



Dear Healthcare Professional,

**Updated Safety information about Magnevist® and Nephrogenic Systemic Fibrosis (NSF)**

Bayer Schering Pharma AG (BSP) in consultation with the European regulatory authorities, including the Irish Medicines Board, would like to inform you about important updated safety information (contraindications and warnings) to the Summary of Product Characteristics (SmPC) for Magnevist® (Gadopentetate dimeglumine) concerning the potential risk of Nephrogenic Systemic Fibrosis (NSF). Magnevist® is a gadolinium-containing contrast agent for Magnetic Resonance imaging (MRI), and is used for cranial and spinal MRI and for general MRI of the body.

Revisions to the SmPC for Magnevist will be submitted in all EU Member States. The relevant sections of the SmPC to be amended are as follows:

**Section 4.3 (Contraindications)**

Use of Magnevist® is contraindicated in patients with severe renal impairment (GFR <30 ml/min/1.73m<sup>2</sup>).

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**Section 4.4 (Special warnings and precautions for use)**

**Impaired renal function**

There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of Magnevist and some other gadolinium-containing contrast agents in patients with severe renal impairment (GFR <30ml/min/1.73m<sup>2</sup>). Therefore Magnevist should not be used in these patients (see section 4.3 for Contraindications).

The risk for the development of NSF in patients with moderate renal impairment is unknown, therefore Magnevist should be used with caution in patients with moderate renal impairment (GFR 30-59 ml/min/1.73m<sup>2</sup>).

All patients should be screened, in particular patients over the age of 65, for renal dysfunction by obtaining a history and/or laboratory tests.

Haemodialysis shortly after Magnevist administration in patients currently receiving haemodialysis may be useful at removing Magnevist from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.

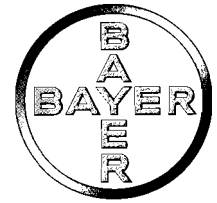
**Newborns and infants**

In neonates and infants up to 1 year of age Magnevist should only be used after careful consideration due to their immature renal function.

**Section 4.8 (Undesirable effects)**

Cases of NSF have been reported with Magnevist®.

NSF, also known as nephrogenic fibrosing dermopathy (NFD), was first described in the medical literature in 2000, with the first identified case occurring in 1997. A possible causal link between NSF and gadolinium-containing MRI contrast agents was first described in early 2006 (Grobner). NSF is seen only in patients that have dialysis-requiring renal failure or significantly impaired renal function, and causes fibrosis of the skin and connective tissues throughout the body. Signs and symptoms may include progressive thickening and induration of the skin with or without pigment alterations; contractures around the joints that may



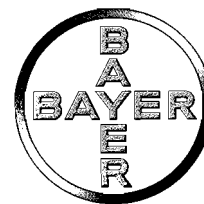
impair mobility; swelling (mostly of the lower extremities); redness; pruritus; and a burning sensation. Males and females are affected in approximately equal numbers, with onset generally during middle age, although paediatric cases have also been reported. The clinical course of NSF can be progressive and may be fatal. Currently, there is no known cure for NSF. Improvement of renal function seems to slow or arrest NSF, and may result in a gradual reversal.

The aetiology of NSF/NFD is still unknown, but is likely to be multifactorial. Various other concomitant factors in addition to gadolinium-containing contrast agents such as metabolic acidosis (Grobner, 2006) or vascular injury (Cowper, 2003) may also be related to development of NSF. A skin biopsy is necessary to make a definitive diagnosis of NSF.

Since July 2006 to May 31<sup>st</sup>, 2007, Bayer Schering Pharma AG has received 78 reports of patients who developed NSF after Magnevist® administration. All reports have been filed with the Health Authorities. For the majority of these reports, available information is insufficient for an adequate causality assessment. 27 of these reports have been classified as possibly related to the administration of Magnevist® based on all available information. In these reports, patient age ranges from 30 years to 80 years. 25 patients were on dialysis (time on dialysis ranges from less than 1 year to more than 20 years); one patient had chronic kidney disease with GFR <30 ml/min, but was not reported to be on dialysis; and one patient experienced acute renal failure, but the dialysis status was not known. Further investigations into these reports are ongoing.

Bayer Schering Pharma AG is working jointly with the European regulatory authorities to update the prescribing information in the SmPC for Magnevist® as described. The purpose of this letter is, however, to

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Page 4 of 5

inform you of this new product related information in advance of the formal modification of the SmPC.

Bayer Schering Pharma AG is committed to the safety of patients receiving our products and to keeping our customers informed about using these products safely and effectively. Bayer

Schering Pharma AG is following closely any reports of NSF, and is working with hospitals and experts in the field to conduct thorough investigations of the reports.

Any cases of NSF or other suspected adverse reactions suspected in association with Magnevist should be reported to the Marketing Authorisation Holder [see contact details for Irish agent below] or Irish Medicines Board in the usual way.

Should you require any further information, please contact HE Clissmann, the Irish Agent for Bayer Schering Pharma, at the following address:

HE Clissmann  
Irish Agent  
Bayer Schering Pharma AG  
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Yours sincerely,

A handwritten signature in black ink that reads "Conn Clissmann". The signature is written in a cursive, flowing style.

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Conn Clissmann  
HE Clissmann



Page 5 of 5

**References:**

Gadolinium – a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis

Grobner T, Nephrol Dial Transplant 2006 21: 1104-1108

*Erratum*

Gadolinium – a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis

Grobner T, Nephrol Dial Transplant 2006 21: 1104-1108

Nephrogenic fibrosing dermopathy – the first 6 years

Cowper SE, Current Opinion in Rheumatology 2003, 15: 785-790

Nephrogenic fibrosing dermopathy: suspect identified, motive unclear

Cowper SE, Bucala R, Am J Dermatopathol 25(4): 358, 2003