

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 22-090

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-090

NDA APPROVAL

Bayer Healthcare Pharmaceuticals
Attention: Ayse U. Baker, Ph.D., MBA
Associate Director
Oncology and Diagnostic Imaging
340 Changebridge Road
Montville, NJ 07045

Dear Dr. Baker:

Please refer to your new drug application (NDA) dated June 29, 2007, received July 2, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Eovist® (Gadoxetate Disodium) Injection.

We acknowledge receipt of your submissions dated July 20, August 10, 17, and 21, September 5 and 27, October 11 and 15, November 1 and 14, December 6, 10, 14, 17, and 18, 2007; January 2, 7, 13, 14, 21, 29, and 30, February 29, March 7 and 27, April 9, 18, and 23, 2008, May 5, 7, 14, 16, 19 and 27, June 12 and 27, 2008.

This new drug application provides for the use of Eovist® Injection for use in magnetic resonance imaging (MRI) of the liver in adult patients to provide contrast in the T1 weighted images to aid in the detection and characterization of focal liver pathologies in pre-surgical evaluation.

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 Eovist® 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.

REQUIRED PEDIATRIC ASSESSMENTS

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 deferring pediatric studies for ages 0 to 2 months for this application until additional safety data have been collected. Eovist[®] is eliminated via the renal and hepatobiliary systems. Hence, impairment or immaturity of these systems, as may importantly occur in patients less than 2 months of age, may increase the risk for serious adverse reactions to Eovist[®]. Prior to initiation of clinical studies in pediatric patients less than 2 months of age, you must provide nonclinical (animal) data supporting the safety of your product in this patient population. We are deferring studies in pediatric patients > 2 months to 18 years because this product is ready for approval for use in adults and the pediatric studies in this population have not been completed.

Your deferred pediatric study in patients less than 2 months of age is required by section 505B(a) of the FDCA and is a required postmarketing study. However, initiation of this study is contingent upon submission of nonclinical data supporting the safety of the study. These nonclinical data should be obtained from new born animals that model pediatric patients aged less than 2 months. We recommend submission of a protocol for the nonclinical study(ies) prior to the initiation of these studies. In the event your nonclinical data do not support the safety of the pediatric study, we will consider whether a waiver of the pediatric study requirement is appropriate for this population. The status of this postmarketing study in patients less than 2 months of age must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This required study is listed below, as described in your submission of June 27, 2008.

1. Deferred pediatric study under PREA for use in magnetic resonance imaging (MRI) of the liver in pediatric patients ages 0 to 2 months with known or suspected hepatobiliary pathology. This study will obtain evaluable safety and imaging data from at least 10 subjects, however, due to the anticipated rarity of these clinical conditions in this pediatric population, progress towards recruitment will be assessed at one year after study start and the targeted number of patients may require adjustment. Any adjustment in the sample size will be supplied in a protocol amendment that contains supportive information and a request for FDA concurrence. Descriptive statistics will summarize safety and efficacy outcomes. Efficacy determination will be based upon extrapolation from studies in other patient populations.

Protocol Submission:	November, 2011
Study Start:	May, 2012
Final Report Submission:	May, 2014

Your deferred pediatric study in patients ages > 2 months to 18 years is required by section 505B(a) of the FDCA and is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This required study is listed below, as described in your submission of June 27, 2008:

2. To conduct the study entitled, "An observational study of the administration of Eovist® in pediatric patients who are referred for a routine contrast enhanced liver MRI because of suspected or known focal liver lesions." This study will enroll subjects aged > 2 months to 18 years and obtain evaluable safety and imaging data from at least 50 subjects. Efficacy will be assessed based upon comparison of uncontrasted images to Eovist®-contrasted images. Descriptive statistics will summarize safety and efficacy outcomes.

Protocol Submission: November, 2008

Study Start: May, 2009

Final Report Submission: May, 2013

Submit final study reports to your NDA 22-090. Use the following designator to prominently label all submissions:

Required Pediatric Assessment(s)

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Act of 2007 (FDAAA) amends the 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 Eovist® 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, $GFR < 30 \text{ mL/min/1.73m}^2$) 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:

3. A trial to collect clinical data sufficient to assess the magnitude of risk for the development of NSF with your product among patients with moderate ($\text{GFR} < 60 \text{ mL/min/1.73m}^2$) to severe renal insufficiency.

The timetable you submitted on June 12, 2008, states that you will conduct this trial according to the following timetable:

Protocol Submission:	October, 2008
Trial Start Date:	December, 2008
Final Report Submission:	December, 2013

Submit the protocol to your IND 54,875 with a cross-reference letter to this NDA 22-090. Submit all final report(s) to your NDA 22-090. 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)

You are required to report periodically to FDA on the status of this clinical trial pursuant to sections 505(o)(3)(E)(ii) and 506B of the FDCA, as well as 21 CFR 314.81. Under section 505(o)(3)(E)(ii), you are also required to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue associated with your product.

POSTMARKETING COMMITMENT

We remind you of the following postmarketing clinical trial commitment agreed upon in your submission dated June 12, 2008:

4. To conduct a single center crossover study to evaluate the possible influence of Erythromycin as an example of an inhibitor of the organic anion transporting peptide on the hepatocyte uptake of Eovist[®] in liver MR imaging in healthy subjects.

Protocol Submission:	December, 2008
Trial Start Date:	May, 2009
Final Report Submission:	May, 2010

Submit clinical protocols to your IND 54, 875. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this NDA 22-090. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical trials, number of patients entered into each trial. All submissions, including supplements, relating to these postmarketing commitments should be

prominently labeled "Postmarketing Commitment Protocol", "Postmarketing Commitment Final Report", or "Postmarketing Commitment Correspondence."

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 agreed upon labeling. 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 22-090."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the agreed upon text for the 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 22-090." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product 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.

Please submit one market package of the drug product when it is available.

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

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

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.

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

Sincerely,

{See appended electronic signature page}

Karen Weiss, M.D.
Deputy Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

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LABELING