CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-711

OTHER REVIEW(S)

SEALD LABELING REVIEW

Template version: November, 2008

APPLICATION NUMBER	NDA 21-711
APPLICANT	EPIX Pharmaceuticals, Inc.
DRUG NAME	VASOVIST (gadofosveset trisodium)
SUBMISSION DATE	July 1, 2008
SEALD REVIEW DATE	12-19-08
SEALD REVIEWER(S)	Kim Shiley, BSN and Laurie Burke, RPh, MPH

12 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Other Review(s) - 1

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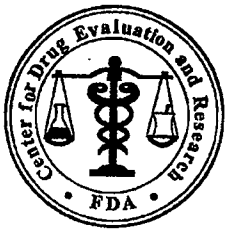
/s/

Kimberly Shiley
12/22/2008 01:52:09 PM
CSO
SEALD comments sent to Review Division on 12-22-08

Laurie Burke
12/22/2008 02:02:36 PM
INTERDISCIPLINARY



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:	December 19, 2008
To:	Rafel D. Rieves, M.D., Director Division of Medical Imaging and Hematology Products, HFD-160
Through:	Kellie Taylor, Pharm.D., MPH, Team Leader Denise Toyer, Pharm.D., Deputy Director Division of Medication Error Prevention and Analysis, HFD-420
From:	Tara Turner, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis, HFD-420
Subject:	Labeling Review
Drug Name(s):	Vasovist (Gadofosveset Trisodium) Injection 244 mg/mL
Application Type/Number:	NDA #: 21-711
Applicant:	Epix Pharmaceuticals, Inc.
OSE RCM #:	2008-1333

CONTENTS

EXECUTIVE SUMMARY

The results of the Label and Labeling Risk Assessment found that the presentation of information on the proposed container label, carton and insert labeling appears to be vulnerable to confusion that could lead to medication errors. Specifically, the concerns surround the presentation of the established name, product strength, and route of administration, as well as the instructions for proper dosage of the drug product.

The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed post-approval, and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Medical Imaging and Hematology Products (DMIHP) to evaluate the labeling of Vasovist for the potential to contribute to medication errors. The applicant submitted container labels, shipper labels, and insert labeling for our review.

1.2 REGULATORY HISTORY

The Division of Medication Error Prevention and Analysis previously reviewed container labels, carton and insert labeling for Vasovist and provided recommendations for improvement (see OSE Review #04-0026, dated May 28, 2004). Subsequently, the Agency issued two approvable letters dated January 12, 2005 and November 21, 2005, followed by a lengthy appeals process. Both letters addressed product labeling as follows: "Labeling comments are deferred at this time. Please submit updated draft product labeling with your resubmission." The applicant re-submitted the NDA on June 30, 2008, including draft labeling.

1.3 PRODUCT INFORMATION

Vasovist (gadofosveset trisodium) is a gadolinium-based blood pool contrast agent proposed to be indicated for use with magnetic resonance angiography (MRA) to evaluate aortoiliac occlusive disease in adults with known or suspected peripheral vascular disease. Vasovist should be administered to adults as an intravenous bolus injection, manually or by power injection, at a dose of 0.12 mL/kg body weight over a period of time up to 30 seconds followed by a 25-30 mL normal saline flush. Vasovist is a sterile solution for intravenous injection, containing 244 mg/mL of gadofosveset trisodium. The product is packaged in 10 mL and single use glass vials in shrink-wrapped packages of 10 vials. Vasovist should be stored at room temperature and should be protected from light and freezing. b(4)

2 METHODS AND MATERIALS

This section describes the methods and materials used by medication error prevention staff to conduct a label, labeling, and/or packaging risk assessment. The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to

inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

2.1 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because medication error prevention staff analyze reported misuse of drugs, we staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. We use FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted on June 30, 2008 the following labels and labeling for our review (see Appendices A through D for images):

- Container Label: 10 mL vial
- Shipper Label: 10 mL vial
- Container Label
- Shipper Label:
- Insert Labeling (no images)

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3 RESULTS

3.1 LABEL AND LABELING RISK ASSESSMENT

Review of the container label and carton labeling identified areas of vulnerability that could lead to medication error, specifically with respect to clear communication of the established name, product strength, and route of administration, as well as the instructions for proper dosage of the drug product.

3.1.1 All Labels and Labeling

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[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

7 Page(s) Withheld

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/s/

Tara Turner
12/19/2008 04:17:59 PM
DRUG SAFETY OFFICE REVIEWER

Kellie Taylor
12/19/2008 04:29:23 PM
DRUG SAFETY OFFICE REVIEWER

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Medical Imaging and Hematology

Application Number: NDA 21-711

Name of Drug: VASOVIST® (gadofosveset trisodium) Injection

Applicant: Epix Pharmaceuticals, Inc.

Material Reviewed:

Submission Date: June 30, 2008

Receipt Date: July 1, 2008

Submission Date of Structure Product Labeling (SPL): June 30, 2008

Type of Labeling Reviewed: Word/SPL

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies were identified in the proposed labeling.

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Recommendations

The requested changes were noted in the draft labeling sent to Epix Pharmaceuticals on Monday, December 15, 2008. It was requested that the label be returned to the Division as soon as possible.

James Moore, PharmD., M.A.
Project Manager, DMIHP

Supervisory Comment/Concurrence:

Kyong Kang, PharmD.
Chief, Project Management Staff
December 17, 2008

Drafted: JM/December 9, 2008
Revised/Initialed:KK/JM/December 11, 2008
Finalized: JM/December 17, 2008
Filename: CSO Labeling Review Template (updated 1-16-07).doc
CSO LABELING REVIEW OF PLR FORMAT

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/s/

James Moore
12/17/2008 07:09:43 PM
CSO

Kyong Kang
12/19/2008 10:09:40 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
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Maternal Health Team Label Review

Date: 10-31-2008 **Date Consulted:** 9-19-2008

From: Leyla Sahin, M.D.
Medical Officer, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

Through: Karen Feibus, MD
Team Leader, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

To: Division of Medical Imaging and Hematology Products (DMIHP)

Drug: Vasovist; NDA 21-711

Subject: Pregnancy and Nursing Mothers labeling

Materials Reviewed: Pregnancy and Nursing Mothers subsections of Vasovist labeling

Consult Question: Please review sections of the proposed label as they relate to pregnancy and lactation.

INTRODUCTION

On June 30, 2008, Epix Pharmaceuticals submitted a new drug application (NDA) to the Division of Medical Imaging and Hematology Products for Vasovist (gadofosveset trisodium), a gadolinium-based blood pool contrast agent. The sponsor's proposed indication for Vasovist is for use with magnetic resonance angiography (MRA) to evaluate aortoiliac occlusive disease (AIOD) in adults with known or suspected peripheral vascular disease. On September 19, 2008, DMIHP consulted the Maternal Health Team (MHT) to review the pregnancy and nursing mothers section of the Vasovist package insert, and provide comment. This review provides revisions to the sponsor's proposed Pregnancy and Nursing Mothers subsections of Vasovist labeling.

BACKGROUND

The Maternal Health Team (MHT) is working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 28, 2008).

As part of the labeling review, the MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the pregnancy and nursing mothers label subsections. In addition, the MHT presents available animal data, in the pregnancy subsection, in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

This review summarizes available information about the use of gadolinium containing radioimaging products during pregnancy and provides revisions to the sponsor's proposed Pregnancy and Nursing Mothers subsections of Vasovist labeling.

SUMBMITTED MATERIAL

Sponsor's Proposed Pregnancy and Nursing Mothers Labeling

8.1 Pregnancy

[redacted]

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8.3 Nursing Mothers

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REVIEW OF DATA

Gadolinium exposure during pregnancy

MHT performed a PubMed search with the following terms: pregnancy and gadolinium, pregnancy and Vasovist, pregnancy and contrast agents. MHT's review of the literature showed a limited number of human exposures to gadolinium contrast agents during pregnancy. A prospective cohort study of 26 women who were exposed to gadolinium derivatives in the first trimester showed successful outcomes (full term births without any malformations) in 23 women, 2 miscarriages, and one elective termination[1]. One case report has described a successful pregnancy in a patient with multiple sclerosis who was inadvertently injected intravenously with gadopentetate dimeglumine during very early pregnancy[2]. No adverse effects were detected at birth in eleven newborns who had been exposed to gadolinium prenatally during the second and third trimesters as part of a placental imaging study[3]. A case series reported normal pregnancy outcomes for a woman who was three months pregnant and a woman who was five months pregnant who received gadopentatate dimeglumine to establish a diagnosis of Crohn's disease[4]. There were no adverse outcomes in the newborns of 15 pregnant women who were exposed to gadolinium-enhanced MR imaging to diagnose placenta accrete and placenta percreta[5].

Practice guidelines from professional radiology organizations in the United States and Europe address the use of gadolinium containing drug products during pregnancy. The American College of Radiology Guidance Document for Safe MR Practices from 2007 states that:

- MR contrast agents should not be routinely provided to pregnant patients

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[1] De Santis M, Straface G, Cavaliere AF, Carducci B, Caruso A: Gadolinium periconceptional exposure: pregnancy and neonatal outcome. Acta Obstet Gynecol Scand 2007;86:99- 101.

[2] Barkhof F, Heijboer RJ, Algra PR: Inadvertent i.v. administration of gadopentetate dimeglumine during early pregnancy [letter]. Am J Roentgenol 158: 1171, 1992.

[3] Marcos HB, Semelka RC, Worawattanakul S: Normal placenta: gadolinium-enhanced dynamic MR imaging. Radiology 1997;205:493-6.

[4] Shoenut JP, et al. MRI in the diagnosis of Crohn's Disease in two pregnant women. J Clin Gastroenterology 1993; 17(3):244-7.

[5] Jaraquemada JM, Bruno C: Gadolinium-enhanced MR imaging in the differential diagnosis of placenta accreta and placenta percreta. Radiology 2000;216:610-611.

- Pregnant patients can undergo MR scans at any stage of pregnancy if the risk-benefit ratio warrants the study to be performed
- The potential risks, including long-term risks to the developing fetus, with administration of gadolinium-based MR contrast agents remain unknown and may be harmful.

Based on a review of the literature, which has been discussed above, in 2005 The European Society of Urogenital Radiology issued Guidelines[6] which state that when MR examination is necessary, gadolinium media may be given to the pregnant woman.

Gadolinium exposure and lactation

MHT conducted a PubMed search with the following terms: gadolinium and lactation/breastfeeding, contrast agents and lactation/breastfeeding, Vasovist and lactation/breastfeeding. MHT's review of the literature identified two case reports of lactating women who were exposed to gadopentetate dimeglumine. Milk levels of gadolinium were 0.01[7] – .023[8]% of the maternal dose. Data from 19 lactating women who received an intravenous dose of gadopentetate dimeglumine suggested that a mean of 0.009% (range 0.001% - 0.04%) of the maternal dose was excreted in milk over the following 24 hours[9]. The authors of this study commented that this dose is less than 1/100th of the therapeutic dose for a neonate (200 μmol per kilogram of body weight), and study data suggest that very little orally administered gadopentetate dimeglumine is systemically absorbed[10]. For these reasons, they and other commentators[11] question older recommendations that breastfeeding be delayed for 24 hours after maternal exposure to this agent.

Both the American College of Radiology[12] and the European Society of Urogenital Radiology[6] have policies that do not recommend disrupting nursing after a mother receives a gadolinium contrast agent. Both organizations conclude that based on the above mentioned studies, the amount of gadolinium in breast milk is very small, and its oral absorption is minimal. The extremely low risk to the neonate from the contrast agent is not considered sufficient to warrant disruption to breastfeeding.

Reviewer comment

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[6] Webb JA, Thomsen HS, Morcos SK, Members of Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR). The use of iodinated and gadolinium contrast media during pregnancy and lactation. Eur Radiol. 2005;15:1234-40.

[7] Schmiedl U, Maravilla KR, Gerlach R, Dowling CA. Excretion of gadopentetate dimeglumine in human breast milk. AJR. 1990;154:1305-6.

[8] Rofsky NM, Weinreb JC, Litt AW. Quantitative analysis of gadopentetate dimeglumine excreted in breast milk. J Magn Reson Imaging. 1993;3:131-2.

[9] Kubik-Huch RA, Gottstein-Aalame NM, Frenzel T, Seifert B, Puchert E, Wittek S, Debatin JF: Gadopentetate dimeglumine excretion into human breast milk during lactation. Radiology 2000;216:555-8.

[10] Laniado M, et al. MR imaging of the gastrointestinal tract: value of Gd-DTPA. Am J Roentgenology 1988:150;817-821.

[11] Chen MM, et al. Guidelines for computed tomography and magnetic resonance imaging use during pregnancy and lactation. Obstetrics and Gynecology 2008:112;333-340.

[12] ACR Committee on Drugs and Contrast Media. Administration of contrast medium to breastfeeding mothers. ACR Bull. 2001;57:12-3.

The above recommendations are based on studies involving gadolinium products with half lives of approximately two hours. Vasovist has a half life of approximately 17 hours, and although interruption of breastfeeding is not indicated, women who feel uncomfortable breastfeeding following exposure to Vasovist can temporarily interrupt nursing (pump and discard milk) for five half lives, or about 85 hours to allow near-complete clearance of the drug..

CONCLUSIONS

The MHT recognizes that due to the limited number of exposed pregnant or lactating women, and the fact that other gadolinium agents, not Vasovist, were the drug of exposure, these post-marketing data do not reliably estimate the frequency or absence of drug-associated adverse outcomes due to Vasovist. The MHT also recognizes that long term risks of fetal exposure to Vasovist are unknown. However, the MHT is of the opinion that it is useful to include available human data regarding pregnancy or lactation, even if limited. While gadolinium products should be avoided in pregnancy, there are potential clinical situations when using a gadolinium product may be necessary to optimize the care of the mother and fetus. Due to minimal excretion in breast milk, and limited gastrointestinal absorption, gadolinium-based contrast agents appear to be safe for the neonate. The MHT's goal is to make the Pregnancy and Nursing Mothers sections of labeling a more effective communication tool for clinicians, and therefore our recommendation is to include the available human data in the label.

RECOMMENDATIONS

Provided below are the MHT's recommended revisions to the sponsor's proposed labeling. Additions are underlined, and deletions are struck out.

8.1 Pregnancy

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8.4 Nursing Mothers

It is not known whether gadofosveset is secreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VASOVIST Injection is administered to a woman who is breastfeeding.

Limited case reports show that 0.01-0.04% of the maternal gadolinium dose is excreted in human breast milk. Studies of other gadolinium products have shown limited gastrointestinal absorption. These studies were conducted with gadolinium products with shorter half-lives than VASOVIST.

Less than 1% of gadofosveset at doses up to 0.3 mmol/kg was secreted in the milk of lactating rats.

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/s/

Leyla Sahin
11/4/2008 04:36:39 PM
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