NDA 009190/S-032

SUPPLEMENT APPROVAL

Guerbet LLC, USA
Attention: Gabriel Lebovic
Director of Regulatory Affairs, North America
214 Carnegie Center, Suite 300
Princeton, NJ 08540

Dear Mr. Lebovic:[1]

Please refer to your supplemental new drug application (sNDA) dated November 16, 2022, received November 16, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for LIPIODOL® (ethiodized oil) Injection.

This "Changes Being Effected" sNDA **Safety Related Labeling Changes** provides for the update of section **'4 CONTRAINDICATIONS'** of the Lipiodol Prescribing Information with the addition of a contraindication for Lipiodol's use in the hysterosalpingography (HSG) procedure in patients with known or suspected gynecologic (GYN) malignancy.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling with minor editorial revisions listed below **with red font** and reflected in the enclosed labeling

I. HIGHLIGHTS OF PRESCRIBING INFORMATION

CONTRAINDICATIONS

- **Lipiodol Hysterosalpingography is contraindicated in:** pregnancy, acute pelvic inflammatory disease, marked cervical erosion, endocervicitis and intrauterine bleeding, in the immediate pre-or postmenstrual phase, and within 30 days of curettage or conization or patients with known or suspected reproductive tract neoplasia due to the risk of peritoneal spread of neoplasm.

[1] 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.

II. 4 CONTRAINDICATIONS

Hysterosalpingography
Lipiodol Hysterosalpingography is contraindicated in pregnancy, acute pelvic inflammatory disease, marked cervical erosion, endocervicitis and intrauterine bleeding, in the immediate pre-or postmenstrual phase, and within 30 days of curettage or conization or patients with known or suspected reproductive tract neoplasia due to the risk of peritoneal spread of neoplasm. [see Use in Specific Populations (8.1)].

III. 17 PATIENT COUNSELING INFORMATION

Thyroid Dysfunction

Advise patients concerning the risk of hyper- or hypothyroidism following the use of Lipiodol due to ethiodized oil remaining in the body for several months. Instruct patients to follow up with their physician if they become pregnant or develop any signs of thyroid dysfunction in the months after administration [see Warnings and Precautions (5.4), Use in Specific Populations (8.1 and 8.3)].

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.[2] 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*.[3]

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 [21CFR 314.50(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

[2] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[3] 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.

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.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs. You must submit final promotional materials and Prescribing Information, 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 FDA.gov. Information and Instructions for completing the form can be found at FDA.gov.

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- related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

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 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 (21CFR 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
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