

**Annex II**  
**Scientific conclusions**

## Scientific conclusions

In accordance with Article 107k of Directive 2001/83/EC, the CHMP considered the PRAC recommendation adopted on 6 July 2017.

### ***Overall summary of the scientific evaluation by the PRAC***

#### **Background**

Gadolinium containing contrast agents (GdCAs) are complexes of paramagnetic gadolinium (III) with different types of organic chelators. They are used for contrast enhancement in magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA). GdCAs can be differentiated by their structure: linear (gadodiamide, gadopentetic acid, gadobenic acid, gadoxetic acid, gadoversetamide) or macrocyclic (gadoteridol, gadobutrol, gadoteric acid), and by the overall charge on the complex formed (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 was 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 gadolinium-containing contrast agents, which lead to the categorisation of GdCAs into three risk groups for NSF (high risk, medium risk and low risk).

Since the finalisation of the referral, several studies in animals and in humans have been published showing accumulation of gadolinium following administration of GdCAs in tissues such as liver, kidney, muscle, skin and bone. Furthermore, recent publications have shown that gadolinium also accumulates in the brain.

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.

The PRAC considered all the available data related to the safety and efficacy to the medicinal products containing gadodiamide, gadopentetic acid, gadobenic acid, gadoxetic acid, gadoteridol, gadobutrol, gadoteric acid and gadoversetamide within the procedure under Article 31 of Directive 2001/83/EC.

#### **Benefits**

The benefit of GdCAs has been demonstrated based on their ability to improve the quality of imaging for MRIs compared to unenhanced MRI scans by supporting the diagnostic performance of such scans in the detection of disease, prognosis and patient management in order to achieve a particular clinical outcome. This contrast enhancement has shown to be important for the visualisation of the anatomy,

physiology and functionality of many different areas of the body and internal organs as part of a diagnostic workup investigating a wide range of diseases including cancer, inflammatory diseases and degenerative conditions.

The approved indications for GdCAs are general and relate to the whole body scanning/imaging, which includes all organs, with the exception of GdCAs with targeted indications related to the specific physicochemical properties that allow the enhancement of specific features.

For liver imaging, some GdCAs allow the possibility of a delayed phase imaging. Indeed there are two phases of liver MRI enhancement with GdCAs:

- the dynamic phase, for which all the authorised GdCAs can provide enhancement of liver imaging,
- the delayed phase that relies on selective uptake of a GdCA by functioning hepatocytes, which results in enhancement and visualisation of the normal hepatic parenchyma while improving the delineation and detection of lesions such as cysts and hepatocellular carcinomas.

Two linear GdCAs, gadoxetic acid and gadobenic acid, have been shown to have an uptake by hepatocytes and are the only liver-specific agents that can provide both the dynamic and the delayed phase imaging. This is a clinically relevant benefit as they allow enhancement of dynamic phase liver imaging for highly vascularised hepatic lesions and also detection of lesions that are visible only in the delayed phase.

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.

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).

In addition, two GdCA products, gadopentetic acid and gadoteric acid, are authorised as formulations for intra-articular administration for magnetic resonance arthrography and they are able to enhance specific lesions. They are administered at low concentrations, approximately 200-fold lower than the intravenous use GdCA products, and the potential for patients to receive large numbers of repeated exposures is less for the MR arthrography indication than for the indications for the intravenous product.

## **Risks**

### ***Non-clinical data***

#### **Toxicity of non-chelated gadolinium**

Non-chelated gadolinium has been shown to be toxic in non-clinical studies, with effects including cellular necrosis, fibrosis, and lesions related to mineral deposition. An in vitro study in rat neurons reported gadolinium-induced cytotoxicity via oxidative injury. In addition, toxicities have been observed with GdCAs in other organs, such as kidney (leading to NSF) and skin (leading to skin plaques), which are considered to be related to Gadolinium released from the chelate.

## Deposition of gadolinium in the brain

There is currently a cumulative amount of evidence in the literature that gadolinium is deposited in the brain. There are several publications in rat models that have demonstrated a T1-weighted signal enhancement in the deep cerebellar nuclei (DCN) – the equivalent to the dentate nucleus (DN) in humans- after administration of the linear agents. Enhancement after gadobenate dimeglumine (Multihance) or gadopentetate dimeglumine (Magnevist) appeared more progressively compared with gadodiamide. No such enhancement was observed with gadoterate meglumine (Dotarem).

Further studies have tried to characterise and quantify the amount of deposition of gadolinium in the brain. In rat studies, residual Gd found in the rat brain after repeated administration of linear GdCAs was present in at least 3 distinctive forms - soluble small molecules, presumably intact GdCA, soluble macromolecules and to the largest extent an insoluble form. The brain soluble fractions from animals receiving linear agents contained a proportion of macromolecules; gadolinium-bound macromolecules were not detected in the brain of animals that received macrocyclic agents. The highest amount of gadolinium recovered from the rat brain tissue was found to be with gadodiamide, followed by gadobenate and gadopentetate.

A rat study also confirmed the finding that dose-dependent level of Gd in the brain for linear agents was likely to be related to cumulative dose rather than a single large or repeat small dose regimens.

Data from non-clinical electron microscopy (EM) studies of brain tissue have also provided evidence of filamentous electron-dense Gd deposits in the regions where T1 hyper intensity has been observed following dosing with gadodiamide.

Non-clinical evidence also shows potential for release of gadolinium from the chelating ligand in the brain with linear GdCAs; the potential of release from the chelating ligand is not seen with macrocyclic GdCAs. Gadolinium bound to macromolecules is expected to have a higher relaxivity and would be capable of generating a T1-weighted signal at low concentration.

The precise molecular forms of the soluble macromolecular bound Gd are not known but it is plausible that the macromolecules are bound to a dechelated  $Gd^{3+}$  ion.

The increased potential to release gadolinium in the brain would be expected with the linear agents, which have a lower kinetic and thermodynamic stability and are thus more prone to release gadolinium in the tissue environment. It is reasonable to suppose that gadolinium can de-chelate from linear GdCAs and bind to macromolecules in human brains similarly as what is observed in rodent brains.

## Duration of gadolinium retention in the brain

For the linear agents evaluated in non-clinical studies the T1 signal intensity in the DCN has been shown to persist for at least 1 year without any reduction in intensity. Repeat toxicity studies for gadodiamide showed that the absolute low levels of gadolinium in the brain were observed at 1 week post-dosing. The levels remained low at 20 weeks and no further reduction was observed at week 50, suggesting that there may be retention of gadolinium in the brain in the long term with no evidence of clearance up to 1 year. Gd presence in the brain following the last administration of other linear agents, gadopentetic acid and gadobenic acid also remained at the same level after the same period.

Only a transient increase in T1 signal intensity and gadolinium concentration (measured by ICP-MS<sup>1</sup>, thus not distinguishing the molecular form of Gd) was observed with macrocyclic agents. Another study showed that at one year, Gd levels in the brain following administration of gadoteric acid, a macrocyclic agent, are over 30 fold lower compared to gadodiamide (linear).

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<sup>1</sup> ICP-MS: Inductively coupled plasma mass spectrometry

Another study showed that administration of the linear GdCAs gadodiamide and gadobenidic acid directly into the cerebrospinal fluid (CSF) resulted in increased signal intensity in the DCN in rats up to 5 weeks after administration. The macrocyclic agent gadobutrol did not show hyperintensity after this time period.

Therefore, data shows that linear agents are deposited in the brain and are retained and persist for up to one year or longer. Data appears to suggest that macrocyclic agents are also deposited in the brain but show only a transient increase in Gd and undergo early washout.

## ***Clinical data***

### **Accumulation in the brain**

Enhancement of the DN and globus pallidus (GP) in unenhanced scans after previous use of linear GdCAs has been observed across multiple studies in humans. A number of studies have shown a correlation between the number of exposures to linear GdCAs and the signal intensity changes. 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 GdCAs.

The T1 signal enhancement was documented in several non-clinical as well as clinical studies, demonstrating that the data is consistent across mouse, rat and human, which confirms the robustness of the findings of signal intensity increases.

There have been more recent MRI studies that have documented signal intensity increases in the brain in association with macrocyclic GdCAs, suggesting that these agents may also deposit gadolinium in the brain. However, these studies have significant limitations (e.g. studies could not exclude exposure to linear GdCA prior to study period) and do therefore not establish a causal relationship with macrocyclic agents.

Data in post mortem tissue samples have shown that the highest concentration of gadolinium in the brain was observed in patients that had several exposures to gadodiamide, suggesting that number of doses received had an impact on the deposition of gadolinium. The study also found that changes in signal intensity were strongly correlated with the amount of gadolinium detected by 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.

There is also a concern that gadolinium deposits in some tissues, particularly bone, could be released at a later stage for example during loss of bone density in aging or pregnancy/breastfeeding, exposing patients to further systemic distribution of gadolinium.

## **Impact of renal impairment**

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.

The available data in humans support a conclusion 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.

Renal impairment is also known to increase the long term retention of Gd in rats in line with the propensity of GdCAs to release Gd in vivo. Repetitive administration of gadodiamide in rats with renal failure was associated with an increase in the T1 hypersignal in the deep cerebellar nuclei relative to controls with normal renal function.

Therefore, it can be concluded that renal impairment is not a requirement for Gd deposition, but it may however increase the amount of Gd deposited in the brain.

## ***Other safety aspects***

### **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 have some degree of renal elimination, which varies from 50% for gadoxetic acid to 100% for most other members of the class. Elimination of GdCAs is therefore reduced in patient with renal dysfunction. Prolonged elimination time in patients with renal impairment and release of gadolinium from GdCAs are the main factors that contribute to the development of NSF.

Gadolinium containing 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) and a switch to the use of low risk products.

Linear GdCAs are associated with a significant risk of NSF. The implemented risk minimisation measures appear to be effective based on annual reviews of spontaneous case reports.

### **Hypersensitivity**

Hypersensitivity or anaphylactoid reactions with GdCAs can manifest as a range of clinical signs and symptoms. Many of these are common but typically non-serious reactions, such as rash, urticaria, and flushing. The absolute rate of hypersensitivity reactions with GdCAs is low and reported as approximately 0.01% to 0.001% across the studies investigating rates of hypersensitivity reactions. The vast majority of these reactions are non-serious, with a very low percentage of patients experiencing severe hypersensitivity reactions. There is no 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.

### **Gadolinium-associated plaques**

Gadolinium-associated plaques with sclerotic bodies on histology have been reported with some gadolinium-containing contrast agents in patients who do not otherwise have symptoms or signs of nephrogenic systemic fibrosis.

### ***Feasibility of clinical studies***

PRAC considered potential clinical studies to be conducted in order to fully address the serious concerns of plausible neurological effects. Such studies are considered unlikely to be feasible in view of the heterogeneity of the patient population that undergoes MRI.

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.

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). Such long-term safety studies are unlikely to be feasible 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.

### **Benefit/risk balance**

#### *Intravenous 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, deposition in other tissues and its potential risks, 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.

## Re-examination procedure

Following the adoption of the PRAC recommendation during the March 2017 PRAC meeting, two MAHs (Bracco and GE Healthcare) expressed their disagreement with the initial PRAC recommendation.

The PRAC confirmed it had considered the totality of the data submitted by the MAHs in the context of the initial referral procedure. Notwithstanding this, and given the detailed grounds provided by the MAHs, the PRAC carried out a new assessment of the available data in the context of the re-examination.

## PRAC conclusions 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 Transmission electron microscopy (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 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 (20x2.5 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 (10x2.5mmol), 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 the conclusion that these 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 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/II/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 expert group 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 PRAC assessment report.

## **Final benefit-risk balance**

### *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 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.

## Grounds for PRAC recommendation

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 (gadoteric 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:

- variation to the terms of the marketing authorisation for the intraarticular linear agent gadopentetic acid (Magnevist), and the intravenous linear agents gadoxetic acid (Primovist) and gadobenic acid (Multihance) with changes to SmPC sections 4.1, 4.2, 4.4 and 5.2, including removal of indications,
- variation to the terms of the marketing authorisation for the macrocyclic agents (gadoteridol (Prohance), gadobutrol (Gadovist), gadoteric acid (Dotarem and Artirem)) with changes to SmPC sections 4.1 and 4.2.

The benefit-risk balance of medicinal products containing intravenous gadobenic acid (in all other indications than liver imaging), gadodiamide, gadopentetic acid (IV presentation), and gadoversetamide is no longer favourable and these marketing authorisations should be suspended.

For lifting the suspension, the PRAC recommended that 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.

## CHMP opinion

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

### ***Detailed explanation of the scientific grounds for the differences from the PRAC recommendation***

The CHMP, having considered the PRAC recommendation, is of the view that the following clarifications to the PRAC grounds and recommendation are necessary:

In relation to the statement about the macrocyclic early washout “macrocyclic agents show only a transient increase in Gd in the brain and undergo early washout”, the CHMP considered it sufficient to reflect the observation that measurements of gadolinium in the brain over longer periods showed differences between linear and macrocyclic agents in terms of accumulation over time. Therefore this statement is not maintained.

The CHMP further considered the statement addressing the potential harm associated with the gadolinium accumulation in the brain: *“although no adverse neurological effects, such as cognitive or movement disorders, have 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 possible in view of data supporting dechelation of linear agents in vivo and the known toxicity of unchelated gadolinium based on non-clinical data”*. Taking into account the extensive exposure and the absence of clinical or non-clinical adverse outcomes of gadolinium accumulation in the brain, CHMP considered that such harmful effects and potential interaction with disease processes are “possible” rather than “plausible”, as the latter would imply a stronger potential for harm; in this sense, “yet” was also removed.

The ground concerning the skin plaques *“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”* is based on a limited number of cases, and therefore CHMP did not consider it relevant as ground for the suspension of some of the IV linear GdCAs.

With regards to the condition for lifting the suspension the MAH shall submit evidence *“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”*, CHMP agreed in general with the proposal, however considered it necessary clarifying the meaning of this condition to avoid misunderstandings. Therefore the condition should not mention “including the brains in human.”

Furthermore the CHMP took the opportunity to clarify that toxicities of non-chelated gadolinium discussed in the non-clinical section of the scientific grounds above have been observed with GdCAs in skin and other tissues (leading to NSF and skin plaques), which are considered to be related to Gadolinium released from the chelate. Furthermore, the CHMP noted that the changes to the package leaflet for Multihance (gadobenic acid) had not been fully implemented in the PRAC assessment report; the correct wording is provided in the Annex to this opinion.

## Grounds for CHMP opinion

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 and clinical data, both linear and macrocyclic agents have the ability to distribute to the brain. However, after the use of linear agents gadolinium is retained longer at measurable levels and persists for up to one year or more.
- Although no adverse neurological effects, such as cognitive or movement disorders, have 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 possible in view of data supporting dechelation of linear agents in vivo and the known toxicity of unchelated gadolinium based on 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.
- 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.
- CHMP 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 CHMP also concluded that there are practical difficulties for an effective restriction of the number of doses administered during the lifetime of a patient.
- The CHMP 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 CHMP 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 CHMP 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, CHMP considered that the benefits of this product outweigh its risks.

## Overall conclusion

The CHMP, as a consequence, considers that the benefit-risk balance of medicinal products containing intravenous gadobutrol, gadoteric acid, gadoteridol, gadoxetic acid, intravenous gadobenamic acid in the indication of liver imaging, intra-articular gadoteric acid and intra-articular gadopentetic acid remains favourable subject to amendments to the product information.

Therefore the CHMP recommends the variation to the terms of the marketing authorisations for medicinal products containing intravenous gadobutrol, gadoteric acid, gadoteridol, gadoxetic acid, intravenous gadobenamic acid in the indication of liver imaging, intra-articular gadoteric acid and intra-articular gadopentetic acid.

The CHMP, in addition, considers that the benefit-risk balance of intravenous medicinal products containing gadodiamide, gadopentetic acid, and gadoversetamide is no longer favourable.

Therefore, pursuant to Article 116 of Directive 2001/83/EC, the CHMP recommends the suspension of the marketing authorisations for intravenous medicinal products containing gadodiamide, gadopentetic acid, and gadoversetamide.

For the suspension of intravenous medicinal products containing gadodiamide, gadopentetic acid, and gadoversetamide to be lifted, the marketing authorisation holder(s) shall submit 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.

Furthermore, CHMP agreed that a communication to healthcare professionals through a joint DHPC should be sent by the MAHs, to which the MAHs agreed.