February 19, 2015

DIVISION OF MEDICAL IMAGING PRODUCTS

CLINICAL REVIEW

Application Type: Pediatric Supplemental New Drug Application.

Application Number: NDA 22090, SN 0140.

PDUFA Goal Date: March 27, 2015.

Reviewer Name: Harris E. Orzach, M.D.

Drug Name: Eovist (U.S.A.), EOB Primovist (Japan), Primovist (elsewhere).

Active Ingredient: Gadoxetate disodium.

Approved 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 liver disease.

Intended Use: Eovist is approved for use in adults. This supplemental application provides new information on the use of Eovist in the pediatric population, specifically, for ages greater than 2 months, and less than 18 years. The applicant proposes to add this information to the pediatric use section (8.4) of the prescribing information. The applicant does not plan changes to the indications and usage section of the labeling.

SUMMARY

The sponsor has fulfilled the following pediatric post-marketing requirement as stated by the agency:

(b) (4)

This study would enroll subjects aged greater than 2 years of age, and less than 18 years of age, and obtain evaluable safety and imaging data from at least 50 subjects. Efficacy would be assessed based upon comparison of non-contrast images to paired non-contrast and Eovist images. Descriptive statistics would summarize safety and efficacy outcomes.

This study was retrospective, multicenter and was designed to evaluate the activity and safety of Eovist in pediatric patients who had already undergone an Eovist liver MRI, because of suspected or known focal liver lesions. Such a study design was necessary because focal liver lesions in the pediatric population are rare. A blinded read of the MRI images was performed by an independent radiologist.

Eovist administered in doses ranging from 0.1 to 0.2mL/kg aided visualization of the primary liver lesions by increasing the contrast and the border delineation the lesions in the majority of the 51 study subjects. The value of Eovist in the detection or characterization of the lesions could not be determined. There was no appreciable difference in visualization between the 0.1 ml/kg and higher doses. There were no reports of drug reactions or safety issues in the pediatric population studied.

Single and repeat-dose toxicology studies of Eovist in neonate rats did not raise safety concerns. Specifically no clinical, hematological, or clinical chemistry abnormalities were identified. Minor renal histology changes were reversible. No NSF-like pathology and no treatment-related increase in tissue calcification was observed. In summary the preclinical data support the safety of Eovist use in in pediatric patients with renal and hepatic immaturity.

Recommendation on Regulatory Action: The reviewer recommends approval of the supplemental NDA for Eovist (Gadoxetate Disodium) based on the following considerations: extrapolation of safety and efficacy from adequate and well controlled studies in the adult population; evidence of improved visualization of liver lesions and of safety from the results of the pediatric observational study in the present submission**;** lack of safety signals in the preclinical single- and repeat-dose toxicology study in newborn/juvenile animals in a previous submission; apparent abrogation of risk of NSF across gadolinium-based contrast agents (GBCAs) by limiting the use of these agents in susceptible patients with chronic severely diminished renal function.

Support from pharmacokinetic data is not available. However the finding that Eovist improves the delineation of liver lesions in the delayed hepatic imaging phase is a strong pharmacodynamic indicator that the distribution of contrast in the liver is similar in adults and pediatric patients.

The new information in this supplement supports the utility of Eovist in improving visualization of liver lesions in the pediatric patients studied (ages between 2 months and 18 years). For this reason, the reviewer considers that the current indication for use statement of Eovist in adults only is unduly restrictive.. An adequate clinical or PK study does not appear to be feasible due to the rarity of focal liver lesions in pediatric patients. For this reason I recommend removing the age restriction in the indication statement and describing in the pediatric study section the preclinical and clinical study results and our current understanding of the risk of NSF.

With regard to the safety of Eovist in mature newborns, the level of concern for NSF has lessened due to the accumulated clinical and preclinical data reviewed by the agency since the 2008 approval of Eovist. For this reason I recommend that the Division request an update on the status of the 0-2 month PMR study from the applicant and reassess the need for the study.

POST-MARKETING RISK MANAGEMENT: None is needed.

POSTMARKETING COMMITMENTS: None are needed.

INTRODUCTION AND REGULATORY HISTORY

Mechanism of Action: Eovist is a paramagnetic MRI contrast agent, which is both extracellular and hepatocyte-specific. In comparison to purely extracellular agents, Eovist is also selectively taken up by hepatocytes, followed by sequestration in the bile. After IV injection, there is increased signal in normal liver in delayed TI weighted sequences, which accentuates contrast of the liver with focal lesions.

Regulatory History: Eovist was approved in Europe in 2004 and in the US in July 2008 for use in patients 18 years of age and older. The US approval was accompanied by a post-marketing requirement to conduct a study among adult patients with moderately reduced renal function (glomerular filtration rate <60 mL/min/1.73m^2) and with severely reduced renal function. FDA requested a similar study in 2007 from the manufacturers of the five other members of the class of gadolinium-based contrast agents to further elucidate the risk for nephrogenic systemic fibrosis (NSF) in patients with various degrees of renal insufficiency.

At the time of 2008 approval the agency also required an observational study in at least 50 pediatric subjects aged > 2 month to 18 years to address the Pediatric Research Equity Act (PREA). This study would provide descriptive safety and diagnostic performance information for Eovist.

Pediatric assessment in subjects aged 0 to 2 month was deferred until additional safety data had been collected to address the potential risk of Eovist in pediatric patients with immature renal and hepatic function. At the time of the original approval there was a special concern that infants less than two month of age might be at special risk for NSF-like problems or NSF. The 2008 approval letter specifically requested preclinical safety data from newborn /juvenile animals and one of the summary reviews cites the need for clinical safety data from the planned NSF post-marketing study in adults with decreased renal function before the initiation of the study in pediatric patients less than two months of age could be considered.

Subsequently the agency released the applicant from the NSF study requirement in adults with decreased renal function because of lack of feasibility.

Indicated Age Groups for Other Marketed Gadolinium-based Contrast Agents

1. Gadavist (Gadabutrol): Adults and pediatric patients 0 years and older, for imaging CNS and breast.
2. Multihance (Gadobenate dimeglumine): Adults and children 2 years and older, for CNS, brain, spine and associated tissues; MRA of renal or aorto-ilio-femoral occlusion disorder.
3. Magnavist (Gadopentatate dimeglumine): Adults and children 2 years and older, for brain, spine head and neck, body.
4. Prohance (Gadoteridol): Adults and children over 2 years of age: for brain, spine and associated tissues, and head and neck.

5. Omniscan (Gadodiamide): Adults and children greater than 2 years of age: intrathoracic (non-cardiac), intra-abdominal, pelvic, retroperitoneum.
6. Optimark (gadoversetamide): Adults only, for brain, spine and associated tissues, liver.
7. Ablavar (Gadofosveset trisodium): Adults, for MRA of aorto-iliac occlusive disease.
8. Dotarem (Gadoterate meglumine): Adults and children 2 years of age and older, for brain, spine and associated tissues.

The accumulated experience with the GBCA indicated for use in pediatric patients raises no concerns about potential differences in contrast enhancement across age groups.

PRECLINICAL TOXICOLOGY

The 2008 Eovist approval letter made the conduct of the deferred pediatric study in pediatric patients ages 0 to 2 months contingent on nonclinical data supporting the safety of the study. The applicant performed the study entitled "Repeated Dose Toxicity Study in Neonatal Rats after Intravenous Administration on PND 10, 17 and 24 with a Following Recovery Period of up to 8 Weeks". This study was conducted to evaluate the systemic toxicity of gadoxetate disodium in neonatal/juvenile rats at the starting age of postnatal day 10.

The principal study results were as follows:

1. All animals survived and scheduled sacrifice did not reveal any treatment-related effects on organs up to a dose of 0.75mmol/kg.

2. Renal tubular vacuolation was observed in animals from the 0.25mmol/kg dose level. There were reversible atrophic clear cell tubules, but no accompanying renal damage at low dose.

3. There was no evidence of dose-related mineral deposits up to and including the dose of 0.75mmol/kg.

4. Findings in the multiple-dose study did not differ from those of single-dose toxicity study in neonate rats.

The FDA Pharmacology Toxicology reviewer (Olayinka Dina DVM, PhD) concluded that the study design, results and conclusions are acceptable and that the PMR requirement for the repeat-dose toxicity study has been satisfied.

SOURCES OF CLINICAL DATA

The clinical data are derived from a single retrospective study.

STUDY TITLE, DESIGN AND PROTOCOL

Title: An Observational Study of the Administration of Eovist in Pediatric Subjects (> 2 months and < 18 years of age), who are Referred for a Routine Contrast Enhanced Liver MRI, because of Suspected or Known Liver Lesions. (Phase IV).

Study Objectives: To obtain safety and additional diagnostic information on Eovist in pediatric subjects from 2 months to 18 years of age, who had a liver MRI utilizing this contrast agent.

Study Design: This was a retrospective, multicenter study evaluating efficacy and safety, utilizing patients who had already undergone an Eovist liver MRI, because of suspected or known focal liver lesions. Such a study design was necessary due to the fact that focal liver lesions in the pediatric population are relatively rare, diffuse liver disease being more common in this population. In the US there are approximately 100-150 new cases of pediatric liver tumors per year

Methodology: Medical records at multiple centers/hospitals were reviewed by the principal investigator or his designee every 3-6 months, in order to acquire 50 patients who had received Eovist liver MRI to investigate known or suspected focal liver lesions. Those who qualified and for whom informed consent was obtained were entered in the study.

Records were reviewed up to one year after Eovist administration and the following variables were recorded: Patient demographics (age gender and race), indication for scan, dose/volume of Eovist, date of MRI, adverse events (AEs) up to 24 hours, 1 year follow-up for all serious and unexpected AEs, occurrence of NSF, pregnancy and final diagnosis. Additional data recorded in the electronic case report forms (e-CRF) were the following: 1. Medical and surgical history (allergies, electrolyte disturbances, diffuse liver disease). 2. e-GFR, clinical chemistry and hematology from 14 days prior to 24 hours after injection. 3. Concomitant medications and procedures. 4. Physical examination findings and vital signs from 24 hours pre to 24 hours post injection. 5. MR sequences performed, and use of power injector vs. manual injection.

A blinded read of the MRI images was performed by an independent radiologist, and results were entered in e-CRFs. Non-contrast images were initially evaluated. Then, the non-contrast images were evaluated along with the post-contrast images, which is how interpretation would occur in the clinical setting.

Principal Endpoint: This outcome evaluated the additional diagnostic information obtained from the combined pre-contrast/post-contrast images, as compared with the pre-contrast images. This composite outcome consisted of the following: improved border delineation of primary lesion, improved contrast of primary lesion, change in number of lesions (less equal or more), change in size of primary lesion (larger or smaller), or change in lesion characterization (improved, unchanged, worsened).

Additional Endpoints: These consisted of the following: Change in diagnosis, change in confidence in diagnosis, number of non-malignant and malignant lesions, and change in recommended next course of therapy/subject management. True positive, true negative and accuracy of diagnoses were calculated based on the final diagnosis as stated in the patient's reports.

Truth Standard: The final diagnosis from the patient's record was to be used as the standard of truth.

Endpoint Determination: Blinded reads were performed by an independent radiologist, comparing the pre-contrast images to the combined pre and post-contrast images, the latter being the method of interpretation used in routine clinical practice. Because of the study design, visualization endpoints are more reliable than characterization endpoints.

RESULTS

Patient Demographics: There were 52 subjects in the safety analysis, and 51 in the efficacy analysis, as one subject did not have pre-contrast images. A total of 14 patients were 2 months to 2 years of age, 25 were 2-12 years, and 13 were 12-18 years; 54% were female, 69% Caucasian, 25% Asian, and 6% Black or African-American

Table 1 shows the distribution of lesions in the pediatric patients studied, and this differs somewhat from a typical distribution in adults.

Table 1. Distribution of lesions

Final diagnosis	(N=52) N(%)
Benign Lesions	28 (53.8)
Atypical hepatocellular lesion/consistent with high grade dysplastic nodule	1 (1.9%)
Benign tumors	5 (9.6%)
Biliary atresia	1 (1.9%)
FNH	11 (21.2%)
No abnormal finding	1 (1.9%)
Focal steatosis	1 (1.9%)
Hemangioma	1 (1.9%)
History of HCC status post liver transplantation	1 (1.9%)
Liver focal lesions in Caroli disease	1 (1.9%)
No liver lesions of neuroblastoma[a]	1 (1.9%)
Oxysterol 7A hydroxylase deficiency	1 (1.9%)
Suspected hepatic angioma	1 (1.9%)
Telangiectasis lesions	1 (1.9%)
Wolman disease	1 (1.9%)
Malignant Lesions	24 (47.1%)
Enhanced lesion	16 (30.8%)
Hepatic tumor	1 (1.9%)

Hepatoblastoma	2 (3.8%)
Hepatocellular carcinoma	3 (5.8%)
Liver formation unknown origin	1 (1.9%)
Liver tumor	1 (1.9%)

Efficacy Evaluation: Table 2 is reproduced from the NDA and summarizes the principal efficacy endpoints. For the majority of subjects, the examination of paired contrast and non-contrast images provided additional information defined as one or more of the following: improved border delineation of the primary lesion, increased contrast of the primary lesion compared to background, better characterization of the primary lesion, change in the number of lesions, and in the size of the lesions

Table 2. Additional diagnostic information

Additional diagnostic information	Proportion of subjects[a] N (%)	95% CI
Improved border delineation of primary lesion (yes vs no)	36 (70.6)	(56, 82)
Increased contrast of primary lesion (yes vs no)	40 (78.4)	(65, 89)
Change in size of the primary lesion (larger and smaller vs no change)	13 (25.5)	(14, 40)
Change in lesion numbers (less and more vs equal)	17 (33.3)	(21, 48)
Change in information about lesion characterization (improved and worsened vs unchanged)	39 (76.5)	(62, 87)
Overall (change in at least 1 of 5 variables above)	44 (86.3)	(74, 94)

[a] Proportion of subjects (combined pre-contrast and post-contrast images compared with pre-contrast images)

Table 3 summarizes the changes in lesion assessment based on examination of paired non-contrast and contrast images. With regard to recommended next course of therapy, the administration of Eovist accounted for a change in therapy/management in 88% of subjects. Based on pre-contrast studies , the suggested management was post-contrast MRI in 82%, and ultrasound in 16%. Based on post-contrast studies, the next course of therapy/management was biopsy in 53%, and observation in 29%.

Table 3: Changes in lesion assessment N (%)[a] (N=51)

Change in diagnosis	
Yes	25 (49%)
No	26 (51%)
Change in confidence of diagnosis	
Yes[b]	37 (72%)
No	14 (27%)
Change in number of nonmalignant lesions	
Yes	18 (35%)
No	33 (65%)
Change in number of malignant lesions	
Yes	11 (22%)
No	40 (78%)
Change in recommended course of management	
Yes	45 (88%)
No	6 (12%)

[a] Percentage is calculated as number of subjects in the category divided by 51 subjects with available pre-contrast and combined pre-contrast/post-contrast images.
[b] The change was increase in diagnostic confidence for 36 of 37 subjects and decrease in 1 subject

Table 4 shows the change in diagnosis which was given by the readers, which occurred when viewing the post-contrast images, as compared to the pre-contrast images. They gave a more specific diagnosis in all cases, calling both benign and malignant diagnoses post-contrast, from pre-contrast studies that showed no lesion, benign and malignant lesions. However, when compared to the final diagnoses, their readings were frequently incorrect with regard to malignancy or benignity. They called benign lesions malignant in 8 out of 25 cases, and called malignant lesions benign in 4 out of 25 cases. Therefore, although the lesions are better visualized/defined with Eovist, allowing the readers to make a more specific diagnosis, this diagnosis is frequently incorrect. While contrast is needed for optimal detection/visualization of lesions, biopsy is essential in the majority of lesions for accurate characterization. This is especially important in differentiating benign from malignant lesions.

Table 4: Change in diagnosis – comparison of precontrast versus combined precontrast/postcontrast images (only subjects for whom a change was documented) (N=25)

Subject no.	Diagnosis Precontrast	Diagnosis Combined pre-contrast	Final diagnosis category
14001-0002	No lesion[a]	Adenoma	Benign
14001-0005	No lesion	Benign tumors	Benign
14001-0008	No lesion	FNH	Benign
14001-0010	No lesion	Metastasis	Benign
14004-0013	No lesion	Benign tumors	Malignant
14004-0017	No lesion	Benign tumors	Malignant
20001-0011	No lesion	Benign tumors	Malignant
22001-0003	No lesion	Malignant tumor	Benign
14001-0007	Benign tumors[b]	FNH	Benign
14004-0002	Benign tumors	Malignant tumor	Malignant
14004-0018	Benign tumors	Malignant tumor	Benign
20001-0005	Benign tumors	Hemangioendothelioma	Benign
22001-0002	Benign tumors	Malignant tumor	Benign
22001-0006	Benign tumors	FNH	Benign
61001-0001	Benign tumors	FNH	Malignant
14004-0007	Malignant tumor	Hepatoblastoma	Malignant
14004-0010	Malignant tumor	Metastasis Cyst	Malignant
14004-0011	Malignant tumor	Hepatoblastoma	Malignant
14004-0014	Malignant tumor	Hepatoblastoma	Malignant
20001-0003	Malignant tumor	Hepatoblastoma	Malignant
14001-0004	HCC	HCC Dysplastic nodule	Benign
14002-0001	HCC	HCC Other (regenerative nodule)	Benign
14004-0004	Metastasis	Malignant tumor	Malignant
22001-0001	Focal steatosis	Metastasis	Benign
20001-0008	Other (small, probably fat-containing lesion)	Metastasis	Benign

Key: FNH = focal nodular hyperplasia; HCC = hepatocellular carcinoma a 'No lesion' was categorized as benign.
b Type of benign or malignant lesion not specified.
Note: Subjects with 2 diagnoses in the blinded read study were only counted as 1 subject. If 1 diagnosis was malignant and 1 diagnosis was benign, this subject was categorized as 'malignant'.

In table 5, the next course of management/therapy based on the pre-contrast images is noted to be predominantly obtaining a post-contrast MRI examination. Therefore, it seems that the pre-contrast images do not aid the clinician with arriving at a definitive diagnosis/plan. The

post-contrast examination aids the clinician, in that it suggests biopsy or follow-up examination as the next step in management/therapy.

Table 5: Change in recommended next course of subject management/therapy – comparison of precontrast versus combined precontrast/postcontrast images (only subjects for whom a change was documented)

Recommended next course of Management/Therapy	Precontrast N (%)[a] N=45	Combined precontrast / postcontrast N (%)[a] N=45
Ultrasound	0	1 (2.2)
Biopsy	0	24 (53.3)
Follow-up examination	1 (2.2)	13 (28.9)
Other	37 (82.2)[b]	2 (4.4) No
action	0	3 (6.7)
Other/ultrasound	7 (15.6)	0
Other/biopsy	0	2 (4.4)

a Percentage is calculated as number of subjects in the category divided by 45 subjects with available precontrast and combined precontrast/postcontrast images.
b 'Other' included contrast enhanced MRI, with or without additional sequences, such as STIR and DWI

SAFETY

No safety issues with Eovist were identified up to a dose of 0.2ml/kg (0.05mmol/kg). The labeled dose in adults is 0.1 ml/kg body weight, or 0.025 mmol/kg. Double the labeled dose was given to 18 patients at one site.

No adverse drug reactions, unexpected AEs or deaths were reported. There were no signs or symptoms of NSF. There were no clinically notable effects on blood laboratory parameters or vital signs.

Forty percent (21 of 52) subjects experienced at least 1 serious adverse event (SAE) up to one year after injection. Most frequent events were febrile neutropenia in 7 subjects, and pyrexia in 3 subjects. None of the SAEs considered related to Eovist administration.

Table 6 shows serious adverse events in 21 of 52 subjects (42%), subdivided into mild (4%), moderate (21%), and severe (17%). There were no events related to Eovist injection, or to the MRI procedure itself.

Table 6: Overall summary of adverse events.

	Number of subjects (%)(N=52)
Subjects with any (S)AE	22 (42.3)
Subjects with maximum intensity of all (S)AEs[a]	
Mild	2 (3.8)
Moderate	11 (21.2)
Severe	9 (17.3)
Subjects with Eovist/Primovist-related (S)AE	0
Subjects with procedure (MRI)-related (S)AE	0
Subjects with (S)AE resulting in death	0
Subjects with SAE	21 (40.4)

a For subjects with (S)AEs that occurred more than once, only the maximum intensity is presented.
Key; AE = adverse event; MRI = magnetic resonance imaging; SAE = serious adverse event

Table 7 further subdivides serious adverse events by age group and time of occurrence after Eovist injection. No events occurred within 24 hours of injection. The adverse events were approximately equally divided among the >24 hour to 120 days, >120 to 240 days and the >240 to 365 day time periods post-injection. The majority of the serious adverse events were divided among the >2 months to < or = 2 year and the > 2years to < or = 12 year age groups.

Table 7: Serious adverse events by age group and time of occurrence post- Eovist/Primovist MRI

	Time of occurrence post-Eovist/Primovist MRI			
Age group Preferred term	< 24 hr	> 24 hr to 120 days	> 120 to 240 days	>240 to 365 days
> 2 mo to ≤ 2 yr (N=14)				
Any SAE	0	6 (11.5)	6 (11.5)	5 (9.6)
Febrile neutropenia	0	3 (5.8)	1 (1.9)	0
Vomiting	0	1 (1.9)	0	0
Gastroenteritis rotavirus	0	1 (1.9)	0	0
Sepsis	0	1 (1.9)	0	0
Feeding disorder	0	1 (1.9)	0	0
Hypertension	0	1 (1.9)	0	0
Gait disturbance	0	0	1 (1.9)	0
Enterococcal	0	0	1 (1.9)	0

bacteraemia				
Parainfluenzae virus infection	0	0	1 (1.9)	0
Rhinovirus infection	0	0	1 (1.9)	1 (1.9)
Renal tubular acidosis	0	0	1 (1.9)	
Abdominal pain	0	0	0	1 (1.9)
Small intestinal obstruction	0	0	0	1 (1.9)
Device occlusion	0	0	0	1 (1.9)
Herpes zoster	0	0	0	1 (1.9)
Tracheitis	0	0	0	1 (1.9)
Upper respiratory tract infection	0	0	0	1 (1.9)
Portal shunt	0		0	1 (1.9)
> 2 to ≤ 12 yr (N=25)				
Any AE	0	4 (7.7)	5 (9.6)	3 (5.8)
Febrile neutropenia	0	2 (3.9)	2 (3.9)	0
Pyrexia	0	0	3 (5.8)	1 (1.9)
Anemia	0	1 (1.9)	0	0
Thrombocytopenia	0	1 (1.9)	0	0
Cecitis	0	1 (1.9)	0	0
Pneumatosis intestinalis	0	1 (1.9)	0	0
Cholangitis, acute	0	1 (1.9)	0	0
Clostridium difficile colitis	0	1 (1.9)	0	0
Lobar pneumonia	0	1 (1.9)	0	0
Neuropathy peripheral	0	1 (1.9)	0	0
Bacteremia	0	0	1 (1.9)	0
Septic shock	0	0	1 (1.9)	0
Abdominal pain	0	0	0	1 (1.9)
Pneumonia	0	0	0	1 (1.9)
Staphylococcal infection	0	0	0	1 (1.9)
Hepatocellular carcinoma	0	0	0	1 (1.9)
Headache	0	0	0	1 (1.9)
> 12 to < 18 yr (N=13)				
Any AE	0	0	1 (1.9)	1 (1.9)
Intracranial aneurysm	0	0	1 (1.9)	0
Appendicitis	0	0	0	1 (1.9)

LABELING REVIEW

There is enough improvement in structural delineation of liver lesions with the use of Eovist contrast injection in the age group >2months and < 18 years that removing the restriction of use to adults only is

warranted. There is insufficient information on lesion detection and characterization in the observational study to extend that indication to pediatric patients.

The adult dose is 0.1 ml/kg body weight which is 0.025 mmol/kg. The same dose in the pediatric population studied allowed adequate visualization of liver lesions. As a result it is reasonable to state in the labeling that no dose adjustment is necessary in pediatric patients.

There were no safety issues related to the Eovist injection and the juvenile toxicology study showed no evidence of liver injury and no diffuse fibrotic, calcified lesions suggestive of NSF were identified (b) (4)

A study of Eovist in infants may not be feasible. Because of the favorable safety information in the submission and the lessening concern with risk of NSF in general and in pediatric populations with immature renal function, I recommend that no restriction of use of Eovist in term infants be added to the labeling.

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/s/

HARRIS E ORZACH
02/24/2015

LIBERO L MARZELLA
02/24/2015
I concur with the primary clinical reviewer's assessment and recommended action.