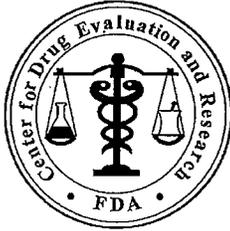


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 22-090

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: November 9, 2007

To: Rafel (Dwayne) Rieves, M.D., Director (Acting)
Division of Medical Imaging and Hematology Products (DMIHP)

Thru: Gerald Dal Pan, M.D., M.H.S., Director
Office of Surveillance and Epidemiology (OSE)

From: OSE Gadoxetate Risk Management Team
Suzanne Berkman, Pharm.D., Senior Drug Risk Management Analyst (OSE-IO)
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Subject: RMP Review

Drug Name(s): Primovist (gadoxetate disodium) injection

Application Type/Number: 22-090

Applicant/sponsor: Bayer HealthCare Pharmaceuticals

OSE RCM #: 2007-1510

1 BACKGROUND

1.1 INTRODUCTION

This review follows a request from the Division of Medical Imaging and Hematology Products (DMIHP) to review and comment on the proposed Risk Management Plan (RMP) for PRIMOVIST (gadoxetate disodium) injection dated June 29, 2007, and submitted to OSE for consultation on July 12, 2007.

Primovist (gadoxetate disodium) is a gadolinium-based contrast agent (GBCA). Bayer Healthcare Pharmaceuticals is submitting gadoxetate for US-FDA approval for

the use in magnetic resonance imaging of the liver in adult patients to enhance the T1-weighted images which improves the detection, localization, and characterization of focal liver pathologies (e.g., hepatocellular carcinoma and metastases) in a pre-surgical evaluation. In patients with known or suspected focal liver disease, the dynamic and the delayed T1-weighted images improve the characterization of lesions such as hepatocellular carcinomas, metastases, focal nodular hyperplasias, hemangiomas, and cysts.

1.2 REGULATORY HISTORY

According to the sponsor, gadoxetate is approved in 34 countries and marketed in 17 countries worldwide. Currently, there are five GBCAs (Magnevist, MultiHance, Omniscan, OptiMARK, and Prohance) approved for use in the US. Bayer Healthcare also markets Magnevist.

Based on post-marketing reports from all five US-marketed GBCAs, these agents show an increase risk of development nephrogenic systemic fibrosis (NSF) in patients with acute or chronic severe renal insufficiency ($GFR < 30 \text{ mL/min/1.73m}^2$), or in patients with renal dysfunction due to hepato-renal syndrome or patients in the peri-operative liver transplantation period. At least 250 cases of NSF have been reported after administration of GBCAs.¹ As a result of these cases the FDA requested the prescribing information for all GBCAs be updated to include a Boxed Warning describing who is most at risk for NSF as outlined above. The Warnings section had been updated with additional information about the risk of NSF associated with GBCAs and a recommendation to screen patients for renal dysfunction prior to GBCA administration.¹ Further, the FDA requested that each of the sponsors conduct a study to collect clinical data sufficient to assess the magnitude of risk for the development of NSF with GBCA among patients with moderate ($GFR < 60 \text{ mL/min/1.73m}^2$) to severe renal insufficiency.

2 MATERIAL REVIEWED

The following materials were reviewed:

- Dear Healthcare Professional letter titled “Important Drug Warning for Gadolinium-Based Contrast Agents” dated September 12, 2007, by Bayer Healthcare Pharmaceuticals, Bracco, GE Healthcare, and Mallinckrodt.
- Email communication from Sibylle Jennings (Bayer) to DMIP regarding Primovist “Clarification of Risk Management Plan” dated July 18, 2007.
- Bayer Healthcare General Correspondence to DMIHP regarding proposed study protocol for Magnevist postmarketing commitment dated July 16, 2007.
- Magnevist Prescribing Information. Bayer Healthcare Pharmaceuticals; July 2007.

¹ Dear Healthcare Professional letter titled “Important Drug Warning for Gadolinium-Based Contrast Agents” dated September 12, 2007, by Bayer Healthcare Pharmaceuticals, Bracco, GE Healthcare, and Mallinckrodt.

- Primovist Risk Management Plan submitted June 29, 2007, by Bayer Healthcare
- Gadolinium-based contrast agents for magnetic resonance imaging. FDA Public Health Advisory, May 23, 2007.
- Marzella L, Blank M, Gelperin K, Johann-Liang R. Safety risks with gadolinium-based contrast agents. *J Magn Reson Imaging* 2007;26(3):816.

3 SUMMARY OF SAFETY CONCERNS AND RISK MANAGEMENT PLAN

The sponsor's submission does not identify any risks beyond NSF. The sponsor states that in the foreign post-marketing experience, approximately — patients have received gadoxetate with "few reported drug reactions" (no details provided in the RMP submission) that are consistent with the known safety profile of GBCAs. Therefore, based on the sponsor's assessment, Bayer feels that routine risk minimization (i.e., labeling) and routine pharmacovigilance (i.e., spontaneous adverse event reporting) comprise an adequate risk management plan for Primovist.

From March 26, 2004, through August 29, 2007, Bayer states that no cases of nephrogenic fibrosing dermopathy or similar were reported with gadoxetate. In email correspondence² on July 18, 2007, Sibylle Jennings from Bayer states that "the risk management plan for Primovist will principally follow the currently discussed risk management measure suggested by the FDA for marketed GBCA.... [Bayer] plans to submit the risk management plan for Primovist within 2 months following agreement with the FDA on the risk management measures for Magnevist."³

A study protocol for Magnevist titled "prospective non-randomized observational (pharmacoepidemiologic) cohort study (open-label, multicenter) to assess the magnitude of potential risk for the development of NSF with the administration of Magnevist in patients with moderate to severe renal impairment" was submitted on July 16, 2007.

The sponsor expects to submit a revised RMP to include the pharmacoepidemiology study in December for Primovist.⁴

Based on the sparse amount of information provided in the RMP submission and very preliminary review⁵ of the safety data by DMIHP, OSE has not identified any additional safety concerns for gadoxetate that warrant consideration of a Risk Minimization Action Plan (RiskMAP) at this time.

4 DISCUSSION

The risk management proposal for gadoxetate, as described at this time is consistent with routine risk minimization activities such as labeling in conjunction with routine pharmacovigilance, and a plan to develop a pharmacoepidemiologic study. We note that the proposed label drafted by the sponsor does not include the "class" Boxed Warning and Warning section information on NSF incorporated into the other currently approved GBCAs. However, the sponsor is expected to submit revised labeling in accordance with the class labeling provision by November 17, 2007.⁴

² Email communication from Sibylle Jennings (Bayer) to DMIP regarding Primovist "Clarification of Risk Management Plan" dated July 18, 2007.

³ Magnevist is also manufactured by Bayer Healthcare Pharmaceuticals.

⁴ Per email communication with Tiffany Brown, MPH, project manager, DMIHP.

⁵ Per email communication on 10.31.07 with Cynthia Welsh, MD, medical officer.

5 CONCLUSIONS AND RECOMMENDATIONS

The proposal does not constitute a formal risk minimization action plan (RiskMAP). In absence of any additional safety concerns identified by DMIHP, we agree with the sponsor that the proposed risk management approach is adequate at this time and consistent with other GBCAs, assuming that Bayer submits a revised plan with a pharmacoepidemiologic study.

We recommend that the Boxed Warning and Warning section information on NSF included in all other GBCAs be incorporated into the final labeling for Primovist, unless there is substantial evidence refuting the association of this risk with gadoxetate.

If DMIHP would like additional comment on the pharmacoepidemiologic study once it is submitted, please consult an epidemiologist in OSE to review the proposal.

If DMIHP would like additional comment on the revised RMP expected to be submitted or, if DMIHP raises further concern with the risk outlined above or identify additional risks associated with gadoxetate warranting more extensive risk management activities or a formal RiskMAP please send a consult to OSE Risk Management Team.

**APPEARS THIS WAY
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mary Dempsey
11/9/2007 08:58:22 AM
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