Office of Clinical Pharmacology NDA Review	
Number	NDA 22-090
Type/Category	Supplement-11 (Efficacy)
Brand (generic) Name	Eovist (Gadoxetate disodium)
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 focal
Dosage Form	Solution for Injection
Route of Administration	Intravenous
Dosing Regimen and Strength	Single dose, 0.1 mL/kg
Applicant	Bayer HealthCare Pharmaceuticals, Inc.
OCP Division	DCP V
OND Division	DMIP
Submission Dates	June 10, 2014 (SDN 388) September 17, 2014 (SDN 402) December 19, 2013 (SDN 369)

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1. EXECUTIVE SUMMARY

Eovist injection (gadoxetate disodium) is a gadolinium based contrast agent that was approved in July 2008. The approval included a post-marketing requirement (PMR) for an observational study of the administration of Eovist in pediatric subjects (> 2 months and < 18 years) who are referred for a routine contrast enhanced liver MRI because of suspected or known focal liver lesions. The current submission is an efficacy supplement to make changes to the package insert on the basis of the study submitted to fulfill the PMR. This review includes review of the completed study report for the PMR pediatric study, as well as the current efficacy supplement.

The observational study did not include pharmacokinetics of gadoxetate in the studied population. The approved dose of Eovist for adults is 0.1 ml/kg (0.025 mmol/kg). The observed safety and efficacy data, however, was at doses ranging from 0.09 to 0.2 ml/kg. An examination of the data revealed no apparent differences in efficacy across doses and age groups. The use of the adult dose (0.1 ml/kg) provided adequate image contrast enhancement.

Based upon the radiologists scores of images, additional diagnostic information was obtained in 86% of patients when combined unenhanced images and Eovist enhanced liver Magnetic Resonance (MR) images were compared to unenhanced MR images alone. Due to the retrospective nature of the study and small numbers, no statistically-based conclusions can be made about efficacy of Eovist in the pediatric population. No safety signals were noted.

1.1. RECOMMENDATIONS

This supplemental NDA is acceptable from a clinical pharmacology perspective. The PMR for an observational study in pediatric patients (PMR # 2) appears to have been fulfilled, but the final determination will be made by the clinical division, as the PMR was for an observational study without pharmacokinetics or exposure-response analysis. Recommendations for package insert language appear in section **3. Detailed Labeling Recommendations** of this review.

1.2 PHASE 4 REQUIREMENTS AND COMMITMENTS

1.2.1 Post Marketing Requirements

None.

1.2.2 Post Marketing Commitments

None.

Signatures:

_____	_____
Christy S. John, Ph.D. Reviewer Division of Clinical Pharmacology V	Gene Williams, Ph.D. Team Leader Division of Clinical Pharmacology V

_____
NAM Atiqur Rahman, Ph.D.
Division Director
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1.3. SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

The applicant conducted an observational/retrospective, multicenter study evaluating the safety and efficacy of Eovist in pediatric patients. No PK data was collected. The investigators retrospectively collected MR imaging data from 52 patients for this study. The approved dose of Eovist in adults is 0.1 mL/kg (0.025 mmol/kg). The patients in the study received doses ranging from 0.09 to 0.2 ml/kg. An examination of the data revealed no apparent differences in MR imaging across doses and ages groups.

Although there is no PK data collected in the study, the pharmacodynamics response data (contrast enhancement) could be used as a surrogate for PK and for efficacy. Additional diagnostic information was obtained in 86% of patients when combined unenhanced images and Eovist enhanced liver MR images were compared to unenhanced MR images alone. However, due to the retrospective nature of the study and small numbers, no statistically-based conclusions can be made about efficacy of Eovist in the pediatric population. No safety signals were noted.

2. QUESTION-BASED REVIEW

2.6. Intrinsic Factors

2.6.2. Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

2.6.2.4. Pediatric Patients

The applicant conducted an observational/retrospective, multicenter study evaluating the safety and efficacy of Eovist in pediatric patients. No PK data was collected. The investigators identified 52 patients for participation in this study. The approved dose of Eovist in adults is 0.1 mL/kg (0.025 mmol/kg). The observed data, however, was at doses ranging from 0.09 to 0.2 ml/kg. The reviewer sent an information request to the applicant stating that, “The approved dose for Eovist is 0.1 mL/kg. The range of doses used was 0.09 mL/kg to 0.2 mL/kg with a mean volume of 0.14 mL/kg. Please describe the effect of dose on the clinical efficacy.”

The applicant responded with an analysis that defined two dose groups. Dose Group 1 was patients who received ≤0.1 mL/kg and Dose Group 2 was patients who received a dose > 0.1 mL/kg. Twenty nine patients received a dose of ≤0.1 ml/kg and 21patients received a dose of >0.1 ml/kg. The results of the applicant's analysis are shown in **FDA Table 1.** (means) and **FDA Table 2.** (medians). A statistical comparison of efficacy by age and dose group was not conducted due to the observational, non-randomized nature of the study. The tables show that values for efficacy variables were similar for the two dose groups.

In order to assure that the results showing no differences in contrast enhancement by dose were not confounded by dose correlating with age, the reviewer performed an analysis to determine if there was consistency of dosing across age groups. The results are shown in **FDA Table 3.** Dosing was similar for all age groups. The data is from an observational study that was not powered for making comparisons. However, based on similarity across dose and age groups, the data supports that the approved adult dose (0.1 mL/kg) provides similar contrast enhancement to the 0.2 mL/kg dose.

Based on the radiologists reading scores, additional diagnostic information was obtained in 86% of patients when combined unenhanced images and Eovist enhanced liver MR images were compared to unenhanced MR images alone. Due to the retrospective nature of this study and small numbers, statistically-based conclusions cannot be made regarding efficacy of Eovist in the pediatric population. No safety signals were noted.

FDA Table 1. Efficacy variables by dose group, values are means (standard deviation), N=50

Dose	Age	N	Change in number of lesions (1=less/ fewer, 2=equal, 3=more/ greater)	Improved border delineation of the primary lesion (1=no, 2=yes)	Increased contrast of primary lesion vs background (1=no, 2=yes)	Change in size of primary lesion; 1=larger, 2=no change, 3=smaller)	Change in information about lesion characterization; (1=improved, 2=unchanged, 3=worsened)
≤0.1	9.1 (5.6)	29	2.38 (0.55)	1.79 (0.41)	1.83 (0.38)	1.72 (0.52)	1.28 (0.45)
>0.1	6.3 (5.5)	21	2.00 (0.44)	1.62 (0.49)	1.76 (0.43)	1.86 (0.32)	1.14 (0.35)

FDA Table 2. Efficacy variables by dose group and age medians, N=50

Dose	Age	N	Change in number of lesions (1=less/ fewer, 2=equal 3=more /greater)	Improved border delineation of the primary lesion (1=no, 2=yes)	Increased contrast of primary lesion vs background (1=no, 2=yes)	Change in size of primary lesion; 1=larger, 2=no change, 3=smaller)	Change in information about lesion characterizatio n; (1=improved, 2=unchanged, 3=worsened)
</= 0.1	10	29	2	2	2	2	1
>0.1	5	21	2	2	2	2	1

FDA Table 3. Doses administered to different pediatric age groups

Age (Years)	Dose (Mean) in mL/kg	Standard Deviation
<2	0.16	0.050
2-5	0.14	0.051
6-9	0.14	0.054
10-14	0.13	0.044
15-18	0.12	0.035

3. DETAILED LABELING RECOMMENDATIONS

The entirety of the applicant's proposed package insert is included as Appendix 4.2. The reviewer's edits are shown below in **FDA Table 4.** The applicant did not propose changes to clinical pharmacology related sections. (b) (4)

(b) (4)

FDA Table 4. Package Insert Recommendations

Applicant's Proposed Package Insert	Reviewer's Edits
(b) (4)	(b) (4)

(b) (4)

(b) (4)

4. APPENDIX

4.1 Applicant's proposed package insert

APPEARS THIS WAY ON ORIGINAL

15 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTY S JOHN
02/20/2015

GENE M WILLIAMS
02/20/2015
I concur with the recommendations.

NAM ATIQUR RAHMAN
02/20/2015
I accept the recommendation of the review team.