

Dear Colleague,

## Gadolinium-containing MRI contrast agents and Nephrogenic Systemic Fibrosis (NSF)

Nephrogenic Systemic Fibrosis (NSF) is a debilitating and sometimes fatal condition. It has been associated with some intravenous gadolinium-containing magnetic resonance imaging (MRI) contrast agents in patients with severe renal impairment. On the basis of the available evidence, the UK Commission on Human Medicines (CHM) together with the European Pharmacovigilance Working Party (PhVWP) of the Committee for Medicinal Products for Human Use (CHMP) recommended:

- **Do not use** Omniscan (gadodiamide) in patients with severe renal impairment (ie, GFR [glomerular filtration rate] <30mL/min/1.73m<sup>2</sup>) or in patients who have had, or who are awaiting, liver transplantation. Prescribers are also warned that gadodiamide should be used in neonates and infants up to 1 year of age only after careful consideration.
- **Careful consideration** should be given to the use of other gadolinium-containing MRI contrast agents in patients with severe renal impairment (ie, GFR <30mL/min/1.73m<sup>2</sup>).

Eight gadolinium-containing contrast agents are authorised in the UK: gadodiamide (Omniscan<sup>®</sup>), gadopentetic acid (Magnevist<sup>®</sup>), gadobenidic acid (MultiHance<sup>®</sup>), gadobutrol (Gadovist<sup>®</sup>), gadofosveset (Vasovist<sup>®</sup>), gadoteric acid (Dotarem<sup>®</sup>), gadoteridol (ProHance<sup>®</sup>) and gadoxetic acid (Primovist<sup>®</sup>).

### Nephrogenic systemic fibrosis (NSF)

NSF, also known as nephrogenic fibrosing dermopathy (NFD), is a rare condition characterised by the formation of connective tissue in the skin which becomes thickened, coarse and hard, sometimes leading to contractures and joint immobility. Patients with NSF can have systemic involvement of other organs including the lungs, liver, muscles, and heart. Five per cent of patients have a rapidly progressive fulminant clinical course. NSF has been reported only in patients with renal insufficiency. Although most affected patients have advanced or end-stage renal disease, a few cases have been reported in patients with only moderate renal dysfunction.

In early 2006, a possible causal link between NSF and gadolinium-containing MRI contrast agents was first identified. In an article, five of nine patients with end-stage renal failure (ESRF) who had received gadodiamide developed NSF 2–4 weeks later<sup>1</sup>. Shortly after this publication, a separate study reported that 13 patients with ESRF who had NSF had all received gadodiamide (median time from exposure 25 days [range 2–75])<sup>2</sup>.

Approximately 200 worldwide cases of NSF in those with renal impairment have now been reported with gadolinium-containing MRI contrast agents, most of which are associated with the least-stable agents<sup>3</sup> Omniscan and OptiMARK (the latter is not authorised in the EU). A small number of cases have been associated with Magnevist, one of which was considered directly attributable to Magnevist in a patient given multiple high doses of this contrast agent. We are not aware of reports of NSF with the other gadolinium-containing contrast agents.

### Mechanism

The mechanism by which some gadolinium-containing contrast agents are more likely to trigger NSF than other agents is not understood fully, but is thought to be related to their different physicochemical properties that affect the extent to which they release free gadolinium ions<sup>3, 4</sup>. Deposition of free gadolinium ions in

tissues and organs might stimulate NSF through induction of fibrosis<sup>5</sup>. Patients with severe renal impairment are at increased risk of NSF because they take longer to eliminate the contrast agent from the body—the half-life of gadodiamide increases from 1.3 hours in healthy volunteers to 34.3 hours in patients with ESRF<sup>6</sup>. Cases of NSF have also been reported in patients who have had or are awaiting liver transplantation. There are no known cases of NSF in patients with normal renal function.

### **Continuing investigation**

This matter will remain under continuous review, and new information and prescribing advice will be communicated as necessary.

Suspected adverse drug reactions should be reported to the Medicines and Healthcare products Regulatory Agency (MHRA) by use of a Yellow Card, which is available from MHRA, CHM Freepost, London SW8 5BR or electronically via the MHRA website (<http://www.mhra.gov.uk>).

Further information about NSF and gadolinium-containing MRI contrast agents can be found at the websites of Medicines and Healthcare products Regulatory Agency (MHRA) <http://www.mhra.gov.uk>; the European Society of Urogenital Radiology (ESUR) <http://www.esur.org>; and the International Center for Nephrogenic Fibrosing Dermopathy Research (ICNFDR) <http://www.icnfd.org>.

Yours faithfully,

### **Professor Sir Gordon Duff**

Chairman, Commission on Human Medicines

### **References**

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<sup>2</sup> Marckmann P, Skov L, Rossen K, Dupont A *et al*. Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. *J Am Soc Nephrol*. 2006 Sep;**17**(9):2359-62.

<sup>3</sup> Idée JM, Port M, Schaefer M, Le Greneur S, Corot C. Clinical and biological consequences of transmetallation induced by contrast agents for magnetic resonance imaging: a review. *Fundam Clin Pharmacol*. 2006 Dec;**20**(6):563-76.

<sup>4</sup> Thomsen HS, Morcos SK, Dawson P. Is there a causal relation between the administration of gadolinium based contrast media and the development of nephrogenic systemic fibrosis (NSF)? *Clin Radiol*. 2006 Nov;**61**(11):905-6.

<sup>5</sup> Morcos SK. Nephrogenic systemic fibrosis following the administration of extracellular gadolinium based contrast agents: Is the stability of the contrast agent molecule an important factor in the pathogenesis of this condition? (*In press*).

<sup>6</sup> Joffe P, Thomsen HS, Meusel M. Pharmacokinetics of gadodiamide injection in patients with severe renal insufficiency and patients undergoing hemodialysis or continuous ambulatory peritoneal dialysis. *Acad Radiol* 1998;**5**:491-502.