Bayer HealthCare
Pharmaceuticals

May 10, 2007

INFORMATIONAL UPDATE ON NSF

Dear Valued Customer,

As part of our on-going efforts to keep you updated regarding Nephrogenic Systemic Fibrosis (NSF), Bayer HealthCare Pharmaceuticals (formerly Berlex Laboratories), vendors of Magnevist® (gadopentetate dimeglumine), would like to provide you with important information.

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NSF, formerly known as Nephrogenic Fibrosing Dermopathy (NFD), is a rare but serious systemic disease first described in the medical literature in 2000. To date, the disease has been seen only in patients with significantly impaired renal function, most of whom had renal failure requiring dialysis at the time they developed NSF. NSF is characterized by fibrosis of the skin and other tissues throughout the body. The exact etiology of NSF is unknown but is likely to be multifactorial; specifically, the disease has recently been associated with the use of gadolinium-containing contrast agents. The clinical course of NSF can be progressive and may be fatal. Currently there is no known cure for NSF, although various treatments have been employed with variable success.

As of April 12, 2007, Bayer HealthCare Pharmaceuticals and its global affiliate had received and evaluated information about 53 patients reported to have developed NSF following Magnevist administration. All 53 have been reported to the FDA. Forty-seven reports originated from the US, 1 from Canada and 5 from Europe. Twenty-two of these 53 reports originated from a single US center. A majority of these 53 patients had experienced onset of signs and symptoms consistent with NSF prior to 2006, but all cases were only recently reported (after July 1st, 2006) as associated with Magnevist. The time span between the administration of MR contrast medium and the first recognized signs and symptoms in these 53 cases ranged between several days and several years. Some of these reports were confounded by administration of other gadolinium containing contrast agents or by lack of specific documentation of the brand of contrast agent used.

In terms of standardized causality assessments by Bayer HealthCare Pharmaceuticals, 19 of the 53 reports have been assessed as "possibly"[1] related to the administration of Magnevist; 30 have been assessed as "unclassifiable"[1] (meaning that currently available information is not sufficient to verify the diagnosis of NSF by deep skin biopsy and histopathology and/or to link the cases exclusively to the administration of Magnevist); and 4 have been assessed as "unlikely"[1] to be related to the administration of Magnevist. Further investigations into these reports are ongoing, and new information will be presented to the FDA as it becomes available.

Bayer HealthCare
Pharmaceuticals

Of the 19 reports of NSF assessed as "possibly" related to Magnevist, patient ages ranged from 30 to 80 years (median age = 61 years) and 17 patients were on dialysis at the time of Magnevist administration (time on dialysis ranging from less than one year to 20 years); one patient had chronic kidney disease (CKD) with GFR < 30 ml/minute, but was reported not to be on dialysis; and for one patient, the dialysis status was not known. Information on contrast volumes administered has been received for 15 of the 19 reports; assuming a body weight of 75 kg for those patients in which body weight was not available, all of these 15 patients had received a dose of Magnevist greater than the approved dose of 0.1 mmol/kg body weight prior to development of NSF.

On December 22, 2006, the FDA issued an update to its June 8, 2006 Public Health Advisory on MRI Contrast Agents Containing Gadolinium and Nephrogenic Fibrosing Dermopathy (www.fda.gov/cder/drug/infopage/gcca/default.htm). The FDA believes that there is a potential for NSF to occur with the use of any of the approved gadolinium-based contrast agents, and recommends to select imaging methods other than gadolinium-enhanced MRI or MRA whenever possible when a patient with moderate to end-stage kidney disease needs an imaging study. On February 28, 2007 the ACR (American College of Radiology) also issued recommendations regarding gadolinium-based contrast use in patients with kidney disease as part of the ACR Guidance Document for Safe MR Practices: 2007, in the section titled: "Renal disease, gadolinium-based MR contrast agents and nephrogenic systemic fibrosis (NSF)" (pages 12-16) (www.acr.org/mr_safety). The ACR guidance document stated that a potential association with NSF might exist for all five FDA-approved gadolinium-based MR contrast agents.

Bayer HealthCare Pharmaceuticals is committed to the safety of patients receiving our products and to keeping our customers informed about using these products safely and effectively. In this context, we would like to highlight the following recommendations from the recent ACR guidance document:

- All requests for MR should be pre-screened for a patient history of kidney disease or dialysis.
- For all patients with stage 3, 4, or 5 chronic kidney disease (CKD)[2] or those with acute kidney injury (AKI), it is recommended that one consider refraining from administering any gadolinium-based contrast agents unless a risk–benefit assessment for that particular patient indicates that the benefit of doing so clearly outweighs the potential risk(s).
- When risk–benefit assessments warrant administration of a gadolinium-based contrast agents to patients with stages 3–5 renal disease (moderate to end-stage) or AKI, consideration should be given to administering the lowest dose that would provide the diagnostic benefit being sought.
- It is recommended that all patients identified as having moderate to end-stage (stages 3–5) CKD in whom a gadolinium-based contrast agent is to be administered provide informed consent when practical, which includes a review of known risks and benefits as well as the possible availability of alternative imaging methods, if any.
- For administration of gadolinium-based contrast agents to patients on hemodialysis, it is recommended that hemodialysis be initiated no later than 2 hours following the administration of the contrast agent. An additional hemodialysis session should be considered within 24 hours of the first session.

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Bayer HealthCare Pharmaceuticals encourages customers to carefully review the FDA and ACR websites and to become thoroughly familiar with these guidelines, recommendations and any additional updates to these sources concerning the use of gadolinium-based contrast agents in patients with renal impairment. As information in this area continues to evolve, we will continue to keep you updated via our website (www.imaging.bayerhealthcare.com/nsf) and through other communication as appropriate.

Since its approval in 1988, Magnevist has established a record as a safe and reliable contrast agent with over 80 million applications worldwide, in more than 100 countries, and has been cited in more than 14,000 scientific publications[3]. As with other contrast media, the possibility of serious or life-threatening anaphylactic or anaphylactoid reactions, including cardiovascular, respiratory and/or cutaneous manifestations, should always be considered. As with other paramagnetic contrast agents, caution should be exercised in patients with renal insufficiency, especially at higher doses. As with other injectable products, cases of phlebitis and thrombophlebitis have been reported; assessment of the dosed limb for the development of injection site reactions is recommended. For additional product information please see attached package insert.

Please contact our Medical and Product Information Services at 1-888-BAYER84 for more information, or visit our website at www.imaging.bayerhealthcare.com. The FDA and Bayer HealthCare Pharmaceuticals urge health care providers and patients to report adverse event information to either: the FDA via the MedWatch program by phone (1-800-FDA-1088), by fax (1-800-FDA-0178), or by the Internet (www.fda.gov/medwatch); or to Bayer HealthCare Pharmaceuticals by phone (1-888-84BAYER, and choose menu option #4).

Sincerely,

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1. These terms are standardized causality assessment terms as implemented in the electronic database used by Bayer HealthCare Pharmaceuticals and its parent company to record all spontaneously reported adverse events. The full list of available terms for reports where causality has been assessed consists of: "certain", "probable", "possible", "unlikely", "none", and "unclassifiable".
2. For more specific information on the stages of CKD, please visit the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) website at:
http://kidney.niddk.nih.gov/kudiseases/pubs/yourkidneys/#7
3. Results based on a comprehensive search of the literature in the following databases through December 2006: MEDLINE, BIOSIS, SciSearch, EMBASE, International Pharmaceutical Abstracts, Derwent Drug File, and CA SEARCH.