Bayer HealthCare
Pharmaceuticals

Libero Marzella, MD, Acting Director
Division of Medical Imaging Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 22-090, eCTD sequence number: 0135
IND 54,875, eCTD sequence number: 0115
Eovist® (gadoxetate disodium) Injection
DEFERRAL EXTENSION REQUEST
RESPONSE TO PREA NON-COMPLIANCE LETTER

26-Jul 2013

Bayer HealthCare
Pharmaceuticals Inc.
P.O. Box 1000
Montville, NJ 07045-1000
Phone: (973) 487-2184
Fax: (973) 487-2016
lisa.chao@bayer.com

Dear Dr.Marzella:

Reference is made to NDA 22-090 for Eovist® (gadoxetate disodium) Injection 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. Reference is also made to the July 3, 2008 approval letter and the following required pediatric assessment:

> To conduct the study entitled, "An observational study of the administration of Eovist® Injection 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 |

Reference is also made to the "Acknowledge Revised Post-marketing Requirement / Commitment Milestones" letter from FDA on March 22, 2011. Further reference is made to the "Notification of Non-Compliance with PREA" letter which is dated June 13, 2013.

Prior to the availability of a "Deferral Extension Request" which is a new provision under the Food and Drug Administration Safety and Innovations Act (FDASIA), Bayer had requested and received acknowledgement from FDA of

revised post-marketing requirement milestone dates for the above-mentioned pediatric study, and it is with this acknowledgement and understanding of the revised milestone dates that Bayer has been conducting the study (detailed regulatory history can be found in Attachment 1). The purpose of this submission is to respond to the "Notification of Non-Compliance with PREA" letter and to request a Deferral Extension for the Final Report Submission of the pediatric study.

The reason for the delay of the Final Report Submission is due to FDA's request (February 19, 2009, received email comments) to revise Bayer's proposed protocol to include a 12 month follow-up period after administration of Eovist (to capture serious and unexpected medical events). On March 17, 2009 (NDA Seq. 058), Bayer had agreed to the FDA-requested protocol change and at that time also formally requested to revise the post-marketing requirement milestone dates accordingly. To amend the protocol and incorporate FDA's requested changes, Bayer requested that the Study Start Date be revised from May 2009 to Sep 2009. Furthermore, since each subject now required a 12 month follow-up, Bayer requested that the Final Report Submission be extended from May 2013 to August 2014.

Bayer contacted FDA several times to obtain feedback and concurrence on the proposed revised post-marketing requirement milestone dates. On February 8, 2011, an FDA-initiated teleconference was held where FDA acknowledged Bayer's need to extend milestone dates, however Bayer was informed that the original milestone dates could not be changed. FDA planned to make a notation on the FDA "Postmarket Requirements and Commitments" website, providing the reason for the delay (i.e additional 12-month follow up period). FDA attendees included Dr. R.D. Rieves, Division Director, Dr. L. Marzella, Medical Office Team Leader, and Dr. I. Krefting, Deputy Director for Safety.

On March 22, 2011, Bayer received an "Acknowledge Revised Post-marketing Requirement / Commitment Milestones" Letter from FDA. FDA provided written acknowledgement that Bayer's requested revised milestone dates were due to the protocol amendment to incorporate changes requested by FDA, and stated that "the original schedule serves as the basis for defining the status of the post-marketing requirement". With no other regulatory mechanism available at that time, FDA recommended to include the revised schedules (along with the original schedules) in our annual progress reports.

Bayer has diligently worked to conduct and complete the pediatric study, and believes it has been compliant with previous discussions with FDA toward the

Bayer HealthCare
Pharmaceuticals

fulfillment of this post-marketing requirement. Despite the challenges of this study (due to the very low incidence of liver lesions in the pediatric population), study enrollment was completed in 2012. The Final Report could have been submitted by May 2013 (original due date), however, due to the addition of the 12 month follow-up, the study achieved last-patient-last-visit in April 2013. Bayer is currently in the process of preparing the clinical study report. In light of the current status of the pediatric study, Bayer is requesting a Deferral Extension for the Final Report Submission of December 31, 2013 (which is prior to the original revised milestone date of August 2014 that was previously acknowledged by FDA).

This submission is provided in e-CTD format in accordance with the FDA Guidance for Industry – *"Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions using e-CTD Specifications (June 2008)"*. This submission is being submitted electronically via the FDA electronic Gateway.

Bayer HealthCare Pharmaceuticals certifies that this submission has been scanned for viruses and is virus free using TREND MICRO™ Office Scan™ , Program Version 10.5 or higher. For any questions regarding eCTD technical aspects of this electronic submission, please contact Jerianne Lilore at (973) 487-2868 or by email at jerianne.lilore@bayer.com

Sincerely,

Bayer HealthCare Pharmaceuticals Inc.

Lisa Chao, Ph.D.
Associate Director, Global Regulatory Affairs