DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 019596/S063 and 021037/S036

SUPPLEMENT APPROVAL

Bayer HealthCare Pharmaceuticals Inc.
Attention: Dolores Fliss
Deputy Director, Global Regulatory Affairs
100 Bayer Blvd., P.O. Box 915
Whippany, NJ 07981

Dear Ms. Fliss:

Please refer to your Supplemental New Drug Application (sNDA) dated January 18, 2018, received January 18, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Magnevist® (gadopentetate dimeglumine) Injection and Magnevist® (gadopentetate dimeglumine) Injection Pharmacy Bulk Package.

We also refer to our approval letter dated April 26, 2018 which contained the following error in the FULL PRESCRIBING INFORMATION: CONTENTS, reference to the MEDICATION GUIDE which is included at the end of the table of contents (TOC) in the Pharmacy Bulk Pack labeling. Patient labeling (including the Medication Guide) should not appear in the TOC of the prescribing information (PI). This is because patient labeling is not part of the PI but a separate labeling document that appears after the PI. The attached labeling has been corrected.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain April 26, 2018, the date of the original approval letter.

We also refer to our letter dated December 18, 2017, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Gadolinium Based Contrast Agents (GBCAs). This information pertains to the risk of gadolinium retention for months or years in several organs including the brain for longer time periods than expected based on the current pharmacokinetic models. We consider this information to be a signal for possible adverse behavioral and neurological effects related to gadolinium retention in the brain and of possible systemic adverse reactions due to gadolinium retention in other organs.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.
Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Sharon Thomas
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 5483
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 in pediatric

patients unless this requirement is waived, deferred, or inapplicable. Because none of these criteria apply to your application, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

We remind you of the following postmarketing requirements listed in the December 18, 2017, **LABELING SUPPLEMENT AND PMR REQUIRED** letter:

1. A study in mice to evaluate the effect of (a) perinatal and (b) early postnatal Magnevist® (gadopentetate dimeglumine) Injection exposure on behavioral, neurological, and histopathological changes during postnatal development and in adult mice. The study should also evaluate Magnevist® (gadopentetate dimeglumine) Injection brain and other organs' retention in both dams and pubs.

2. A study in juvenile non-human primate (NHP) to evaluate the effect of Magnevist® (gadopentetate dimeglumine) Injection behavioral, neurological, and histopathological changes. The study should also evaluate retention of Magnevist® (gadopentetate dimeglumine) Injection the brain and other organs.

3. A prospective two-arm clinical trial in neurologically normal adults (for example, patients undergoing breast cancer screening) compared to matched controls to evaluate the effects of repetitive administration of Magnevist® (gadopentetate dimeglumine) Injection on neurologic and systemic function using a comprehensive battery of neurobehavioral testing and other clinical and laboratory tests over the course of at least five Magnevist® (gadopentetate dimeglumine) Injection administrations. The trial should be sufficiently powered to exclude a pre-specified magnitude of decline. As a secondary objective, trial subjects should also have the option of providing blood and urine samples at the time of re-imaging, so that normative estimates of gadolinium concentration across an extended range of post-administration time points may be documented.

We anticipate your proposal to address these requirements including your proposed timetables for draft protocol submissions, final protocol submissions, study completions, and final report submissions in the Meeting Package for the June 28, 2018, GBCA companies Joint Type C meeting due May 25, 2018.

Prominently identify the submission that contains your proposal and proposed milestone dates with the following wording in bold capital letters at the top of the first page of the submission:

REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21CFR314.81(b)(2)(vii) requires you to

report annually on the status of any postmarketing commitments or required studies or clinical trials.
FDA will consider the submission of your annual report under section 506B and 21CFR314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21CFR314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or

electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

REPORTING REQUIREMENTS

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

If you have any questions, call Rene' Tyson, Safety Regulatory Project Manager, at (301) 796-1476.

Sincerely,

{See appended electronic signature page}

Ira Krefting, M.D.
Deputy Director for Safety
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosures: Package Inserts and Medication Guide

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

/s/

IRA P KREFTING
04/26/2018