

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-711**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

NDA 21-711

**NDA APPROVAL**

Epix Pharmaceuticals  
Attention: Margaret Uprichard, PharmD.  
Senior Vice President  
Regulatory Affairs and Quality  
4 Maguire Road  
Lexington, MA 02421

Please refer to your new drug application (NDA), dated June 30, 2008, received July 1, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vasovist® (Gadofosveset Trisodium) Injection.

We acknowledge receipt of your submissions dated August 14, October 3 and 22, December 16, 17, 18, and 19, 2008.

The June 30, 2008, submission constituted a complete response to our November 21, 2005, action letter.

This new drug application provides for the use of Vasovist® (Gadofosveset Trisodium) Injection as a contrast agent in magnetic resonance angiography (MRA) to evaluate aortoiliac occlusive disease (AIOD) in adults with known or suspected peripheral vascular disease.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

Your application for Vasovist® (Gadofosveset Trisodium) Injection was not referred to an FDA advisory committee because your product is a member of the class of previously approved gadolinium-based contrast agents, and the product did not pose unique concerns beyond those applicable to other members of this class.

**PEDIATRIC RESEARCH EQUITY ACT (PREA)**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. AIOD is not a condition applicable to the pediatric patient population.

**POSTMARKETING REQUIREMENTS UNDER 505(o)**

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk, that is, risk for the development of nephrogenic systemic fibrosis (NSF) in patients with renal insufficiency with the class of gadolinium-based contrast agents, of which Vasovist<sup>®</sup> (Gadofosveset Trisodium) Injection is a member. NSF is a potentially fatal condition. This known risk applies to patients with acute or chronic severe renal insufficiency (glomerular filtration rate, GFR < 30 mL/min/1.73m<sup>2</sup>) or patients with acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is therefore not sufficient to assess this known serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this known serious risk and monitor the incidence of NSF among patients with moderate to severe renal insufficiency.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following clinical trial:

1. A clinical trial to collect clinical data sufficient to assess the magnitude of risk for the development of NSF with your product among patients with moderate (GFR < 60 mL/min/1.73m<sup>2</sup>) to severe renal insufficiency.

The timetable you submitted on December 17, 2008, states that you will conduct this trial according to the following timetable:

Protocol Submission:	June, 2009
Trial Start Date:	September, 2009
Final Report Submission:	September, 2014

Submit the protocol to your IND 51,172 with a cross-reference letter to this NDA 21-711. Submit all final report(s) to your NDA 21-711. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing clinical trial as appropriate:

**Required Postmarketing Protocol under 505(o)**  
**Required Postmarketing Final Report under 505(o)**  
**Required Postmarketing Correspondence under 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii), requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

#### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the submitted labeling (package insert) submitted December 23, 2008. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 21-711."

#### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and container labels that are identical to the December 17, 2008, enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "Final Printed Carton and Container Labels for approved NDA 21-711." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

#### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see [www.fda.gov/cder/ddmac](http://www.fda.gov/cder/ddmac).

### **LETTERS TO HEALTH CARE PROFESSIONALS**

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch  
Food and Drug Administration  
Suite 12B05  
5600 Fishers Lane  
Rockville, MD 20857

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

### **MEDWATCH-TO-MANUFACTURER PROGRAM**

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at [www.fda.gov/medwatch/report/mmp.htm](http://www.fda.gov/medwatch/report/mmp.htm).

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**If you have any questions, call James Moore, Regulatory Project Manager, at (301) 796-2050.**

**Sincerely,**

*{See appended electronic signature page}*

**Richard Pazdur, M.D.**  
**Office Director**  
**Office of Oncology Drug Products**  
**Center for Drug Evaluation and Research**

**Enclosure**

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Richard Pazdur  
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