NDA 021064/S-032

SUPPLEMENT APPROVAL

LANTHEUS MEDICAL IMAGING INC
Attention: Laura Lee
Director, Regulatory Affairs
331 Treble Cove Road, Building 300-2
North Billerica, MA 01862

Dear Ms. Lee:

Please refer to your supplemental new drug application (sNDA) dated March 31, 2023, received March 31, 2023, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for DEFINITY®, Vial for (Perflutren Lipid Microsphere) Injectable Suspension and DEFINITY RT®, Vial for (Perflutren Lipid Microsphere) Injectable Suspension.

We also refer to our letter dated March 2, 2023, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we have determined should be included in the labeling for DEFINITY and DEFINITY RT. This information pertains to the serious risk of inducing severe, acute pain episodes in patients with sickle cell disease following administration of DEFINITY or DEFINITY RT.

This supplemental new drug application provides for revisions to the labeling for DEFINITY and DEFINITY RT.

The agreed upon changes to the language included in our March 2, 2023, SAFETY LABELING CHANGE NOTIFICATION, letter are as follows (additions are noted by underline blue font and deletions are noted by blue font with ~~strikethrough~~).

I. Changes to Section **5 FULL PRESCRIBING INFORMATION**, for DEFINITY and DEFINITY RT

5 WARNINGS AND PRECAUTIONS

5.5 Pain Episodes in Patients with Sickle Cell Disease
In postmarketing reports, acute pain episodes shortly following DEFINITY administration have been reported in patients with sickle cell disease (SCD). The pain episodes included moderate to severe back pain and vaso-occlusive crisis [see Adverse Reactions (6.2)]. (b) (4) If a patient with sickle cell disease experiences new or worsening pain, discontinue DEFINITY.

II. Changes to Section **2 DOSAGE AND ADMINISTRATION** for DEFINITY

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- DEFINITY is intended for administration only after activation in the VIALMIX or VIALMIX RFID apparatus. Before injection, this product must be activated and prepared according to the instructions outlined below. The VIALMIX or VIALMIX RFID apparatus should be ordered from Lantheus Medical Imaging, 331 Treble Cove Road, North Billerica, MA, 01862. For customer orders call 1-800-299-3431.

2.4 DEFINITY Activation, Preparation and Handling Instructions

Special Instructions for the DEFINITY Radio Frequency Identification (RFID)-Tagged Vial
This information is for vials containing DEFINITY that have been labeled with a Radio Frequency Identification (RFID) tag. Full instructions for use of VIALMIX RFID are provided on the VIALMIX RFID screen and User's Guide.

- The RFID tag allows for the exchange of product information such as activation time and activation rate.
- VIALMIX RFID will only activate DEFINITY RFID-tagged vials. Function of the RFID technology is not dependent on vial orientation as it is placed in the VIALMIX RFID. If the RFID tag is damaged or otherwise non-functional, the VIALMIX RFID will notify the user and the vial with the nonfunctional RFID tag cannot be used to activate DEFINITY with VIALMIX RFID. Discard the nonfunctional RFID-tagged DEFINITY vial.
- •Follow all manufacturers' guidelines and do not operate any part of the VIALMIX RFID (b) (4) -with DEFINITY RFID-tagged vials within 6 inches (15 cm) of a pacemaker and/or defibrillator.

APPROVAL & LABELING

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21CFR314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information), 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 *SPL Standard for Content of Labeling Technical Qs and As*.[2]
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 [21CFR314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), 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).

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.

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

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

If you have any questions, please contact 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 Imaging and Radiation Medicine
Office of Specialty Medicine
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):
- Content of Labeling
  - Prescribing Information

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

IRA P KREFTING
06/05/2023 09:08:57 AM