

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201277Orig1s000

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

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

FINAL REVIEW

Date: March 31, 2011

To: Libero Marzella, MD, PhD, Director (Acting)
Division of Medical Imaging Products (DMIP)

Through: Claudia Karwoski, PharmD., Director
Division of Risk Management (DRISK)
Office of Surveillance and Epidemiology (OSE)

From: **Scientific Lead**, Jeanne Perla, Ph.D., DRISK
Risk Management Analyst

Team Leader, Suzanne Robottom, PharmD., DRISK

Subject: Final Review of Sponsor's Risk Management Plan

Drug Name (Established Name): Gadavist (gadobutrol)

Therapeutic Class: Gadolinium-based contrast agent

Dosage and Route: 0.1 mL/kg body weight (0.1 mmol/kg) IV

Application Type/Number: NDA 201277

Applicant: Bayer HealthCare Pharmaceuticals

OSE RCM #: 2010-2075

1 INTRODUCTION

This review documents the Division of Risk Management review and agreement with Bayer's proposed risk management plan for gadobutrol, a gadolinium based contrast agent (GBCA). Bayer's risk management plan consists of routine measures (labeling) and post-marketing pharmacovigilance.

1.1 Background

The primary concern over the last several years with all GBCAs is the risk of nephrogenic systemic fibrosis (NSF), a rare, but serious, condition associated with the use of GBCAs in certain patients with kidney dysfunction.

On January 21, 2011, the Peripheral and Central Nervous System Drugs Advisory Committee Meeting was held to discuss the following:

1. Do the clinical trial and post marketing data support gadobutrol approval?
2. Do you concur with the labeling of gadobutrol without a NSF contraindication in the at-risk population?
3. What is your level of concern regarding the potential for gadobutrol medication errors that may lead to overdosage? Discuss ways to minimize the error potential.

The Advisory Panel voted 16-0 in favor of approving gadobutrol (question 1) and 15-1 that gadobutrol did not need to be contraindicated in patients with chronic, severe kidney disease or acute kidney injury (question 2). The nephrologists on the panel commented that gadobutrol should not be considered as a "higher" risk product, but they also noted that it is uncertain if it should be considered as "lower" risk. Thus, the Agency clarified that if it is considered "higher" risk, gadobutrol would have a NSF contraindication in the at-risk population.

1.2 Regulatory History

According to the sponsor, "Gadobutrol 1.0" was first approved in Switzerland in 1998, and was launched for the first time in Switzerland in 1999. Gadobutrol has received marketing authorization in 64 countries and is marketed in 60 countries. The sponsor states that in the foreign post-marketing experience, approximately (b) (4) patients have received gadobutrol as of January 31, 2010.

Currently, there are seven GBCAs (Magnevist, MultiHance, Omniscan, OptiMARK, Eovist, Ablavar and Prohance) approved for use in the US.

On September 9, 2010, the Agency issued a Drug Safety Communication announcing required changes in the drug label for GBCAs to minimize the risk of NSF. The decision to require these new recommendations in the drug labeling was based on FDA's review of the safety of GBCAs. FDA determined that Magnevist, Omniscan, and Optimark are associated with a greater risk of developing NSF than other GBCAs in certain patients with kidney disease. As a result, use of these particular agents is contraindicated in patients with acute kidney injury or chronic, severe kidney disease. FDA also determined that enhanced screening to identify patients at risk for NSF is necessary, and advised patients and healthcare professionals to report cases of NSF to FDA.

2 MATERIALS REVIEWED

The following materials were reviewed

- May 14, 2010 Original Application containing proposed “US Risk Management/Risk Minimization Plan for Gadobutrol”
- August 23, 2010 Clinical Review

3 SUMMARY OF SAFETY CONCERNS

The Sponsor identified three potential risks for gadobutrol:

A. Nephrogenic Systemic Fibrosis (NSF)

The sponsor states that a possible association between the administration of GBCAs to patients with severe kidney impairment and NSF was first reported in 2006. NSF has been diagnosed in patients with severe renal impairment (glomerular filtration rate <30 mL/min/1.73 m²) and in patients with acute renal insufficiency of any severity due to hepato-renal syndrome or in the perioperative liver transplantation period.

The sponsor notes that in May 2007, FDA requested class labeling for all approved GBCAs, including a Boxed Warning, on the possible association between these agents and NSF. We note that FDA required a second labeling change in September 2010; after Bayer submitted the gadobutrol application.

B. Potential for Medication Errors

The sponsor states the potential for medication errors is possible with gadobutrol as it is the only extracellular magnetic resonance contrast agent formulated at a 1.0 molar concentration (others are formulated at 0.5 molar). This results in half the volume of gadobutrol for a standard dose of 0.1 mmol Gd/kg body weight (=0.1 mL/kg body weight) in comparison to other GBCAs formulated at 0.5 molar (=0.2 mL/kg body weight). Therefore, if using the volume recommendations for other GBCAs formulated at 0.5 molar concentration, there is a potential for administering a double dose (0.2 mmol/kg) of gadobutrol.

C. Potential for Overdose

The sponsor states that in clinical trials, gadobutrol has been studied at doses up to 1.5 mmol/kg body weight with no significant differences in the safety of the product observed at the higher doses compared to the lower doses. No signs of intoxication from an overdose have so far been observed during clinical use. In patients with severely impaired renal function, gadobutrol can be removed by hemodialysis.

4. PROPOSED GADOBUTROL RISK MANAGEMENT/RISK MINIMIZATION PLAN

The sponsor did not propose a Risk Evaluation and Mitigation Strategy (REMS). Instead, a Risk Management Plan was submitted. This plan proposes the following measures:

- labeling, including a boxed warning, and additional information in the warning section for gadobutrol
- post-marketing surveillance with a targeted adverse event questionnaire for NSF
- quarterly reporting (and an annual report) focused on NSF
- PSUR/PADER reporting

5. DISCUSSION

DMIP states that other than the risk of NSF and rare reports of anaphylaxis, there are no other serious safety issues.¹

The sponsor has proposed risk management plan consistent with routine measure including labeling and a post-marketing pharmacovigilance plan. The sponsor's risk management proposal is consistent with other approved GBCAs that carry the relatively lower risk labeling for NSF.

We note that other GBCAs did have a PMR in place to further characterize the risk of NSF. However, the ODE Memo signed by Shaw T. Chen on March 11, 2011, states that such a PMR is not necessary at this time given the declining incidence of GBCA-NSF cases reported since the class labeling changes and professional education efforts.

6 CONCLUSION AND RECOMMENDATION

In absence of any unique or additional serious safety concerns for gadobutrol identified by DMIP, we agree with the sponsor that the routine labeling and pharmacovigilance is adequate at this time and is consistent with other GBCAs.

¹ Chen, S. ODE-IV Action Memo. Signed March 11, 2011.

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

/s/

SUZANNE C BERKMAN ROBOTOM
03/31/2011

CLAUDIA B KARWOSKI
03/31/2011
concur