CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-090

SUMMARY REVIEW

DIVISION DIRECTOR'S REVIEW MEMORANDUM

NDA:	22-090
DRUG:	Gadoxetate Disodium
TRADENAME:	Eovist® Injection
FORMULATION:	Single use vials that contain 10 mL solution; with 181.34 mg/mL of gadoxetate disodium (equivalent to 0.25 mmol/mL) with specified excipients in sterile, preservative-free solution
ROUTE:	Intravenous administration as a bolus injection administered at a rate of 2 mL/second, followed by routine flush with saline.
DOSE:	0.1 mL/kg (0.025 mmol/kg)
SPONSOR:	Bayer Healthcare Pharmaceuticals, Inc.
SUBMITTED:	June 21, 2007
PDUFA DUE DATE:	May 2, 2008
DD MEMO COMPLETED:	June 7, 2008
DD MEMO PREPARERS:	Dwaine Rieves, MD, Director Division of Medical Imaging and Hematology Products

SPONSOR'S PROPOSED INDICATION:

"Eovist Injection is a gadolinium-based contrast agent indicated for intravenous use in T1-weighted magnetic resonance imaging (MRI) of the liver to detect and characterize lesions in adults with known or suspected liver disease."

RELATED DRUGS:

Five gadolinium-based contrast agents are approved by FDA and are currently marketed, as follows:

1) Omniscan (gadodiamide/GE Healthcare) indicated for use in MRI to visualize lesions in the brain, spine and associated tissues as well as within the thoracic, abdominal, pelvic cavities and retroperitoneal space.

2) Magnevist (gadopentetate/Bayer Healthcare) indicated for use in MRI to visualize lesions in the central nervous system and "in the body."

3) Optimark (gadoversetamide/Covidian) indicated for use in MRI to visualize lesions within the central nervous system and the liver.

4) Prohance (gadoteridol/Bracco) indicated for use in MRI to visualize lesions in the "brain, spine and associated tissues."

5) Multihance (gadobenate/Bracco) indicated for use in MRI to visualize lesions in the "brain, spine and associated tissues."

RELATED REVIEWS:

Clinical:	Cynthia Welsh, M.D.; Louis Marzella, M.D., Ph.D.
Statistics:	A. G. Mucci, Ph.D, Jyoti Zalkikar, Ph.D.

Chemistry:	Eldon Leuzinger, Ph.D.
Microbiology:	Bryan Riley, Ph.D.
Pharm-toxicology:	Yanli Ouyang, Ph.D., Adebayo Laniyonu, Ph.D.
Clin Pharmacology:	Christy John, Ph.D, Young Moon Choi, Ph.D.
Project Manager:	James Moore, Pharm.D.
DSI (inspection):	Karen Storms and Joseph Salewski
OSE:	Suzanne Berkman, Pharm.D.
DDMAC:	Sean Bradley
Advisory Committee:	None

RECOMMENDED REGULATORY ACTIONS:

1) Approval of Eovist for the proposed indication:

Eovist is a gadolinium contrast agent that functions, for the most part, in a similar manner as all other products in the class of gadolinium-based contrast agents. Specifically, it acts as a parmagnetic molecular source to improve the contrast detected in MRI images. The molecular structure of Eovist is somewhat unique in that it was engineered for uptake of the molecule by hepatocytes and the clinical development program was dedicated to development of the agent for specific use in the imaging of the liver.

Eovist has been marketed in Europe for approximately four years, under the name, Primovist. The "Primovist" name was assessed as promotional by FDA during the NDA review process and the company changed the proposed trade name to "Eovist" (for US-specific marketing).

Four clinical studies robustly demonstrated Eovist diagnostic efficacy and the safety data indicated that the safety concerns for Eovist are similar to those for the currently marketed gadolinium contrast agents. Indeed, no unique safety concerns were identified during the review.

2) Requirement of the sponsor to conduct a post-marketing trial:

The approval is accompanied by a post-marketing "requirement" to conduct a trial among patients with moderate to severe renal insufficiency (glomerular filtration rate < 60 mL/min/1.73m^2) to severe renal insufficiency. This requested trial is identical to the trial FDA requested in 2007 for the manufacturers of the five other members of the class of gadolinium-based contrast agent. The request is based upon the known correlation of risk for nephrogenic systemic fibrosis (NSF) with renal failure/with the risk definitively established for patients with severe renal insufficiency but unknown for patients with lesser degrees of renal insufficiency.

3) Agreement of the sponsor to conduct a post-marketing trial:

The approval is accompanied by a post-marketing "commitment" to obtain diagnostic efficacy information pertaining to use of Eovist among patients who are also receiving concomitant treatment with a drug that is an inhibitor of the cellular transport pathway for Eovist. For example, erythromycin might alter the diagnostic performance since it inhibits the Eovist cellular uptake pathway. This is an "agreed-upon" study.

Two of the four studies were "characterization" studies (studies 3 and 4) where the subjects were not necessarily undergoing surgery and the truth standard was either surgical histopathology or other prespecified criteria. The main endpoint in these studies was a comparison between the non-contrasted MRI and Eovist-contrasted MRI for the degree of "correctness" (ie., agreement) with the characterization defined by the truth standard. Various prespecified categories (e.g., cyst, regenerative nodule, focal fat, etc.) were used as outcome variables.

In all four studies, patients underwent a baseline, pre-contrast MRI followed by Eovist with imaging performed immediately (the "dynamic" phase) and at a later time point (~ 20 min) which was called the "hepatic phase). Images from both phases were used in outcome assessment. Like most major imaging studies, the outcomes were based upon highly detailed, systematic review of images by three radiologists who were supplied with no clinical information. A successful outcome was assessed if two of the three radiologists "met the primary endpoint" --that is, they assessed improved sensitivity for studies 1 and 2 and improved correctness for studies 3 and 4.

Overall, the primary endpoints were met in all four studies, as shown in the following tables.

TABLE 1
Sensitivity in Liver Lesion Detection

Diagnostic Procedure	**Reader**	**Study 1 Sensitivity (%) n = 129**	**Study 2 Sensitivity (%) n = 126**
Pre-contrast MRI	Reader 1	76	77
	Reader 2	76	73
	Reader 3	71	72
Combined pre- and EOVIST-contrast MRI	Reader 1	81	82
	Reader 2	78	76
	Reader 3	74	78
Difference: Combined Pre + EOVIST-contrast MRI minus pre MRI (95% confidence interval)	Reader 1	5 (1, 9)*	5 (1, 9)*
	Reader 2	2 (-1, 5)	3 (-1, 7)
	Reader 3	3 (0, 6)*	6 (0, 10)*

* = Statistically significant improvement

TABLE 2

Proportion of Correctly Characterized Lesions

		Study 3		Study 4	
Diagnostic Procedure	**Reader**	**n**	**Proportion correct (%) ****	**n**	**Proportion correct (%) ****
Pre-contrast MRI	Reader 1	182	51	177	60
	Reader 2	182	59	177	64
	Reader 3	182	53	177	48
Combined pre- and EOVIST-contrast MRI	Reader 1	182	67	177	61
	Reader 2	182	76	177	76
	Reader 3	182	58	177	67
Difference: Combined pre- and EOVIST-contrast MRI minus Pre-contrast MRI (95% confidence interval)	Reader 1		16 (7, 25)*		1 (-7, 10)
	Reader 2		17 (9, 25)*		11 (5, 18)*
	Reader 3		5 (-2, 12)		19 (11, 27)*

* = statistically significant improvement

** proportion of correctly characterized lesions with respect to the reference.

Safety outcomes were assessed following Eovist exposure to 1755 subjects. In general, the pattern of adverse events was remarkably similar to other gadolinium-based contrast agents. In the clinical trials, no serious events appeared to be related to Eovist and the reported adverse events were predominantly mild in severity (most common was a sensation of "feeling hot", as was reported in 0.9% subjects). In post-marketing experience in Europe, anaphylactoid reactions have rarely been reported.

As previously noted, the class risks for NSF apply to Eovist.

Statistical Review:

The statistical review was performed by Dr. Anthony Mucci, lead statistician for the NDA. The findings from her review were secondarily reviewed by Dr. Jyoti Zalkikar, Biometric Team Leader.

I have read Dr. Mucci's statistical review report and I concur with his statistical analyses, findings and comments that the sponsor has provided persuasive evidence of Eovist safety and efficacy.

Clinical Pharmacology and Biopharmaceuticals (OCPB) Review

The clinical pharmacology and biopharmaceutical review was performed by Dr. Christy John. The findings from the review were secondarily reviewed by Young Moon Choi, Team Leader. The reviewers determined that Eovist does not prolong the QT interval and has no implications for arrhythmogenesis. The team did express hypothetical

concerns regarding the drug uptake process for Eovist (on a cellular level) and the post-marketing commitment (concomitant erythromycin study) addresses this consideration.

I have read the clinical pharmacology and biopharmaceuticals review report and I concur with the observations and comments.

Chemistry and Microbiology

The Chemistry review was performed mainly by Dr. Eldon Leutziner. The microbiology review was performed by Dr. Bryan Riley. The review team verified that facilities inspections were completed and the facilities were compliant with FDA expectations.

I have read the summary of the chemistry review findings and concur with the results. Dr. Leutziner observed that the supplied chemistry and manufacturing information was sufficient to support the product's approval and had no requests for post-marketing commitments.

I have examined Dr. Riley's summary findings, including inspectional considerations, and concur with the findings.

Pharamcology/Toxicology

The pharmacology/toxicology review was performed by Dr. Yanli Ouyang and was secondarily reviewed by Dr. Adebayo Laniyonu.

I have read the pharmacology/toxicology recommendations and I concur with the observations. The reviewers noted that the submitted pharmacology/toxicology data support the approval of Eovist and with no need for PMC nonclinical studies.

Pediatric Safety and Efficacy

No pediatric data were supplied and the sponsor is to conduct a pediatric study in the post-marketing period.

Proposed Labeling

During the review cycle, FDA and the sponsor developed multiple revisions of the Eovist product label. These revisions largely related to the description of the clinical studies and the safety information. I have reviewed the final product label and concur with the text.

Office of Surveillance and Epidemiology

The "Eovist Risk Management Team (Drs. Suzanne Berkman and Claudia Karwoski as well as Ms. Mary Dempsey) reviewed the Eovist application and determined that a risk management plan was not necessary and that labeling sufficiently addresses safety considerations.

Division of Scientific Investigation (DSI)

As described in a detailed memorandum from Ms. Karen Storms and Mr. Joseph Salewski, multiple domestic as well as foreign clinical sites were inspected and the findings revealed relatively minor deficiencies that did not compromise the clinical study data integrity.

Financial Disclosure

As noted in Dr. Welsh's review, the sponsor has submitted required financial disclosure information and the information is acceptable.

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/s/

Rafel Rieves
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MEDICAL OFFICER