CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-711

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	December 18, 2008
From	Dwaine Rieves, MD
Subject	Division Director Summary Review
NDA/BLA #	21-711
Applicant Name	Epix Pharmaceuticals
Date of Submission	July 1, 2008 (third cycle)
PDUFA Goal Date	December 31, 2008
Proprietary Name / Established (USAN) Name	Vasovist™ Injection Gadofosveset trisodium
Dosage Forms / Strength	solution for intravenous injection/0.25 mmol/mL
Proposed Indication(s)	"Vasovist Injection is a gadolinium-based contrast agent indicated for use as a contrast agent in magnetic resonance angiography (MRA) to evaluate aortoiliac occlusive disease (AIOD) in adults with known or suspected peripheral vascular disease."
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Barbara Stinson, MD & Alex Gorovets, MD (TL)
Statistical Review	Anthony Mucci, PhD & Jyoti Zalkikar, PhD (TL)
Pharmacology Toxicology Review	Siham Biade, PhD & Adebayo Laniyonu, PhD (TL)
CMC Review/OBP Review	Joesphine Jee, PhD & Eric Duffy, PhD (Director)
Microbiology Review	Bryan Riley, PhD, Peter Cooney, PhD (Supervisor)
Clinical Pharmacology Review	Christy John, PhD & Young Moon Choi, PhD (TL)
DDMAC	Michelle Safarik, PA-C
DSI	John Lee, MD & Tejashri Purohit-Sheth, MD
CDTL Review	none (submission predated need for CDTL)
OSE/DMEPA	Linda Wisniewski, RN and Kellie Taylor, PharmD
OSE/DDRE	Kathryn O'Connell, MD, PhD, Claudia Karwoski, PharmD
Pediatric and Maternal Health	Leyla Sahin, MD, Karen Feibus, MD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader
TL = Team Leader

1. Introduction:

This New Drug Application (NDA) was submitted for gadofosveset trisodium injection (Vasovist), a new molecular entity within the class of products generally referred to as "gadolinium-based contrast agents (GBCAs)." GBCAs are drugs used in magnetic resonance imaging (MRI) to improve visualization of structures. In general, MRI with GBCA is thought to offer advantages over other types of imaging because structural detail is obtained without the use of any radiation.

This review will focus upon the regulatory basis for the approval recommendation, particularly the basis for assessment of diagnostic efficacy.

2. Background:

Currently, six GBCA's are approved by the FDA and all are marketed. In general, these agents share many characteristics, including a boxed warning within the labels. The warning relates to the risk for nephrogenic systemic fibrosis (NSF) among certain patients (primarily those with severe renal failure). NSF has been proposed to result from gadolinium deposition within the tissues of patients who lack sufficient renal function to eliminate the gadolinium. None of the six approved GBCAs are approved specifically for visualization of arteries (angiography). Hence, Vasovist will be the first FDA-approved agent for magnetic resonance angiography (MRA).

As a member of the GBCA class, the Vasovist label incorporates the class labeling. However, Vasovist is somewhat unique among the GBCA class members in that it binds to albumin. Consequently, Vasovist has a longer "dwell time" within the blood, compared to the other GBCA.

MRA may be performed without administration of contrast. MRA without contrast is cumbersome and often results in technically unacceptable images. GBCAs have been used "off-label" in an attempt to improve the MRA images. Specifically, the sponsor of Vasovist performed studies to specifically support use of Vasovist in MRA. The diagnostic efficacy for Vasovist was based upon demonstration of improved visualization with Vasovist-MRA compared to MRA performed without Vasovist.

Vasovist is currently marketed in 33 nations. To date, reported adverse reactions are similar to those for other GBCAs.

This application has a complicated regulatory history. The application was originally submitted in October, 2004. That review cycle concluded with the issuance of an "approvable" letter. Failure to provide persuasive diagnostic efficacy was the main basis for lack of approval. Specifically, FDA noted that the sponsor's data did not provide conclusive evidence that Vasovist "added value" to MRA performed without Vasovist. This original application included data from multiple clinical studies that assessed [ ] None of these studies was found to provide persuasive data. The major data deficiency related to the technical process for interpretation of images (if any vessel segment was uninterpretable, then all vessel segments were analyzed as uninterpretable--even if these segments actually could be

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evaluated). The data generally indicated that diagnostic efficacy was based upon a large number of uninterpretable vessel segments for images obtained without the use of Vasovist and imputation of "wrong" diagnoses for these segments.

The sponsor responded to the approvable letter in May, 2005. This response addressed certain manufacturing issues (stability) and included certain re-analyses of the previously submitted data. FDA issued an approvable letter in November, 2005, again citing the lack of persuasive diagnostic efficacy data.

Subsequently, the sponsor disputed the approvable letter to OND and also to the Center Director. The resolution of the final dispute session was a recommendation for the company to work with the review division to develop an acceptable statistical analytical plan and to perform a "reread" of the MR images. The sponsor chose to focus upon the aortoiliac bed and to perform a reread of the two studies performed in this region.

3. Chemistry, Manufacturing and Controls:

I concur with the conclusions reached by the chemistry reviewer (Dr. Jee) regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. There are no outstanding manufacturing issues and no need for post-marketing commitments.

4. Nonclinical Pharmacology/Toxicology:

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval. The pharmacology/toxicology provided some labeling recommendations which were incorporated into draft labeling. No post-marketing commitments were requested.

5. Clinical Pharmacology/Biopharmaceutics:

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. The reviewer provided some recommendations for labeling which were incorporated into the draft labeling text. No outstanding issues were identified and no post-marketing commitments were requested.

The reviewer provided specific recommendations for dosing among patients with renal insufficiency and these recommendations were incorporated into labeling.

6. Clinical Microbiology:

The microbiology reviewer recommended approval and I concur with his findings..

7. Clinical/Statistical-Efficacy:

Dr. Barbara Stinson provided the clinical review for this third cycle. Dr. Anthony Mucci provided the statistical review. I concur with these major findings and recommendations.

FDA regarded the most important component of efficacy to be a demonstration that MRA with Vasovist provided "added value" over MRA performed without Vasovist. Consequently, diagnostic performance characteristics were expected to be better with Vasovist-MRA than MRA without Vasovist.

During several months of pre-submission discussion, the sponsor and FDA developed a statistical analytical plan that provided detailed directions for the handling of "uninterpretable" images, data imputation (if necessary) and an assessment of the value of conversion of images from "uninterpretable without Vasovist" to "interpretable with Vasovist."

Images from two phase 3 clinical studies were reread by radiologists who underwent specific training procedures, both for Vasovist-MRA and non-Vasovist MRA. The images from these two studies were combined and the study results analyzed as an aggregate. Both studies were open label, single arm studies. This paradigm has been used for all currently approved GBCAs and is consistent with FDA guidance; in general, the studies are a form of cross-over in which images are first obtained without Vasovist, then images are obtained after Vasovist is administered.

In both trials, patients with known or suspected peripheral vascular disease underwent MRA with and without Vasovist as well as catheter-based X-ray arteriography. Diagnostic efficacy was based upon comparisons of sensitivity and specificity between MRA with and without Vasovist, with X-ray angiography as the reference standard.

Out of 493 patients enrolled in these two studies, 424 were included in the comparison of the diagnostic efficacy of Vasovist-MRA to that of non-contrast MRA in detection/exclusion of occlusive vascular disease ($\geq$ 50% stenosis) in 7 vessel-segments in the aortoiliac region. The interpretation of MRA images from both trials was conducted by three independent radiologist readers who were blinded to clinical data, including the results of X-ray arteriography. In these 424 patients, the median age was 67 years with a range of 29 to 87 years; 58% of the patients were over 65 years of age; 83% were white and 68% were male.

The primary efficacy analyses were designed to demonstrate superiority in sensitivity and non-inferiority in specificity of Vasovist-MRA as compared to non-contrast MRA at the vessel-segment level. The uninterpretable images were assigned an outcome of "wrong diagnosis". Additionally, success was also based upon acceptable performance characteristics for the uninterpretable non-contrast MRA vessel segments that became interpretable following Vasovist administration. Specifically, the sensitivity and specificity for these Vasovist images were required to exceed 50%. These pre-specified success criteria were to be achieved by at least the same two readers for all primary analyses.

Superiority in sensitivity and non-inferiority in specificity was demonstrated for Vasovist-MRA by all three blinded readers. On average, 316 vessel segments were assessed for sensitivity and 2230 for specificity, by each reader. Table 1 summarizes the efficacy results, by reader.

Table 1. Performance Characteristics of VASOVIST-MRA and Non-contrast MRA

Reader	SENSITIVITY			SPECIFICITY		
	VASO-MRA [A]	Non-contrast MRA [B]	[A] – [B] (95% CI)*	VASO-MRA [A]	Non-contrast MRA [B]	[A] – [B] (95% CI)*
1	89%	69%	20% (15%, 25%)	72%	71%	1% (-3%, 5%)
2	82%	70%	12% (7%, 17%)	81%	73%	8% (4%, 12%)
3	79%	64%	15% (9%, 21%)	85%	85%	0% (-2%, 2%)

*(Based on cluster-corrected McNemar Test)

Among the three readers, 5-12% of the vessel-segments were deemed uninterpretable by non-contrast MRA. For these vessel segments, sensitivity of Vasovist-MRA ranged from 72% [95% CI (54%, 90%)] to 97% [95% CI (93%, 100%)] and specificity ranged from 72% [95% CI (67%,76%)] to 84% [95% CI (81%, 88%)].

Together, these data demonstrate that Vasovist-MRA importantly improves the detection of arterial stenoses, compared to MRA without Vasovist. Additionally, the well-planned systematic re-read resolves concerns related to inappropriate interpretation of uninterpretable vessel segments and insufficient reader training.

8. Safety:

Overall, the major Vasovist safety concerns are similar to those for other GBCAs. Specifically, the label includes warnings and precautions for:

-NSF (class labeling)
-Hypersensitivity reactions (2/1676 subjects in clinical studies experienced anaphylactoid reactions)
-Acute Renal Failure (class labeling; no acute renal failure was observed in clinical studies)
-QTc prolongation and risk for arrhythmias (6% of patients in clinical studies experienced a prolonged QT at 45 minutes following Vasovist administration although no subjects experienced arrhythmias; this prolonged QT was not evident at 24 hours after Vasovist administration. Nonclinical data did not find any QT effects of Vasovist. The warning recommends baseline electrocardiograms for patients at risk for QT-related arrhythmias (e.g., concomitant medications, cardiac conditions) as well as follow-up electrocardiographic monitoring.

In all clinical studies evaluating Vasovist with MRA, a total of 1,676 (1379 patients and 297 healthy subjects) were exposed to various doses of Vasovist. Table 2 shows the most common adverse reactions (≥ 1%) experienced by subjects receiving Vasovist at a dose of 0.03mmol/kg.

Table 2. Common Adverse Reactions in 802 Subjects Receiving Vasovist at 0.03mmol/kg

Preferred Term	n (%)
Pruritis	42 (5)
Headache	33 (4)
Nausea	33 (4)
Vasodilatation	26 (3)
Paresthesia	25 (3)
Injection site bruising	19 (2)
Dysgeusia	18 (2)
Burning sensation	17 (2)
Venipuncture site bruise	17 (2)
Hypertension	11 (1)
Dizziness (excluding vertigo)	8 (1)
Feeling cold	7 (1)

The review team regarded labeling as a sufficient measure for risk management. No risk evaluation and mitigation strategy was regarded as necessary, particularly since Vasovist will be limited to use by trained personnel and will inherently involve patient monitoring.

Post-marketing Requirements (PMR):

The sponsor is to perform one PMR, a trial identical in design to that expected of all other GBCAs. Specifically, the trial will obtain data to assess the magnitude of risk for NSF among patients with mild to moderate renal insufficiency.

9. Advisory Committee Meeting:

This application was not presented to an Advisory Committee because the product is a member of the class of GBCA and did not present unique safety concerns nor difficulty in interpretation of the data from the image reread.

10. Pediatrics:

Based upon the proposed indication that specifically states Vasovist is for use in the detection of aortoiliac disease, the Pediatric Committee and review division concurred with a request for waiver of pediatric studies. Aortoiliac occlusive disease is almost uniformly due to atherosclerosis/hypertension and rarely, if ever, occurs in pediatric patients.

11. Other Relevant Regulatory Issues:

Overall, the review team was unanimous in recommending approval of Vasovist. The one area that remains unresolved at the present time is the trade name of "Vasovist." The Office of Surveillance and Epidemiology (OSE)/Division of Medication Error Prevention and Analysis (formerly DMETS) found the trade name was too similar to Magnevist, another GBCA. Hence, OSE did not concur with the name. The OND review team regarded the trade name as appropriate. In general, the disagreement and concerns related to the following:

OSE: when handwritten, "Vasovist" may resemble "Magnevist"

OND:

- -"Vaso" (prefix) uniquely identifies this GBCA as one for vascular imaging
- -Vasovist has been administered to nearly 50,000 patients in foreign countries with no reports of dispensing errors
- -the drug is marketed as "Vasovist" in 33 nations/throughout the world
- -the safety consequences of any confusion of Vasovist with Magnevist are minimal, since publications cite the use of Magnevist in MRA
- -radiology practice is uniquely different from that of typical prescription drugs in that hospitals/MRI suites are generally likely to be much more attuned to the use of each specific contrast agent, particularly for MRA since MRA requires unique technical settings on scanners and the timing of the image ascertainment must be coordinated to the injection of the contrast agent.

At the present time, the question of the trade name is unresolved; plans are underway for further discussion with management.

In other matters, the FDA inspection of clinical sites disclosed acceptable evidence of data integrity. FDA inspection of the reread facility and process also disclosed compliance with integrity expectations. Financial disclosure expectations have been met.

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/s/

Rafel Rieves
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MEDICAL OFFICER