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SCIENCE MEDICINES HEALTH

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Patient Health Protection

ASSESSMENT REPORT FOR OPTIMARK

International Non-proprietary Name: **gadoversetamide**

Procedure No. **EMEA/H/C/000745/A20/0004**

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

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Table of contents

1. BACKGROUND INFORMATION

Optimark (gadoversetamide) is a chelate complex containing gadolinium and the ligand versetamide. Optimark is an intravenous agent for contrast enhancement which is centrally approved since 23 July 2007 for used only in medical diagnostic with magnetic resonance imaging (MRI) of the central nervous system and liver.

Other gadolinium-containing contrast agents (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* gadopentetic acid (Magnevist, Gado-MRT-ratiopharm, Magnegita).

- **Medium risk:**
  Linear ionic chelates including gadofosveset (Vasovist), gadoxetic acid (Primovist) and gadobenic acid (MultiHance).

- **Low risk:**
  Macrocyclic chelates including gadoteric acid (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.

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.

[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

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 populations. 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.

In view of the above the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004 for Optimark. The European Commission requested the CHMP on 19 November 2008 to assess the above concerns and to give its opinion on measures necessary to ensure the safe and effective use of Optimark, and on whether the marketing authorisation for this product should be varied.

The CHMP reviewed the safety data from clinical studies, non-clinical studies and spontaneous reports provided by Covidien and all the other MAHs concerned by this issue (MAHs involved in the parallel Article 31 referral 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.

After reviewing all the available data to address these concerns, the CHMP adopted an opinion 19 November 2009.

2. SCIENTIFIC DISCUSSION

Clinical Aspects

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[5].

In one centre in Denmark, a high risk of 18% of NSF was reported among patients with chronic kidney disease stage 5 (CKD5)[6] to whom gadodiamide[4] 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[7] during the period 2000 to 2007[8] or in the FINEST study (Fibrose Néphrogénique SisTémique) which included 308 patients with renal impairment (CKD5 in 54%)[9] treated mainly with gadoteric acid[10].

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.

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

Contrast agent	No. NSF reports	
	Unconfounded	Confounded
Omniscan	438	90
OptiMARK	7	11
Magnevist	135	276
MultiHance	0	8
Primovist	0	0
Vasovist	0	0
Gadovist	1*	2
ProHance	1	13
Dotarem	1**	11

*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[4]) based on the 580 unconfounded cases reported up to February 2009 shows a higher risk for gadodiamide[4] (100%), gadoversetamide[1] (94%), and gadopentetic acid[2] (10%) and <1% for gadoteridol[7] and gadoteric acid[10]. No relative risk was estimated for gadobenic acid[11], gadoxetic acid[12], gadofosveset and gadobutrol[13] 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[14]. 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[15]. 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[16].
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[12] (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).

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.

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

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[17,6] 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[6] 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)[18] 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[19,20] 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)[21] 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 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[22,23] 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.

[17] Collidge TA, Thomson PC, Mark PB *et al. Radiology* 2007 ; 245(1) :168-75.
[18] Frenzel T, Lengsfeld P, Schirmer H *et al*. *Invest Radiol* 2008; 43: 817-28.
[19] Pietsch H, Lengsfeld P, Jost G *et al. Eur Radiol* 2009: 19: 1417-24.
[20] Pietsch H, Lengsfeld P, Steger-Hartmann T *et al*. *Invest Radiol* 2009; 44: 226-33.
[21] Abraham JL, Thakral C, Skov L *et al. Br J Dermatol.* 2008; 158 (2): 273-280.
[22] Moran PR, Pekar J, Bartolini M *et al*. *Proc Intl Soc Mag Reson Med* 2002: 10.
[23] Gibby *et al*. *Invest Radiol* 2004; 39: 138-42

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.

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 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. The following restrictions were agreed for the high-risk GdCAs including gadoversetamide:

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 patients being administered high NSF risk GdCAs including gadoversetamide.

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.

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[24] and, post-operatively, acute renal failure requiring dialysis occurs in more than 50% of patients[25], 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.

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[26].

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

The CHMP recommended contraindicating the use of the high risk category of GdCAs in neonates up to 4 weeks of age. 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. 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 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.

Considering that Optimark was approved in July 2007 some of the restrictions requested for the high-risk GdCA were already included in the product information for Optimark. Namely, the contraindication in patients with severe renal impairment and liver transplant patients, and in paediatric patients for which the measures were already in place.

Risk Management Plan

As requested an updated risk management plan was submitted for Optimark. As part of the Post-Authorisation Commitments for Optimark, the MAH has undertaken to conduct basic physicochemical investigations and mechanistic studies to investigate the potential role of gadoversetamide in the aetiology of NSF. As requested by the CHMP, the MAH has developed a plan for the basic physicochemical investigation of Optimark by performing mechanistic *in vitro* and *in vivo* studies.

Results of these *in vitro* and *in vivo* studies led to the design of a major *in vivo* study that is currently ongoing. The goal of this study is to use 5/6 nephrectomy and diet to modify the levels of phosphate ion present in rat tissues, and to determine the impact on tissue deposition of gadolinium, calcium, phosphate, Fe and Zn following treatment with GdCAs. This study is expected to be completed by end of 2009. The MAH was also requested to propose clinical studies involving patients who are undergoing skin biopsies or bone or joint surgery with bone removal. The MAH questioned the usefulness of performing such studies taking into account that previous animal and human studies suggested that gadolinium will be found, but without the ability to determine the form of gadolinium or a better understanding of this condition that may alter gadolinium deposits, it is unclear to the MAH the scientific value that this observations would have.

The CHMP concluded that evidence now exists showing that toxic free gadolinium ions are released *in vivo* through transmetallation, are retained in bone and skin, and are associated with the development of NSF at varying times after gadolinium administration. Of particular concern is the possibility that gadolinium may be mobilised from bone stores in patients who subsequently develop renal failure or other bone demineralising conditions[27]. It is therefore important to establish the extent of retention of gadolinium in human tissues following the use of high risk agents in patients with normal and with impaired renal function. 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.

[27] Abraham JL, Thakral C, Skov L *et al. Br J Dermatol.* 2008; 158 (2): 273-280.

Therefore, the MAH is requested to submit protocols and timelines for the studies of gadolinium accumulation in human bone within 3 month of the decision on this Article 20 of Regulation (EC) No 726/2004 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 decision on this referral procedure.

Risk Minimisation Measures

The CHMP, having considered the data submitted is of the opinion that for the safe and effective use of Optimark, the following additional risk minimisation activities are required for all GdCAs beyond those included in the product information:

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. These labels should contain the following information:

- a short reminder phrase (with a clearly readable font size and format) such as "This sticky label should be stuck onto patient records."
- name of the product
- volume presentation
- batch number

The MAH will submit an educational program aiming to improve the traceability of Optimark and will include information on the use of sticky labels.

Product Information

In line with the above, amendments were agreed to be made to 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. The CHMP agreed changes to be introduced in the Summary of Product Characteristics (SPC), Annex II, and Package Leaflet.

Communication Plan

As part of this 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.

3. DISCUSSION AND BENEFIT/RISK ASSESSMENT

Optimark (gadoversetamide) is a chelate complex containing gadolinium and the ligand versetamide. Optimark is an intravenous agent for contrast enhancement for used only in medical diagnostic with magnetic resonance imaging (MRI) of the central nervous system and liver.

Other gadolinium-containing contrast agents (GdCAs) - gadodiamide, gadopentetic acid, gadobenic acid, gadoxetic acid, gadoteridol, gadobutrol and gadoteric acid - have been available in Europe 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[1] (94%), and gadopentetic acid[2] (10%) and <1% for gadoteridol[7] and gadoteric acid[28]. 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).

Medium risk:
Linear ionic chelates including gadofosveset (Vasovist), gadoxetic acid (Primovist) and gadobenic acid (MultiHance).

Low risk:
Macrocyclic chelates including gadoteric acid (Dotarem), gadoteridol (ProHance) and gadobutrol (Gadovist).

The CHMP recognises that within the high risk group the risk of NSF with gadodiamide[4] and gadoversetamide appears higher than with gadopentetic acid[1] based on physicochemical properties, studies in animals and the number of cases of NSF reported. However as the risk with gadopentetic acid[1] remains substantially higher than the NSF risk with the other lower risk contrast agents, the CHMP recommended that gadopentetic acid[1] 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 the high-risk 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 in 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.

Renal impaired patients and haemodialysis
The use in patients with severe renal is contraindicated. For patients with moderate renal impairment, since the risk is unknown 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 the 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 its use is contraindicated.

Paediatric patients
The use in neonates up to 4 weeks of age is contra-indicated. 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.

[28] Dotarem

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. 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 the toxic free gadolinium ions are retained in human tissues concluded that studies evaluating the potential for long-term retention of gadolinium in the bone are needed. Therefore, the MAH is requested to submit protocols and timelines for the studies of gadolinium accumulation in human bone within 3 month of the decision on this procedure under Article 20 of Regulation (EC) No 726/2004. 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 recommended the submission of a cumulative review on NSF cases annualy for 3 consecutive years commencing within one year of the European Commission decision.

The need to have a harmonised traceability method across Europe for an 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 to all GdCAs.

The Marketing Authorisation of Optimark was therefore subject to the above described measures with the exception of the contraindication in patients with severe renal impairment and haemodialysis, liver transplant patients, and in paediatric patients for which the measures were already in place.

Furthermore, the MAH should submit a proposal for a Direct Healthcare Professional Communication in line with the key message document for communication to healthcare professionals to inform prescribers of the agreed measures to minimise the risk of NSF with Optimark.