to highlight the need to carefully assess the need of enhanced imaging before using GdCAs.

For gadobenic acid the indication was in addition restricted to use in delayed phase liver imaging only.

In addition all these products should be used at the lowest dose that provides sufficient enhancement for diagnostic purposes.

Further warnings and precautions of use relating to the risk(s) associated with the use of intra-articular gadopentetic acid, and gadoxetic acid containing medicinal products were also included.

The Package Leaflets are amended accordingly.

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### **5.1.2. Direct Healthcare Professional Communications/Communication plan**

PRAC agreed that a DHPC should be sent, and that the grounds for the PRAC recommendation could reflect the key messages of such communication.

## **6. Condition(s) for lifting the suspension of the marketing authorisations**

For the suspensions of intravenous gadodiamide, gadopentetic acid, and gadoversetamide containing medicinal products to be lifted, the Marketing Authorisation Holder(s) shall provide the following:

MAHs should provide evidence:

- for clinically important benefits that are currently not established in an identified population or indication and which outweigh the risks related to the product.
- or that the product (potentially modified or not) does not undergo significant dechelation and does not lead to retention of gadolinium in tissues, including the brain in humans.



## 7. Grounds for Recommendation following the re-examination procedure

Whereas

- Data on stability, as well as *in vitro* and non-clinical studies, show that linear gadolinium-containing contrast agents (GdCAs) release gadolinium from the ligand molecules to a greater extent than macrocyclic agents.
- Gadolinium has been measured in the brain, both indirectly by studies showing signal intensity increases, and directly by studies measuring gadolinium concentrations with mass spectrometry, including methods that allow localisation in the brain (LA-ICP-MS) and separation of Gd species (GPC-MS).
- Based on non-clinical data, both linear and macrocyclic agents have the ability to distribute to the brain. However linear agents are retained and persist for up to one year or longer. Macrocyclic agents show only a transient increase in Gd in the brain and undergo early washout.
- Although no adverse neurological effects, such as cognitive or movement disorders, have yet been demonstrated to be caused by gadolinium accumulation in the brain, long-term safety data are limited. Harmful effects and potential interaction with disease processes are plausible in view of data supporting dechelation of linear agents *in vivo* and the known toxicity of unchelated gadolinium. Toxicity has been seen in other tissues where it accumulates (including NSF, skin plaques) and in non-clinical data.
- Gadolinium accumulation has also been reported in a range of other tissues including the liver, kidney, muscle, skin and bone in non-clinical and clinical studies. The evidence strongly suggests a correlation between the potential for release of gadolinium from the ligand and the extent of retention in these tissues and organs.
- Linear GdCAs are associated with a significant risk of NSF, although current risk minimisation measures appear to be effective based on spontaneous adverse drug reaction reporting.
- In addition to NSF, there is also evidence that other harmful outcomes are associated with exposure to linear GdCAs, in particular gadolinium-associated skin plaques.
- Clinical studies, both observational and interventional, to fully address the serious concerns of potential neurological effects are not considered feasible within a reasonable period of time. This is due to the range of potential outcomes of interest, the requirement for long term follow-up, and the heterogeneity of the patient population that undergoes MRI.
- PRAC considered options for risk minimisation measures. However, as no specific patient group with less risk of accumulation in the brain or a safe threshold level for retention in the brain could be identified, the restriction of the use of linear GdCAs to certain indications or certain groups of patients was considered not appropriate. The PRAC also concluded that there are practical difficulties for an effective restriction of the number of doses administered during the lifetime of a patient.
- The PRAC considered that the risk related to linear intravenous GdCAs gadobenic acid (in all indications besides liver imaging), gadodiamide, gadopentetic acid, and gadoversetamide, taking into account the whole safety profile, including the additional potential risk of harm from brain and other tissues accumulation outweighs the benefits.

- The PRAC took into account that the linear intravenous agents, Multihance (gadobenic acid) and Primovist (gadoxetic acid), undergo hepatic uptake, and therefore have clinical utility for imaging poorly vascularised hepatic lesions, especially in the delayed phase imaging, that cannot be adequately studied with agents without hepatic uptake and thus allowing early diagnosis of potentially life threatening diseases. Therefore, the PRAC considered that the benefits of gadobenic acid and gadoxetic acid outweigh the risks related to these products in the context of liver imaging.
- In relation to the Magnevist (gadopentetic acid) for intra-articular injection, in view of the low dose, the limited potential for repeated exposure for patients and the absence of evidence of brain accumulation, PRAC considered that the benefits of this product outweigh its risks.

In view of the above, the PRAC concluded that:

The benefit-risk balance of medicinal products containing intravenous gadobutrol, gadoteric acid, gadoteridol, gadoxetic acid, intravenous gadobenic acid (in the indication of liver imaging), intra-articular gadoteric acid and intra-articular gadopentetic acid is favourable subject to agreed changes to the product information.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for products containing intravenous gadobutrol, gadoteric acid, gadoteridol, gadobenic acid, gadoxetic acid and intra-articular gadoteric acid and intra-articular gadopentetic acid.

The benefit-risk balance of medicinal products containing gadodiamide, gadopentetic acid (IV presentation), and gadoversetamide is no longer favourable.

Therefore, pursuant to Article 116 of Directive 2001/83/EC, the Committee recommends the suspension of the marketing authorisations for reference to the concerned products.

The conditions imposed to lift the suspension of the marketing authorisation are set out in section 6 of this report.

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## **Appendix 1**

### **Divergent positions to PRAC recommendation adopted on 9 March 2017**

## **Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data**

Procedure No: EMEA/H/A-31/1437

Procedure No: Optimark EMEA/H/A-31/1437/C/000745/0034

Gadolinium containing medicinal products

### **Divergent statement**

The following PRAC members do not agree with the PRAC's recommendation that the marketing authorisation(s) for gadobenic acid, gadodiamide, gadopentetic acid (intravenous), and gadoversetamide should be suspended based on the following grounds:

It is agreed that available data from in vitro and non-clinical studies suggest that gadolinium contrast agents have a potential to release gadolinium from the ligand molecules. Furthermore, there is evidence showing that gadolinium can accumulate in the brain following exposure to gadolinium contrast agents.

While studies show a greater potential for gadolinium to accumulate in the brain with the linear gadolinium contrast agents than with the macrocyclic gadolinium contrast agents, it should be acknowledged that currently fewer studies have been done with the macrocyclic agents. Further, there is some data showing possible gadolinium release also from macrocyclic agents, albeit at lower levels than for the linear products.

Available non-clinical studies with gadolinium contrast agents have limitations. Data from these studies have not identified signs of toxicity, but they have not resulted in exposure multiples. There is also a lack of chronic toxicology data.

No adverse neurological effects, such as negative cognitive effects, have been identified from clinical use of gadolinium contrast agents, and there is no clear threshold linked to a potential toxic effect.

It can be concluded that concerns about gadolinium retention and its potential clinical consequences are greater for the linear agents. However, without evidence for a link to adverse clinical consequences and no clear understanding of the quantitative relation between cerebral tissue levels and potential toxic effects, the risk for adverse clinical consequences of brain accumulation of gadolinium has not been identified and remains potential.

Taken together, the efficacy and the clinical benefit of these products are established. In the absence of toxicological and clinical adverse findings, we do not find it proportionate to conclude that the absolute benefit/risk balance for the linear agents are negative, if further restrictions to their use are made to address the potential risk related to greater gadolinium brain retention. Thus, restricting the use of the linear agents to occasional administration and to avoid use in the potentially most sensitive populations such as children and pregnant women are considered a more proportionate regulatory measure than suspension of the marketing authorisations.

### **PRAC Members expressing divergent opinion:**

Júlia Pallós	9 March 2017	
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## **Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data**

Procedure No: EMEA/H/A-31/1437

Procedure No: Optimark EMEA/H/A-31/1437/C/000745/0034

Gadolinium containing medicinal products

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The following PRAC members do not agree with the PRAC's recommendation that the marketing authorisation(s) for gadobenic acid, gadodiamide, gadopentetic acid (intravenous), and gadoversetamide should be suspended based on the following grounds:

It is agreed that available data from in vitro and non-clinical studies suggest that gadolinium contrast agents have a potential to release gadolinium from the ligand molecules. Furthermore, there is evidence showing that gadolinium can accumulate in the brain following exposure to gadolinium contrast agents.

While studies show a greater potential for gadolinium to accumulate in the brain with the linear gadolinium contrast agents than with the macrocyclic gadolinium contrast agents, it should be acknowledged that currently fewer studies have been done with the macrocyclic agents. Further, there is some data showing possible gadolinium release also from macrocyclic agents, albeit at lower levels than for the linear products.

Available non-clinical studies with gadolinium contrast agents have limitations. Data from these studies have not identified signs of toxicity, but they have not resulted in exposure multiples. There is also a lack of chronic toxicology data.

No adverse neurological effects, such as negative cognitive effects, have been identified from clinical use of gadolinium contrast agents, and there is no clear threshold linked to a potential toxic effect.

It can be concluded that concerns about gadolinium retention and its potential clinical consequences are greater for the linear agents. However, without evidence for a link to adverse clinical consequences and no clear understanding of the quantitative relation between cerebral tissue levels and potential toxic effects, the risk for adverse clinical consequences of brain accumulation of gadolinium has not been identified and remains potential.

Taken together, the efficacy and the clinical benefit of these products are established. In the absence of toxicological and clinical adverse findings, we do not find it proportionate to conclude that the absolute benefit/risk balance for the linear agents are negative, if further restrictions to their use are made to address the potential risk related to greater gadolinium brain retention. Thus, restricting the use of the linear agents to occasional administration and to avoid use in the potentially most sensitive populations such as children and pregnant women are considered a more proportionate regulatory measure than suspension of the marketing authorisations.

### **PRAC Members expressing divergent opinion:**

John-Joseph Borg	9 March 2017	
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## **Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data**

Procedure No: EMEA/H/A-31/1437

Procedure No: Optimark EMEA/H/A-31/1437/C/000745/0034

Gadolinium containing medicinal products

### **Divergent statement**

The following PRAC members do not agree with the PRAC's recommendation that the marketing authorisation(s) for gadobenic acid, gadodiamide, gadopentetic acid (intravenous), and gadoversetamide should be suspended based on the following grounds:

It is agreed that available data from in vitro and non-clinical studies suggest that gadolinium contrast agents have a potential to release gadolinium from the ligand molecules. Furthermore, there is evidence showing that gadolinium can accumulate in the brain following exposure to gadolinium contrast agents.

While studies show a greater potential for gadolinium to accumulate in the brain with the linear gadolinium contrast agents than with the macrocyclic gadolinium contrast agents, it should be acknowledged that currently fewer studies have been done with the macrocyclic agents. Further, there is some data showing possible gadolinium release also from macrocyclic agents, albeit at lower levels than for the linear products.

Available non-clinical studies with gadolinium contrast agents have limitations. Data from these studies have not identified signs of toxicity, but they have not resulted in exposure multiples. There is also a lack of chronic toxicology data.

No adverse neurological effects, such as negative cognitive effects, have been identified from clinical use of gadolinium contrast agents, and there is no clear threshold linked to a potential toxic effect.

It can be concluded that concerns about gadolinium retention and its potential clinical consequences are greater for the linear agents. However, without evidence for a link to adverse clinical consequences and no clear understanding of the quantitative relation between cerebral tissue levels and potential toxic effects, the risk for adverse clinical consequences of brain accumulation of gadolinium has not been identified and remains potential.

Taken together, the efficacy and the clinical benefit of these products are established. In the absence of toxicological and clinical adverse findings, we do not find it proportionate to conclude that the absolute benefit/risk balance for the linear agents are negative, if further restrictions to their use are made to address the potential risk related to greater gadolinium brain retention. Thus, restricting the use of the linear agents to occasional administration and to avoid use in the potentially most sensitive populations such as children and pregnant women are considered a more proportionate regulatory measure than suspension of the marketing authorisations.

### **PRAC Members expressing divergent opinion:**

Ulla Wändel Liminga	9 March 2017	
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## **Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data**

Procedure No: EMEA/H/A-31/1437

Procedure No: Optimark EMEA/H/A-31/1437/C/000745/0034

Gadolinium containing medicinal products

### **Divergent statement**

The following PRAC members do not agree with the PRAC's recommendation that the marketing authorisation(s) for gadobenic acid, gadodiamide, gadopentetic acid (intravenous), and gadoversetamide should be suspended based on the following grounds:

It is agreed that available data from in vitro and non-clinical studies suggest that gadolinium contrast agents have a potential to release gadolinium from the ligand molecules. Furthermore, there is evidence showing that gadolinium can accumulate in the brain following exposure to gadolinium contrast agents.

While studies show a greater potential for gadolinium to accumulate in the brain with the linear gadolinium contrast agents than with the macrocyclic gadolinium contrast agents, it should be acknowledged that currently fewer studies have been done with the macrocyclic agents. Further, there is some data showing possible gadolinium release also from macrocyclic agents, albeit at lower levels than for the linear products.

Available non-clinical studies with gadolinium contrast agents have limitations. Data from these studies have not identified signs of toxicity, but they have not resulted in exposure multiples. There is also a lack of chronic toxicology data.

No adverse neurological effects, such as negative cognitive effects, have been identified from clinical use of gadolinium contrast agents, and there is no clear threshold linked to a potential toxic effect.

It can be concluded that concerns about gadolinium retention and its potential clinical consequences are greater for the linear agents. However, without evidence for a link to adverse clinical consequences and no clear understanding of the quantitative relation between cerebral tissue levels and potential toxic effects, the risk for adverse clinical consequences of brain accumulation of gadolinium has not been identified and remains potential.

Taken together, the efficacy and the clinical benefit of these products are established. In the absence of toxicological and clinical adverse findings, we do not find it proportionate to conclude that the absolute benefit/risk balance for the linear agents are negative, if further restrictions to their use are made to address the potential risk related to greater gadolinium brain retention. Thus, restricting the use of the linear agents to occasional administration and to avoid use in the potentially most sensitive populations such as children and pregnant women are considered a more proportionate regulatory measure than suspension of the marketing authorisations.

### **PRAC Members expressing divergent opinion:**

Stephen JW Evans	9 March 2017	
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## **Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data**

Procedure No: EMEA/H/A-31/1437

Procedure No: Optimark EMEA/H/A-31/1437/C/000745/0034

Gadolinium containing medicinal products

### **Divergent statement**

The following PRAC members consider that the benefit-risk of gadobenic acid in all indications besides liver imaging is favourable based on the following grounds:

- We agree with the PRAC that the benefit/risk ratio of macrocyclic GdCAs, gadopentetic acid in intra-articular indication and gadoxetic acid in liver indication is considered to be positive if proposed changes in these product 's information are implemented. We also agree that the risk of brain accumulation of gadolinium which is predominantly related to linear agents is a severe risk and although clinical consequences are not clearly demonstrated at the moment, the patients must be protected.
- However, we believe that both benefits and risks differ for different linear agents, especially the benefit/risk ratio of gadobenic acid is not the same as of other linear agents. The risk of NSF was classified as medium for gadobenic acid compared to other linear GdCAs which have high risk of NSF and since 2010 there have been no new confirmed cases related to the use of gadobenic acid.
- Regarding the accumulation in the brain, although some human data exist, they are less clear and less robust for gadobenic acid than for other linear agents.
- With regard to benefits, gadobenic acid has higher relaxivity compared to macrocyclic GdCAs which can provide detailed imaging of finest structural details, for example brain metastasis. This detailed imaging could be important for some patients.
- During the assessment of referral procedure about GdCA no new important information which could change the benefit/risk ratio of gadobenic acid was detected. Suspension of the marketing authorisation may have great impact on clinical practice in some Member States.

Based on the presented non-clinical and clinical evidence in their totality, we are of the following opinion:

We consider that the benefit/risk balance of gadobenic acid is positive (with the exception of liver scan indication where gadoxetic acid has a better B/R profile) if used as last choice only. Gadobenic acid should be used only when an unenhanced MRI scan is not sufficient and no other GdCA can be used or when it is necessary to obtain additional diagnostic information not available with another GdCA. Also gadobenic acid should not be used repeatedly.

### **PRAC Members expressing divergent opinion:**

Eva Jirsová	9 March 2017	Signature: .....
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## **Appendix 2**

### **Divergent positions to final PRAC recommendation adopted on 6 July 2017**

## ***Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data***

Procedure No: EMEA/H/A-31/1437

Procedure No: Optimark EMEA/H/A-31/1437/C/000745/0034

Gadolinium containing medicinal products

### **Divergent statement**

The following PRAC members do not agree with the PRAC's opinion recommending that the marketing authorisation(s) for gadobenic acid (full body indication), gadodiamide, gadopentetic acid (intravenous), and gadoversetamide should be suspended based on the following grounds:

It is agreed that available data from in vitro and non-clinical studies suggest that gadolinium contrast agents have a potential to release gadolinium from the ligand molecules. Furthermore, there is evidence showing that gadolinium can accumulate in the brain following exposure to gadolinium contrast agents.

While studies show a greater potential for gadolinium to accumulate in the brain with the linear gadolinium contrast agents than with the macrocyclic gadolinium contrast agents, it should be acknowledged that currently fewer studies have been done with the macrocyclic agents. Further, there is data showing gadolinium retention also from macrocyclic agents, albeit at lower levels than for the linear products.

Available non-clinical studies with gadolinium contrast agents administered via the intended route have not identified signs of central nervous system toxicity, although there are limitations, including the lack of chronic toxicology data.

No clinical adverse effects have been identified from Gd brain retention following use of gadolinium contrast agents, and there is no scientifically justifiable threshold linked to a potential toxic effect.

Research both within the non-clinical and clinical area is ongoing, and data from some of the studies will become available within the coming year.

It can be concluded that concerns about gadolinium retention and its potential clinical consequences are greater for the linear agents. However, without evidence for a link to adverse clinical consequences and no clear understanding of the quantitative relation between cerebral tissue levels and potential toxic effects, the risk for adverse clinical consequences of brain accumulation of gadolinium has not been identified and remains largely hypothetical.

Taken together, the efficacy and the clinical benefit of these products are established. In the absence of toxicological and clinical adverse findings, we do not find it proportionate to conclude that the absolute benefit/risk balance for the linear agents are negative, if further restrictions to their use are made to address the hypothetically increased risk related to greater gadolinium brain retention than seen with other available agents. Thus, restricting the use of the linear agents to contexts where an enhanced MRI scan is required to obtain sufficient diagnostic information, to the use of the lowest effective dose and that repeated use should be avoided to the extent possible, are considered a more proportionate regulatory measure than suspension of the marketing authorisations.

**PRAC Members expressing divergent opinion:**

Jolanta Gulbinovič	6 July 2017	Signature: .....
Eva Jirsová	6 July 2017	Signature: .....
Júlia Pallós	6 July 2017	Signature: .....
Carmela Macchiarulo	6 July 2017	Signature: .....
Stephen Evans	6 July 2017	Signature: .....
Maia Uusküla	6 July 2017	Signature: .....
Ulla Wändel Liminga	6 July 2017	Signature: .....