

## Information for Healthcare Professionals and other Stakeholders

### **NEPHROGENIC SYSTEMIC FIBROSIS: AN UNCOMMON AND DEBILITATING DISEASE POSSIBLY ASSOCIATED WITH GADOLINIUM CHELATES**

Villepinte, 28 February 2011

*Any significant information (eg publication of results of a new study, results of the investigation of a pharmacovigilance case) may cause the issue of a new version of this document.*

#### **What is Nephrogenic Systemic Fibrosis (NSF)?**

NSF was first recognized in 1997 in 15 dialyzed patients and described in 2000 (1). This rare and highly debilitating disorder is characterized by extensive thickening and hardening of the skin associated with skin-colored to erythematous papules that coalesce into erythematous to brawny plaques with an “peau d’orange” appearance. Nodules are sometimes also described. Joint contractures may develop, with patients progressively becoming wheelchair-dependent. Patients often complain of pruritus, causalgia and sharp pains (2). The distal extremities are the most common area of involvement (with a distribution from ankles to mid-thighs and from wrists to mid-upper arms), followed by the trunk. The lesions are typically symmetrical. It is worth noting that the face and neck are virtually never involved (3). NSF always occurs in patients with severe or end-stage chronic kidney disease (CKD) (eGFR < 30 ml/mn/1.73 m<sup>2</sup>) (1-3), usually in those requiring a treatment by dialysis (2).

NSF can occur in all age-groups and there is no predilection for a geographic region, race or gender.

So far, there is no recognized treatment for NSF. It has been suggested that improving renal function may slow down the development of the disease and, in some cases, may reverse its course (2).

The mechanism of this highly debilitating disease remains unknown. Current literature suggests a multifactorial aetiology (4).

So far, several factors have been suggested to be frequently associated with the onset of NSF (Table 1):

**Table 1**  
**Recognized or possibly associated factors for NSF**

- Severe or end-stage renal failure (1-3)
- High cumulative dose of gadolinium chelate (5)
- High dose of erythropoietin (5,6)
- High serum phosphate levels (5)
- High serum calcium levels (5)
- Coexisting proinflammatory event (major surgery, infection, vascular event) (7)
- Iron mobilization (4)
- Metabolic acidosis (8) (debated: 7,9)
- History of hypothyroidism (10)
- History of deep venous thrombosis (10)
- Younger age (10)

In 2006, two European teams independently suggested a link between the administration of gadolinium (Gd) chelates used as contrast media for magnetic resonance imaging (MRI) and the occurrence of NSF in patients with renal failure (8,9). Numerous retrospective analyses rapidly followed and confirmed this temporal link (7,11-13).

The time to onset of the symptoms ranges between a few days and a few years following exposure to the gadolinium chelate. The majority of published cases occurred within 3 months (2).

The link between gadolinium-containing contrast media and NSF is considered probable (8, 9, 14, 15, 16) and awareness of this potential adverse reaction to gadolinium chelates is a major requirement for radiologists and specialists in patients with stage 4 and 5 chronic kidney disease.

### **Current Position of European Health Authorities**

In February 2007, the European Pharmacovigilance Working Party (PhVWP) of the European Medicines Agency (EMA) initially advised all contrast media marketing authorization holders to add warnings about the possibility that NSF may occur with gadolinium chelates to section 4.4 of the Summary of Product Characteristics (SPC).

There are two generally recognized categories of gadolinium chelates: macrocyclic molecules where  $Gd^{3+}$  is caged in the pre-organised cavity of the ligand (15), and the linear open chain molecules (15). Gadolinium chelates differ in their thermodynamic stability constants and in their kinetic stability. In general, pre-clinical and ex vivo studies have suggested that macrocyclic molecules are more stable than linear molecules (17-21).

In December 2007, the Scientific Advisory Group (SAG) for Diagnostics of the CHMP (Committee for Medicinal Products for Human Use) agreed with the PhVWP that the risk of developing NSF depends on the type of gadolinium-containing contrast agent used, and advised that these agents should be categorized into three groups:

- High risk: gadoversetamide (OptiMARK<sup>®</sup>), gadodiamide (Omniscan<sup>®</sup>) and gadopentetic acid (Magnevist<sup>®</sup>, Magneqita<sup>®</sup>, and Gado-MRT-ratiopharm<sup>®</sup>);
- Medium risk: gadofosveset (Vasovist<sup>®</sup>), gadoxetic acid (Primovist<sup>®</sup>) and gadobenidic acid (MultiHance<sup>®</sup>);
- Low risk: gadoteric acid (Dotarem<sup>®</sup>), gadoteridol (ProHance<sup>®</sup>) and gadobutrol (Gadovist<sup>®</sup>).

In November 2008 a referral procedure was triggered in order that the CHMP carry out an assessment of the risk of NSF for the authorized gadolinium-containing contrast agents, and recommend measures that could be taken to reduce this risk.

The final CHMP opinion was issued in November 2009, and was ratified by an European Commission decision in July 2010. The conclusions were the following:

Because the risk of developing NSF depends on the type of gadolinium-containing contrast agent used, the active substances are classified into the three categories of risk.

The CHMP's recommendations for the different agents vary according to their risk classification (Table 2).

The CHMP recommended that the prescribing information of all gadolinium-containing contrast agents should include a statement that the type and dose of contrast agent used should be recorded; in that view, "sticky labels" removable from the vials and syringes have to be implemented.

Finally, the CHMP advised that studies should be performed to evaluate the potential of long-term retention of gadolinium in bone. In addition, a cumulative revue of NSF cases should be submitted annually for 3 years.

**Table 2**

**Revised contra-indications and precautions for use of gadolinium-containing contrast agents (CHMP 2010)**

Risk class	LOW RISK: Dotarem <sup>®</sup> , ProHance <sup>®</sup> , Gadovist <sup>®</sup>	MEDIUM RISK: Primovist <sup>®</sup> , Vasovist <sup>®</sup> , MultiHance <sup>®</sup>	HIGH RISK: Omniscan <sup>®</sup> , Optimark <sup>®</sup> , Magnevist <sup>®</sup>
Pregnancy	Not recommended, unless benefit risk ratio assessed as favorable		
Lactation	Continuation or suspension 24h according to mother's decision (in consultation with the physician)		Discontinuation at least 24h
Renal insufficiency (RI), hepatic transplantation, dialysis	Precaution in severe RI and hepatic transplanted patients: minimum diagnostic dose and minimum 7 days between administrations	To be avoided in severe RI and hepatic transplanted patients If used, minimum diagnostic dose and minimum 7 days between administrations	Contra-indication in severe RI and hepatic transplanted patients Precaution in moderate RI patients, according to benefit risk ratio, minimum diagnostic dose and minimum 7 days between administrations
	No evidence supporting the use of haemodialysis for preventing or treating NSF in non-dialyzed patients, may be useful in dialyzed patients		
Paediatric population	Precaution in neonate, minimum diagnostic dose and minimum 7 days between administrations		Contra-indication in neonate < 4 weeks
	Precaution in child < 1 year, minimum diagnostic dose and minimum 7 days between administrations		
Elderly patient	Important to screen patients > 65 years for renal dysfunction		
Screening of renal function	Recommended laboratory test to screen patients for renal dysfunction		Mandatory laboratory test to screen all patients for renal dysfunction

## **Current Position of US Health Authorities (FDA)**

In 2006, the Food and Drug Administration (FDA) alerted the public about cases of NSF reported in patients who received gadolinium chelates.

In 2007, the FDA required the addition of a boxed warning about the risk of NSF to the labelling of gadolinium chelates.

In December 2009, the safety of gadolinium chelates was reviewed during a Joint Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committee meeting.

Following that, in September 2010, the FDA made a Safety Announcement, requiring new changes in the labelling of gadolinium chelates, falling more closely into line with those requested by European Health Authorities.

High-risk gadolinium chelates (Optimark<sup>®</sup>, Omniscan<sup>®</sup>, Magnevist<sup>®</sup>) are contraindicated in patients with acute kidney injury (AKI) or with chronic severe kidney disease.

In addition, the FDA recommended a screening of patients for kidney problems using clinical history and laboratory testing.

The use of gadolinium chelates should be avoided in patients having impaired drug elimination, unless this use is necessary; in that case, signs and symptoms of NSF should be monitored after administration.

Administration of gadolinium chelates should not be repeated in a single imaging session.

Dotarem does not have a Marketing Authorization in the USA.

## **Guerbet Pharmacovigilance Data**

Guerbet markets meglumine gadoterate (Dotarem®), a macrocyclic, ionic gadolinium chelate associated with a high thermodynamic and kinetic stability (15-19).

The Department of International Pharmacovigilance of Guerbet manages the Adverse Events reported in a context of Dotarem® administration in accordance with the regulatory Pharmacovigilance reporting standards; in particular Volume 9A of the Rules Governing Medicinal Products in the European Union - Guidelines on Pharmacovigilance for Medicinal Products for Human Use – September 2009.

For each case reported as NSF and based on the available information, Guerbet has assessed the strength of the diagnosis of NSF and the causality of Dotarem® :

- the strength of the diagnosis of NSF using the clinicopathological score developed by Yale University (USA) on the basis of their registry of more than 250 cases, and discussing the differential diagnoses of the disease ;
- Dotarem® causality considering the available and missing information regarding the medical history of the patient, in particular renal function, the injection of the sole Dotarem® (single-agent case) or other gadolinium chelates (multiple-agent case), the chronology of both the injections and the clinical, biological and imaging events, other possible causative factors such as pro-inflammatory events.

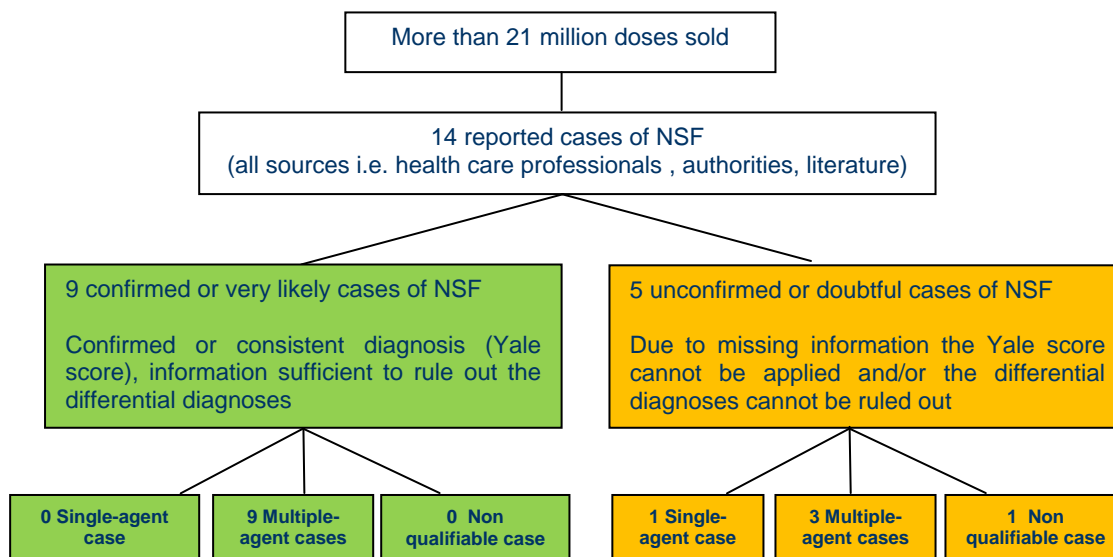
With respect to NSF, Guerbet has registered, to date, 14 medically-confirmed cases of patients who developed signs allowing this diagnosis to be considered and who received Dotarem®, for more than 21 millions of patients who received the product, and more than 850 cases of NSF reported worldwide (source European Medicines Agency, 2010).

On the basis of the available information, the diagnosis of NSF is confirmed or consistent according to the Yale score in only 2/3 of the reported cases, and the causality of Dotarem® is doubtful in all cases (Table 3).

In all cases the administration of Dotarem preceded the first symptoms, except for one patient who developed NSF after injection of linear gadolinium chelates, the disease worsening after she had undergone several Dotarem®-enhanced MRA, in a context of degradation of the renal function due to graft rejection.

**Table 3**

**NSF cases reported for patients having received Dotarem®**



**Position Statement**

At Guerbet, we significantly contribute to improving diagnosis for major disease areas (cardiovascular diseases, cancer, inflammatory and neurodegenerative diseases).

We are strongly committed to providing radiologists, cardiologists and healthcare professionals with a comprehensive range of innovative and effective contrast media to achieve their aim to provide optimum diagnosis for their patients.

A complete research programme is in progress at Guerbet and in cooperation with recognized academic centres to better understand the mechanism of NSF and thoroughly study the role of physicochemical properties of gadolinium chelates in its pathogenesis. The research programme includes a prospective clinical analysis of the safety of Dotarem®.

We are in full collaboration with Health Authorities for Pharmacovigilance issues with total transparency and consistently acting in the best interests of the patients is a fundamental principle at Guerbet. This is particularly true in the case of NSF and will remain so.

## **Further information about NSF and gadolinium chelates**

European Medicines Agency (EMA)

<http://www.ema.europa.eu>

US Food and Drug Administration (FDA)

<http://www.fda.gov/>

European Society of Urogenital Radiology (ESUR)

[http://www.esur.org/Nephrogenic\\_Fibrosis.39.0.html](http://www.esur.org/Nephrogenic_Fibrosis.39.0.html)

International Center for Nephrogenic Fibrosing Dermopathy Research (ICNFDR) (Yale University)

<http://www.icnfd.org>

American College of Radiology (ACR)

[www.acr.org/.../quality\\_safety/contrast\\_manual/NephrogenicSystemicFibrosis.asp](http://www.acr.org/.../quality_safety/contrast_manual/NephrogenicSystemicFibrosis.asp)

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