1 July 2010
EMA/740640/2010
Patient Health Protection

Assessment report for Gadolinium-containing contrast agents

International Non-proprietary Name: gadodiamide, gadopentetic acid, gadobenic acid, gadoxetic acid, gadoteridol, gadobutrol and gadoteric acid

Procedure No. EMEA/H/A-31/1097

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7051
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

1. SCIENTIFIC DISCUSSION

1.1. Introduction

The gadolinium-containing contrast agents (GdCAs) are intravenous agents used for contrast enhancement with magnetic resonance imaging (MRI) and with magnetic resonance angiography (MRA). The GdCAs (gadodiamide, gadopentetic acid, gadobenic acid, gadoxetic acid, gadoteridol, gadobutrol and gadoteric acid) have been available in Europe since the late 1980's for different types of MR scan varying from product to product, including liver, brain and whole body scan. One gadopentetic acid contrast agent[1] was approved for the evaluation of renal function in some Member States.

GdCAs were first associated with nephrogenic systemic fibrosis (NSF) in January 2006 when five end-stage renal failure patients undergoing MRA developed signs of NSF two to four weeks after GdCAs administration[2,3]. This followed a cluster of 25 cases of NSF (20 in Denmark and 5 in Austria) in patients with severe renal impairment, to whom gadodiamide[4] had been administered. Since June 2006 there have been reports of NSF associated with other GdCAs and this issue has been subject to close regulatory reviews leading to risk minimisation measures at the national level.

In early 2007, following advice from the Pharmacovigilance Working Party (PhVWP) of the Committee for Medicinal Products for Human Use (CHMP), the use of gadodiamide and gadopentetic acid was contraindicated in patients with severe renal impairment and corresponding warnings were recommended for the other GdCAs. The PhVWP also advised that the risk of NSF depended on the thermodynamic and kinetic properties of the GdCAs.

The CHMP Scientific Advisory Group for Diagnostics (SAG-Diagnostic) convened in December 2007 supported the categorisation of GdCAs according to NSF risk based on their thermodynamic and kinetic properties, as follows:

- **High risk*:**

a) *Linear non-ionic chelates* including gadoversetamide (OptiMARK) and gadodiamide (Omniscan).

b) *Linear ionic chelate* gadopentetate dimeglumine (Magnevist, Gado-MRT-ratiopharm[5], Magnegita).

- **-Medium risk:**

Linear ionic chelates including gadofosveset trisodium (Vasovist), gadoxetic acid disodium (Primovist) and gadobenate dimeglumine (MultiHance).

- **Low risk:**

Macrocyclic chelates including gadoterate meglumine (Dotarem), gadoteridol (ProHance) and gadobutrol (Gadovist).

* the risk of NSF with Omniscan and OptiMARK appears higher than with Magnevist based on physicochemical properties, studies in animals and the number of cases of NSF reported worldwide. As the risk with Magnevist remains substantially higher than the NSF risk with the medium and low risk GdCAs, the CHMP in 2009 reiterate that Magnevist is to be retained in the high risk group.

[1] Magnevist
[2] Grobner T. *Nephrol Dial Transplant*. 2006 Apr;**21**(4):1104-8.
[3] Grobner T. *Nephrol Dial Transplant*. 2006 Jun;**21**(6):1745. (Grobner, 2006 erratum)
[4] Omniscan
[5] Gadopentetic acid generics

Concerns on the lack of harmonisation with regards to the use of GdCAs during pregnancy and lactation, in patients undergoing liver transplantation, in infants, neonates and children and in the elderly, were raised by the SAG-Diagnostic who also highlighted the need for further research to clarify the issue of NSF associated with GdCAs.

Further to discussions held during 2008 aimed at developing risk minimisation measures for a core Risk Management Plan for all GdCAs, in November 2008 Denmark asked the CHMP, under article 31 of Directive 2001/83/EC, as amended, to provide an opinion on whether the marketing authorisations for all GdCAs should be varied in relation to its use in specific patient population'. Denmark also expressed the interest for the community to have a traceability method for effective monitoring of the use of GdCAs and the need to further explore the long-term consequences of gadolinium accumulation in bone and skin.

The CHMP reviewed the safety data from clinical studies, non-clinical studies and spontaneous reports provided by the MAHs involved in this procedure. The review of the CHMP focussed specifically on the measures to minimise the risk for NSF in specific patient groups, concerns regarding accumulation of gadolinium in bone and skin tissue and further measures to minimise the risk of NSF.

1.2. Clinical Safety

NSF is a rare, serious and life-threatening syndrome involving fibrosis of the skin, joints and internal organs in patients with severe renal impairment. Its association with the GdCAs was first reported in January 2006. The risk of NSF is dependent on the GdCAs' physicochemical properties and on other contributory factors.

Nephrogenic systemic fibrosis (NSF) reported cases

The incidence of NSF, up until the 2007 European recommendations with regards to severe renal impairment and the use of GdCAs, varied widely between EU Member State due to the choice of imaging methods for renally impaired patients and to the choice of contrast agent[6].

In one centre in Denmark, a high risk of 18% of NSF was reported among patients with chronic kidney disease stage 5 (CKD5)[7] to whom gadodiamide was administered. Higher prevalence was seen in CKD5 patients with repeated exposures.

No NSF cases were reported in a retrospective survey of 141 long-term haemodialysis patients who had received gadoteridol[8] during the period 2000 to 2007[9] or in the FINEST study (Fibrose Néphrogénique SisTémique) which included 308 patients with renal impairment (CKD5 in 54%)[10] treated mainly with gadoteric acid[11].

Overall, these articles conclude that the more stable GdCAs (macrocyclic agents) are less likely to induce NSF. This difference of risk is also seen by the NSF reported cases on the MAH databases and estimated usage from launch to February 2009 as follows.

[6] Cowper SE, Robin HS, Steinberg SM *et al. Lancet* 2000; **356:**1000-1.
[7] Marckmann P. *Europ J Radiol* 2008; **66(2)**: 187-90.
[8] ProHance
[9] Reilly RF. *Clin J Am Soc Nephrol* 2008: **3**: 747-751.
[10] Janus N, Launay-Vacher V, Karie S *et al. Europ J Radiol* 2009. In press.
[11] Dotarem

Contrast agent	No. NSF reports		No. administrations (millions)
	Unconfounded	Confounded	
Omniscan	438	90	47
OptiMARK	7	11	0.8
Magnevist	135	276	95
MultiHance	0	8	6
Primovist	0	0	0.15
Vasovist	0	0	0.05
Gadovist	1*	2	2.6
ProHance	1	13	12.3
Dotarem	1**	11	22.4

*Case published on 5 October 2009

**9 years prior to Dotarem administration, the patient had received an unknown GdCA. Case is still under investigation.

The relative risk (assuming a risk of 100% for gadodiamide) based on the 580 unconfounded cases reported up to Februay 2009 shows a higher risk for gadodiamide (100%), gadoversetamide[12] (94%), and gadopentetic acid (10%) and <1% for gadoteridol and gadoteric acid. No relative risk was estimated for gadobenic acid[13], gadoxetic acid[14], gadofosveset[15] and gadobutrol[16] as their usage is too low to allow an estimation of the relative risk.

The CHMP noted that the risk with gadopentetic acid is one-tenth of that observed with gadodiamide and gadoversetamide however, still markedly higher than that associated with the other GdCAs.

Physicochemical and pharmacokinetic properties of GdCAs

All available GdCAs are chelate complexes containing Gd^{3+}, the highly toxic gadolinium ion, which potentially may be released through transmetallation with endogenous ions from the body[17]. The extent of transmetallation differs significantly between the complexes with the linear chelates more likely to release Gd^{3+} than the cyclical chelates where the gadolinium ion is caged in a cavity[18]. Other factors such as renal impairment would likely increase the toxicity of the complexes by slowing the clearance of Gd^{3+}.

In the complexes, the release of Gd^{3+} is minimised by the presence of excess ligand included in the formulation of the less stable gadolinium complexes (excess ligand is present in Omniscan (5%) and OptiMARK (10%) and small amounts in Magnevist, ProHance and Gadovist (0.1%)). However, the excess ligand is known not to fully block Gd^{3+} release[19].

Pharmacokinetic properties of GdCAs also contribute to the risk of NSF as the longer a GdCAs remains in the body the greater the level of risk. All GdCAs have a certain degree of renal elimination, which varies from 50% for gadoxetic acid (with 50% hepatic elimination) to 100% for most other agents. Other unique pharmacokinetic properties of GdCAs could potentially have a contributory role (e.g the prolonged serum half-life of gadofosveset due to its unique binding properties to serum albumin).

[12] Optimark
[13] MultiHance
[14] Primovist
[15] Vasovist
[16] Gadovist
[17] Thomsen HS *et al*. *Clin Radiol* 2006; **61**: 905–06.
[18] Idée JM et al. Fundam Clin Pharmacol 2006; **20**: 563–76.
[19] Sieber MA, Lengsfeld P, Walter J *et al. J Magn Reson Imaging* 2008; 27: 955-62.

The physicochemical properties of GdCAs are especially important for renally impaired patients as these patients have reduced clearance of the GdCA from the body. To date no cases of NSF have been reported in patients with normal renal function.

Other contributory factors

Cumulative dose

Although some NSF cases have been reported following the administration of a single dose of a GdCA namely with gadodiamide and gadopentetic acid, published data[20], show that higher cumulative doses of gadodiamide are associated with an increased risk of NSF.

Dosing interval

A new pre-clinical study conducted by one of the concerned GdCAs' MAH showed that the occurrence of NSF-like skin lesions in rats following exposure to gadodiamide is influenced by the dosing interval: the shorter the interval between injections, the more severe the skin lesions.

Calcium and phosphate levels

It is suggested that high levels of ionised calcium and phosphate promote the release of toxic Gd^{3+} by transmetallation. Marckmann noted that NSF cases had higher serum concentrations of ionised calcium and phosphate at the time of gadodiamide exposure compared with controls. Frenzel et al (2008)[21] reported that phosphate accelerated the release of Gd^{3+} from non-ionic linear GdCAs and, to a lesser degree, from the ionic linear GdCAs. After 15 days, release of Gd^{3+} from the non-ionic linear GdCAs was about ten times higher than from the ionic linear GdCAs. All three macrocyclic agents remained stable in human serum at both normal and elevated phosphate levels.

Gadolinium accumulation in skin and bone tissue

In two non-clinical studies recently available[22,23] skin biopsies were taken from rats (not renally impaired and nephrectomised, respectively) treated for 5 consecutive days with 2.5 mmol GdCA/Kg. Gadolinium could be detected in the skin of animals treated with gadodiamide, gadoversetamide and gadopentetic acid for up to one year and could not be detected after 20 days in animals who received macrocyclic GdCAs. In nephrectomised rats, the gadolinium levels were much higher than those observed in rats not renally impaired: on day 49 the highest concentration of gadolinium was observed with gadodiamide administration, followed by gadoversetamide and gadopentetic acid. NSF skin lesions were only seen in gadodiamide-treated animals, in both studies.

In a study by Abraham *et al* (2008)[24] gadolinium was detected in skin lesions of all 20 patients who develop NSF, whereas in one patient not showing signs of NSF no gadolinium was detected. Gadolinium concentration increased over time in 10 patients. The ratio of gadolinium to calcium in tissue deposits was positively correlated with the GdCA dose and with serum ionised calcium at the time of GdCA exposure.

The authors concluded that toxic free gadolinium $Gd^{3+}$is released by transmetallation *in vivo* and retained in apatite-like deposits. The higher skin concentration of gadolinium shown in later biopsies than in early biopsies could be explained by initial storage of gadolinium in bone and subsequent mobilisation. Concerns were raised on the fact that regardless of the renal function at time of exposure

[20] Collidge TA, Thomson PC, Mark PB *et al. Radiology* 2007 ; **245(1)** :168-75.
[21] Frenzel T, Lengsfeld P, Schirmer H *et al. Invest Radiol* 2008; **43:** 817-28.
[22] Pietsch H, Lengsfeld P, Jost G *et al. Eur Radiol* 2009: **19**: 1417-24.
[23] Pietsch H, Lengsfeld P, Steger-Hartmann T *et al*. *Invest Radiol* 2009; **44**: 226-33.
[24] Abraham JL, Thakral C, Skov L *et al. Br J Dermatol.* 2008; **158 (2)**: 273-280.

to GdCAs, patients could develop at a later stage renal failure or other bone demineralising condition as a result of gadolinium mobilisation from bone storage.

Available data[25,26] on the retention of gadolinium following the use of GdCAs in animals and in humans shows that gadolinium is detected in bone and in other tissues such as the liver, kidney, muscle and spleen.

In view of the toxicity known to result from exposure to GdCAs by release of gadolinium in particular in patients with severe renal impairment, the importance of establishing the extent of gadolinium retention and mobilisation from the bone needs to be further explored. This should be applicable to all GdCAs and with testing of bone samples from patients undergoing hip and knee replacement surgery being recommended. Co-factors that may increase the risk of NSF such as serum calcium and phosphate levels at the time of administration of a GdCA should also be studied and biomarkers evaluated.

1.3. Risk Minimisation Activities

Product Information

The CHMP requested an update of the restrictions and warnings proposed in the product information of all GdCAs in order to minimise of the risk of NSF in special groups of patients with the potential more exposed to develop NSF associated with renal impairment. Other associated factors that contribute to the risk of NSF in renally impaired patients such as the administration of higher cumulative doses, repeated administration, short dosing intervals and ionised calcium and phosphate levels at the time of administration, were also considered.

Use during pregnancy and lactation

Use during pregnancy is not recommended for any GdCAs. The possibility of gadolinium accumulation in human tissues precludes use during pregnancy unless the benefit of an enhanced scan for the condition outweighs the risk of NSF.

Use during lactation and the proposal for discontinuation of breast feeding for at least 24 h after administration was discussed in particular within the SAG-Diagnostic held in 2007. It is acknowledged that only very small amounts of gadolinium are excreted into human breast milk. However, considering the immaturity of foetal kidneys which could delay the excretion of gadolinium and the possibility of long-term accumulation of gadolinium in tissues, it was agreed that discontinuation for at least 24 h is recommended for all patients being administered high NSF risk GdCAs i.e. gadoversetamide, gadodiamide and gadopentetic acid. For all other GdCAs, this precautionary measure should be left to discretion of the mother in consultation with the doctor.

Renally impaired patients and haemodialysis

The previous recommendation in 2007 to contraindicate the use of gadodiamide and gadopentetic acid, based on the evidence between GdCA exposure of patients with severe renal impairment and subsequent development of NSF, was now reconfirmed for the high risk GdCA category.

Strong warnings are included for medium and low NSF risk as regards use in patients with severe renal impair meant including dose restriction to a minimum during a scan and a minimum 7 day interval between administrations.

[25] Moran PR, Pekar J, Bartolini M *et al*. *Proc Intl Soc Mag Reson Med* 2002: 10.
[26] Gibby *et al*. *Invest Radiol* 2004; **39**: 138-42

Since the risk of NSF in moderate renal impairment patients is unknown for the high risk category of GdCAs, it was agreed that the use of these agents in this group of patients should only be considered after careful evaluation of the benefit-risk, and subject to dose restriction of not more than one injection of the minimum dose during a scan with a 7 day interval between administrations.

There is no evidence to support the use of haemodialysis for preventing or treating NSF in patients not already undergoing haemodialysis, but this may be useful for removing GdCAs from the body in patients already on haemodialysis. This information is reflected in all GdCAs' product information.

Liver transplant patients

Pre-operatively, about 15% of patients undergoing liver transplantation also suffer from severe renal impairment[27] and, post-operatively, acute renal failure requiring dialysis occurs in more than 50% of patients[28], therefore patients undergoing liver transplantation are at particular risk of NSF if exposed to GdCAs particularly to the high-risk GdCAs. The contraindication already in place for gadodiamide and gadoversetamide was extended to the gadopentetic acid products. Strong warnings are included in the GdCAs of medium and low NSF risk as regards use in this special population. However, if use is necessary then dose restrictions to a minimum dose during one scan and with a minimum 7 day interval between administrations are recommended.

Paediatric patients

The risk of NSF is unknown in neonates, who are known to be renally immature at birth with a glomerular filtration rate (GFR) of 10ml/min/1.73m^2 which increases to 20-30ml/min/1.73m^2 after two weeks[29].

The CHMP recommended contraindicating the use of the high risk category of GdCAs in neonates up to 4 weeks of age. The use of medium and low risk GdCAs in neonates should only be considered after careful consideration and subject to dose and interval administration restrictions.

Due to the immature renal function of infants below 1 year of age the use of all GdCAs should be subject to careful consideration and to dose and interval administration restrictions to not more than one injection of the minimum dose during a scan with a minimum 7 day interval between dose administrations.

Elderly patients

Considering that this patient population is more prone to experience impairment of renal function, no dose adjustment is recommended but screening of 65 years and older patients for renal dysfunction is of particular importance prior to the administration of GdCAs.

Other precautionary measures

Screening for renal dysfunction

Further to discussion at the SAG-Diagnostics, the CHMP concluded that for all patients to whom high NSF risk GdCAs will be administered, mandatory screening for renal dysfunction by laboratory tests is required. This screening is recommended for all patients who will receive medium and low NSF-risk GdCAs.

Initially it was considered that the assessment could be based firstly on the patient's current medical condition and medical history, and then if medically indicated the appropriate laboratory testing could be performed. However, as changes in renal function are often not reflected symptomatically or

[27] Seu P, Wilkinson AH, Shaked A *et al. AM Surg* 1991; **57**: 806-9
[28] Bilbao I, Charco R, Balsells J *et al. Clin Transplant* 1998; **12** (2): 123-9
[29] www.emea.europa.eu/pdfs/human/paediatrics/3513203en.pdf

clinically it was agreed that, to effectively assess the renal function of all at-risk patients, laboratory testing has to be performed. This is particularly important if high risk agents are to be used and therefore screening should be mandatory for all patients prior to the use of these agents.

Risk Management Plan

The MAHs of all GdCAs submitted a risk management plan. Having considered the data submitted in the responses to the list of questions, the committee is of the opinion that additional risk minimisation activities are required for all GdCAs beyond those included in the product information.

In particular, the CHMP agreed on the need for studies evaluating the potential for long-term retention of gadolinium in bone. Therefore, the MAHs are requested to submit to the CHMP protocols and timelines for the studies of gadolinium accumulation in human bone within 3 months of the Commission Decision on this referral procedure. The testing of bone samples from patients undergoing hip and knee replacement surgery is recommended. Co-factors that may increase the risk of NSF such as serum calcium and phosphate levels at the time of administration of a GdCA should be studied and biomarkers evaluated.

In addition, the MAHs should submit a cumulative review on NSF cases annually for 3 consecutive years commencing one year after the Commission Decision on this referral procedure.

Risk Minimisation Measures

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

To have a harmonised traceability method across Europe for effective monitoring of the use of GdCAs. It was agreed that the use of “sticky labels” detachable from the vials and syringes are an appropriate method and are currently in place for some GdCAs.

1.4. Overall Assessment

The gadolinium-containing contrast agents (GdCAs) – gadoversetamide, gadodiamide, gadopentetic acid, gadobenic acid, gadofosveset, gadoxetic acid, gadoteridol, gadobutrol and gadoteric acid - are intravenous agents used for contrast enhancement with magnetic resonance imaging (MRI) and with magnetic resonance angiography (MRA). The GdCAs are available for different types of MR scan varying from product to product, including liver, brain and whole body scan.

GdCAs have been associated with nephrogenic systemic fibrosis (NSF), a rare, serious and life-threatening syndrome involving fibrosis of the skin, joints and internal organs in patients with severe renal impairment.

The estimated relative risk for NSF calculated based on the number of unconfounded cases and GdCA usage is higher for gadodiamide[4] (100%), gadoversetamide (94%), and gadopentetic acid (10%) and <1% for gadoteridol and gadoteric acid. No relative risk was estimated for the other GdCAs as their usage is too low.

All GdCAs are chelate complexes containing Gd^{3+}, the highly toxic gadolinium ion, which potentially may be released through transmetallation *in vivo*. The transmetallation differs significantly between the complexes with the linear chelates more likely to release Gd^{3+} than the cyclical chelates where the gadolinium ion is caged in a cavity. Other factors such as renal impairment would likely increase the toxicity of the complexes by slowing the clearance of Gd^{3+}.

Based on the above the CHMP recognised that there are different categories of NSF-risk for GdCAs:

High risk:

a) *Linear non-ionic chelates* including gadoversetamide (OptiMARK) and gadodiamide (Omniscan).

b) *Linear ionic chelate* gadopentetic acid (Magnevist, Gado-MRT-ratiopharm, Magnegita, Marktiv).

Medium risk:

Linear ionic chelates including gadofosveset trisodium (Vasovist), gadoxetic acid disodium (Primovist) and gadobenate dimeglumine (MultiHance).

Low risk:

Macrocyclic chelates including gadoterate meglumine (Dotarem), gadoteridol (ProHance) and gadobutrol (Gadovist).

The CHMP recognises that within the high risk group the risk of NSF with gadodiamide and gadoversetamide appears higher than with gadopentetic acid based on physicochemical properties, studies in animals and the number of cases of NSF reported. However as the risk with gadopentetic acid remains substantially higher than the NSF risk with the other lower risk contrast agents, the CHMP recommended that gadopentetic acid should be retained in the high risk group and be subject to the same risk minimisation measures.

In order to minimise the recognised risk associated with GdCAs and the development of NSF, the CHMP agreed on the following measures for the following at risk patient groups:

Use during pregnancy and lactation

Use during pregnancy is not recommended for any GdCA due to the possibility of gadolinium accumulation inn human tissues. Although only small amounts of gadolinium are excreted into human breast milk, the immaturity of foetal kidneys could delay the excretion of gadolinium leading to the possibility of long-term accumulation of gadolinium in tissues. Discontinuation of breast feeding for at least 24 h is therefore recommended for all patients receiving high NSF-risk GdCAs. For all other GdCAs, the continuation or suspension of breast feeding is left to the discretion of the mother in consultation with the doctor.

Renally impaired patients and haemodialysis

The use of high risk GdCAs is contraindicated in patients with severe renal impairment. Strong warnings are included in the GdCAs of medium and low NSF risk as regards use in patients with severe renal impaired but subject to dose restriction to a minimum during a scan and with a minimum 7 day interval between administrations.

For patients with moderate renal impaired, since the risk is unknown for the high risk category of GdCAs it was agreed that use should only be considered after careful consideration of the benefit-risk, subject to dose restriction to not more than one injection of the minimum dose during a scan with a minimum 7 day interval between administrations.

There is no evidence that supports the use of haemodialysis for preventing or treating NSF in patients not already undergoing haemodialysis, but this may be useful at removing GdCAs in patients already on haemodialysis. This information is reflected in all GdCAs' product information.

Liver transplant patients

Patients undergoing liver transplantation are at particular risk of NSF if exposed to GdCAs particularly to the high-risk GdCAs. Therefore the use of high-risk GdCAs is contraindicated in this population. Strong warnings are included for medium and low NSF risk GdCAs as regards use in this particular special population. However, if use is necessary then dose restrictions to a minimum dose during one scan with a minimum 7 day interval between administrations are recommended.

Paediatric patients

The use of the high risk category of GdCAs in neonates up to 4 weeks of age is contra-indicated. The use of medium and low risk GdCAs in neonates should only be considered after careful consideration subject to dose and interval administration restrictions.

Due to immature renal function of infants below 1 year of age, the use of all GdCAs should be subject to careful consideration and to dose and interval administration restrictions to not more than one injection of the minimum dose during a scan with a minimum 7 day interval between dose administrations.

Elderly patients

No dose adjustments are recommended but screening of 65 years and older patients for renal dysfunction is of particular importance prior to the administration of GdCAs.

Other precautionary measures

Screening for renal dysfunction

For all patients to whom high NSF risk GdCAs will be administered, mandatory screening for renal dysfunction by laboratory tests is required. This screening is recommended for all patients who will receive medium and low NSF-risk GdCAs.

Laboratory tests are more effective to assess the renal function of all at-risk patients, since changes in renal function are often not reflected symptomatically or clinically.

In addition to the minimisation measures included in the product information, the CHMP having considered the evidence that toxic free gadolinium ions are retained in human tissues concluded that studies evaluating the potential for long-term retention of gadolinium in bone are needed. Therefore, the MAHs are requested to submit to the CHMP protocols and timelines for the studies of gadolinium accumulation in human bone within 3 months of the decision on this referral procedure. The testing of bone samples from patients undergoing hip and knee replacement surgery is recommended. Co-factors that may increase the risk of NSF such as serum calcium and phosphate levels at the time of administration of a GdCA should be studied and biomarkers evaluated.

The CHMP also requested the submission of cumulative review of NSF cases annually and for 3 consecutive years commencing one year after the decision on this referral procedure.

The need to have a harmonised traceability method across Europe for effective monitoring of the use of GdCAs was agreed. The use of “sticky labels” detachable from the vials and syringes are considered an appropriate method to be implemented for all GdCAs.

1.5. Communication plan

As part of this referral procedure, the CHMP agreed the wording of a key message document for communication to healthcare professionals to inform prescribers of the agreed measures to minimise

the risk of NSF with all GdCAs in patients at risk of developing the condition, to be sent to relevant health care professionals through the National Competent Authorities.

1.6. Changes to the Product information

In line with the above, amendments were agreed to be made to the relevant paragraphs in sections 4.2, 4.3, 4.4, 4.6, 4.8, 4.9 and 6.6. The package leaflet changes reflect the amendments agreed for the SPCs. Detailed changes can be found in Annex III to the Opinion. Labelling changes to reflect the use of "sticky labels" detachable from the vials and syringes will be implemented at a national level.

1.7. Re-examination procedure

On 25 January 2010, the MAH for Omniscan (gadodiamide) submitted the detailed grounds for the re-examination request to the EMEA. These related to the warnings proposed in the product information with respect to screening patients for renal dysfunction put in place to minimise the NSF-risk of GdCAs.

The MAH supported the CHMP proposed risk minimisation for all patients to be screened for renal dysfunction irrespective of the GdCAs. However, screening should only require laboratory testing following evaluation of the patient's medical history and the minimisation measure should be the same for all GdCAs.

The MAH argued that a first screening by medical history would identify patients for whom a glomerular filtration rate measurement (laboratory test) alone would not be a reliable measure of renal function (e.g., patients with acute renal failure). In addition, the MAH pointed out that mandatory laboratory testing of all patients could lead to delay in patient's diagnosis and management. The MAH also considered that differentiation of the amount of screening required *as per* the different categories of NSF-risk for GdCAs is unsupported by any observational evidence or clinical data and therefore no discrimination between the requirements and wording for patients screening before use should be made.

The CHMP acknowledged that indeed medical history could identify some patients with possible renal dysfunction which could then be confirmed by laboratory tests. However, medical history alone should not be relied on, as it would not be sufficient in all patients. Laboratory tests are more effective to assess the renal function in all at-risk patients, since changes in renal function are often not reflected symptomatically or clinically. Encouraging appropriate testing of renal function should ensure identification of patients at risk and ensure use of appropriate diagnostic agents. In addition, a two step approach of the screening would probably cause more delay in the patient's diagnosis and management.

Considering all available data for the referral procedure, as discussed throughout this report, the CHMP recognised different categories of NSF-risk for GdCAs based on their thermodynamic and kinetic properties. The risk minimisation measures applied were based on this categorisation. Therefore and considering the overall benefit/risk, the CHMP agreed that for all patients to be administered high NSF-risk GdCAs mandatory screening by laboratory tests should be performed.

Based on the above, the CHMP concluded that its Opinion of 19 November 2009 should be maintained with the recommended amendments to relevant sections of the Summary of Product Characteristics and Package Leaflet as set out in Annex III to the opinion.

2. OVERALL CONCLUSION

Having considered the overall submitted data provided by the MAHs in writing and in the oral explanations, the CHMP recommended amendments to the marketing authorisations of the medicinal products referred to in Annex I. The relevant sections of the Summary of Product Characteristics and package leaflet are set out in Annex III to the opinion.

Following consideration of the detailed grounds for re-examination provided by the MAH for Ominscan (gadodiamide) in writing, the CHMP concluded that medical history alone should not be relied on, as it will not be sufficient to identify all at-risk patients. Laboratory tests are more effective to assess the renal function of all at-risk patients, since changes in renal function are often not reflected symptomatically or clinically.

Therefore, the CHMP concluded that its Opinion of 19 November 2009 should be maintained with the recommended amendments to relevant sections of the Summary of Product Characteristics and Package Leaflet as set out in Annex III to the opinion.

The conditions affecting the Marketing Authorisations are set out in Annex IV.