CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-711

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 24, 2008
To:	Rafel (Dwaine) Rieves, M.D., Director Division of Medical Imaging and Hematology Products (DMIHP)
Thru:	Claudia Karwoski, Pharm.D., Acting Director, Division Risk Management (DRISK) Office of Surveillance and Epidemiology (OSE)
From:	OSE Vasovist Risk Management Team Kathryn O'Connell, M.D. Ph.D., Medical Officer, DRISK Suzanne Berkman, Pharm.D., Acting Team Leader, DRISK Mary Dempsey, Risk Management Program Coordinator, DRISK
Subject:	RMP Review
Drug Name(s):	Vasovist (gadofosveset trisodium) injection
Application Type/Number:	21-711
Applicant/sponsor:	EPIX Pharmaceuticals, Inc. (with Bayer)
OSE RCM #:	2008-1755

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 VASOVIST (gadofosveset trisodium) injection dated June 30, 2008 and submitted to OSE for consultation on October 30, 2008.

VASOVIST (gadofosveset trisodium, MS-325) is a gadolinium-based blood contrast agent (GBCA). EPIX Pharmaceuticals seeks US-FDA approval for this gadolinium-based blood pool contrast agent for use with magnetic resonance angiography (MRA) to evaluate aortoiliac occlusive disease (AIOD) in adults with known or suspected peripheral vascular disease. According to the submission, MS-325 has the advantages of a first-pass agent, allowing dynamic imaging after bolus injection, as well as the advantages of a "steady-state" agent, due to reversible albumin binding that provides long-lasting blood pool effect allowing high-resolution contrast for imaging MRI.

1.2 REGULATORY HISTORY

According to the sponsor's submission dated June 27, 2008, gadofosveset has been approved for marketing in 33 countries outside the US. The initial ex-US approval of Vasovist was on October 3, 2005 in the European Union. Vasovist was first launched for marketing on April 3, 2006 in The Netherlands. Bayer Pharmaceuticals maintains all responsibility for ex-US approvals and marketing. According to the DMIHP, this is the third review cycle for US approval. The sponsor received an approvable letter on January 12, 2005 requesting a new clinical study due to lack of substantial evidence to support its' superiority to that of non-contrast MRA. The second approvable letter was issued on November 11, 2005, citing inadequately demonstrated efficacy in absence of a new clinical study as requested in the January 12, 2005, approvable letter.

Currently, there are five GBCAs (Magnevist, MultiHance, Omniscan, OptiMARK, and Prohance) approved for use in the US. Bayer Healthcare also markets Magnevist, [redacted] b(4)

In post-marketing reports for US-marketed GBCAs, the products as a class are associated with elevated risk of nephrogenic systemic fibrosis (NSF). This has been observed in patients with (1) acute or chronic severe renal insufficiency (GFR < 30 mL/min/1.73m^2), (2) renal dysfunction due to hepato-renal syndrome, and (3) peri-operative liver transplant recipients. In 2007, at least 250 cases of NSF had been reported after administration of GBCAs.[1] As a result, FDA requested that the prescribing information for all GBCAs be updated to include a Boxed Warning. The Warnings section had previously been updated with additional information about NSF risk and a recommendation to screen patients for renal dysfunction prior to GBCA administration.[1] FDA also requested that each sponsor conduct a study to collect clinical data sufficient to assess the

[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.

magnitude of NSF risk with GBCA among patients with moderate (GFR < 60 mL/min/1.73m^2) to severe renal insufficiency.

2 MATERIAL REVIEWED

The following materials were reviewed:

- NDA 21-711 re-submission, section 3.8 'Benefits and Risk', submitted June 27, 2008 in Summary Statement (\\FDSWA150\NONECTD\N21711\N_000\2008-06-30)
- NDA 21-711 re-submission, 'Draft Package Insert', submitted June 27, 2008
- 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.
- Magnevist Prescribing Information. Bayer Healthcare Pharmaceuticals; July 2007.
- 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.
- Maternal Health Team review dated October 31, 2008

3 SUMMARY OF SAFETY CONCERNS AND RISK MANAGEMENT PLAN

Neither the sponsor nor the review division has identified special risks for this product other than class adverse event, NSF. NSF was not observed in the VASOVIST NDA clinical development program (1676 patients) and has not been reported in postmarketing experience of ex-U.S. b(4)

The sponsor studied the effects of renal impairment in Study MS-325-07, which enrolled 52 patients with renal impairment ranging from none to severe. "The expected prolongation in urinary elimination was present, with the terminal half-life of the drug being about 70 hours in patients with severely impaired renal function instead of about 19 hours in patients with normal renal function. This is in the same relative magnitude seen with extracellular contrast agents where the elimination half-life is ~1 hour in normal subjects and up to 34 hours in severe renal impairment. The overall AE profile and renal function profile was not substantially different. Based on these results, [redacted] b(4)
They also note the lack of a notable difference in the AE profile between subjects with elevated creatinine (who likely represent patients with mild renal impairment), [redacted]

FDA's Maternal Health Team has noted no remarkable safety findings in the small number of exposed pregnant or lactating women, and that this limited data is based on other gadolinium agents, not VASOVIST. They recommended inclusion of the available human data in the label:

[redacted] b(4)

We did not find a risk management plan or section in the submission, but the sponsor states that "the benefits of Vasovist-enhanced MRA greatly outweigh the risks when administered under conditions consistent with the proposed labeling." We presume absence of a risk management plan means the sponsor has determined that labeling and routine pharmacovigilance (i.e., spontaneous adverse event reporting per 21 CFR 314.80) comprise adequate risk management for VASOVIST.

The proposed labeling submitted June 27, 2008 includes the class labeling Boxed Warning regarding NSF:

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)
See full prescribing information for complete boxed warning
Gadolinium-based contrast agents increase the risk of nephrogenic systemic fibrosis (NSF) in patients with:
• acute or chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73m2), or
• acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.
In these patients, avoid use of gadolinium-based contrast agents unless the diagnostic information is essential and not available with non-contrast enhanced[ ] NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle, and internal organs. Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a gadolinium-based contrast agent, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent from the body prior to any re-administration [*see Warnings and Precautions (5.1)*] b(4)

The Warnings and Precautions section notes: [ ] b(4)

4 DISCUSSION AND RECOMMENDATIONS

The submission does not include a formal risk management plan. In the absence of any special safety concerns identified by DMIHP, we agree that safety labeling consistent with other GBCAs, and routine pharmacovigilance, are adequate for gadofosveset. We note that the proposed label drafted by the sponsor does include the "class" Boxed Warning and Warning section information about NSF that is incorporated into labeling for the other currently approved GBCAs. However, the sponsor does not propose a pharmacoepidemiologic study to assess the magnitude of NSF risk with GBCA among patients with moderate [GFR < 60 mL/min/1.73m^2] to severe renal insufficiency. *If* the review division determines that the submitted data does not sufficiently address this potential NSF risk we recommend a study similar to what was requested for the other US-marketed GBCAs. If DMIHP determines that additional renal insufficiency data should be obtained via pharmacoepidemiologic study, consultation with an OSE epidemiologist is available.

If DMIHP identifies additional risks that suggest the need for more extensive risk management activities, such as a REMS, please re-consult the Division of Risk Management.

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/s/

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