CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208870Orig1s000

SUMMARY REVIEW
# Cross-Discipline Team Leader Review

<table>
<thead>
<tr>
<th>Date</th>
<th>August 7, 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>From</td>
<td>Danae Christodoulou, Ph.D.</td>
</tr>
<tr>
<td>Subject</td>
<td>Cross-Discipline Team Leader Review</td>
</tr>
<tr>
<td>NDA</td>
<td>208870</td>
</tr>
<tr>
<td>Applicant</td>
<td>Jubilant DraxImage</td>
</tr>
<tr>
<td>Date of Submission</td>
<td>July 19, 2016</td>
</tr>
<tr>
<td>PDUFA Goal Date</td>
<td>August 20, 2017 – as extended</td>
</tr>
</tbody>
</table>

**Proprietary Name / Established (USAN) names**
- DRAX Exametazime/
  - Kit for the preparation of technetium Tc 99m exametazime for leukocyte labeling

**Dosage forms / Strength**
- Kit: Lyophilized $^{99mTc}$ 0.5 mg/vial
- Tc 99m exametazime: 74-370 MBq/ml (2-10 mCi/ml)

**Proposed Indication(s)**
- For leukocyte (white blood cell) labeled scintigraphy as an adjunct in the localization of intra-abdominal infection, and inflammatory bowel disease.

**Recommendation:** Approval

---

## 1. Introduction

Jubilant DraxImage (JDI) submitted the current NDA as a 505(b)(2) application relying on the approved drug Ceretec™, NDA 19829, by GE Healthcare. Both drugs have the same formulation, strength, dosage form, and route of administration. JDI proposed only one of the two indications approved for Ceretec™, leukocyte labeled scintigraphy as an adjunct in localizing sites of infection. The mechanism of action, dosimetry, biodistribution, pharmacodynamics and pharmacokinetics of Tc 99m Exametazime Injection have been previously described in the approved GE Healthcare’s NDA for Ceretec™. No non-clinical and clinical data have been submitted in support of this NDA. JDI requested a waiver from in vivo bioavailability/bioequivalence (BA/BE) studies comparing the proposed product and the reference drug, Ceretec™, under the provision of 21 CFR 320.22(b)(1)(i) and (ii). In addition, JDI provided physicochemical properties comparison as well as an in vitro equivalence study for White Blood Cell (WBC) labeling efficiency using the proposed drug product and the reference approved drug as a study comparator. Dr. Poonam Delvadia reviewed the in-vitro studies in support of establishing bioequivalence, and Dr. Satish Mishra the statistics supporting the studies. The in vitro studies in support of demonstrating bioequivalence were deemed adequate. The disciplines and reviewers who assessed this NDA are listed in Table 1.
Table 1. FDA Disciplines and Reviewers Involved in the Evaluation of NDA 208870

<table>
<thead>
<tr>
<th>Discipline</th>
<th>Reviewer</th>
<th>Team Leader</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry, Manufacturing and Controls</td>
<td>Dr. Dhanalakshmi Kasi</td>
<td>Dr. Danae Christodoulou</td>
</tr>
<tr>
<td>Drug Product</td>
<td>Dr. Martin Haber</td>
<td>Dr. Donna Christner</td>
</tr>
<tr>
<td>Drug Substance</td>
<td>Dr. Dhanalakshmi Kasi</td>
<td>Dr. Danae Christodoulou</td>
</tr>
<tr>
<td>Process</td>
<td>Mr. Michael Klapal</td>
<td>Dr. Vidya Pai</td>
</tr>
<tr>
<td>Facility</td>
<td>Dr. Poonam Delhadia</td>
<td>Dr. Sandra Suarez</td>
</tr>
<tr>
<td>Biopharmaceutics</td>
<td>Dr. Samata Tiwari</td>
<td>Dr. Nandini Bhattacharya</td>
</tr>
<tr>
<td>Microbiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonclinical Pharmacology/Toxicology</td>
<td>Dr. Olayinka Dina</td>
<td>Dr. Adebayo Laniyonu</td>
</tr>
<tr>
<td>Clinical Pharmacology/Biopharmaceutics</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Clinical</td>
<td>Dr. Phillip Davis, MD</td>
<td>Dr. Nushin Todd, MD, Ph.D.</td>
</tr>
<tr>
<td>Statistics</td>
<td>Dr. Satish Misra</td>
<td>Dr. Jyoti Zalkikar</td>
</tr>
<tr>
<td>Pediatric and Maternal Health</td>
<td>Carrie Ceresa, Pharm.D</td>
<td>Dr. Jane Liedtka</td>
</tr>
<tr>
<td>Radiation Dosimetry</td>
<td>Dr. Stanley Stern</td>
<td>Dr. Alex Gorovets, MD</td>
</tr>
<tr>
<td>Labeling</td>
<td>Zarna Patel, Pharm.D</td>
<td>Hina Mehta, Pharm.D</td>
</tr>
<tr>
<td>Office of Prescription Drug Promotion (OPDP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Division of Medication Error Prevention and Analysis (DMEPA)</td>
<td>Idalia Rychlik, Pharm.D</td>
<td>Dr. Michele Fedowitz, MD</td>
</tr>
<tr>
<td>ADL - DMIP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Background

As discussed above, the proposed Tc-99m Exametazime by JDI contains the same active and inactive ingredients at the same concentrations and in the same dosage form as the referenced approved drug, Ceretec™, by GE Healthcare. Ceretec™, NDA 19829, was approved in 1988 for brain imaging “detection of altered regional cerebral perfusion in stroke”. In 2013, Ceretec™ was approved for the additional indication of “leukocyte labeled scintigraphy as an adjunct in the localization of intra-abdominal infection and inflammatory bowel disease”. The applicant is not including the brain imaging indication in NDA 208870 and submits the current NDA as a 505(b)(2) rather than a (j). No non-clinical, clinical safety and efficacy data have been submitted in the application. The applicant requested a biowaiver from BE/BA studies and submitted physicochemical comparison of key product characteristics and in vitro studies for two clinically relevant attributes, percent labeling efficiency of leukocytes and percent efflux radioactivity of the proposed product versus the referenced approved drug. With respect to safety, efficacy and labeling information the applicant relies on FDA’s findings for Ceretec™ and its labeling.
1. **CMC/Device**

JDI manufactures the kit for the preparation of Tc 99m exametazime. The reconstituted drug, Tc 99m exametazime and the radiolabeled leukocytes are prepared in the radiopharmacy according to the detailed procedure in the “Dosage and Administration” section of the PI. Exametazime, also known as hexamethylpropylene amine oxime or HMPAO, is reconstituted by Tc 99m as sodium pertechnetate, which is eluted by approved Tc 99m generators. The generator used by JDI is the Tc 99m sodium pertechnetate as eluted from the generator complies with the USP monograph for sodium pertechnetate, and the reconstituted Tc 99m exametazime complies with the USP monograph for Tc 99m exametazime.

**Product Quality**

Quality standards for Tc 99m exametazime were assessed through the quality of the precursor exametazime, inactive ingredients, manufacturing process, supporting batch analysis and stability. Exametazime is a racemate ligand, (oxime) and contains two chiral centers with four theoretical stereoisomers. The precursor to the drug substance consists of (4). The other two stereoisomers are described. See chemical structures in Dr. Martin Haber’s drug substance review in Panorama. The manufacturing process:

The chemical structure was elucidated by FT-IR, $^1$HNMR, $^{13}$C NMR, Mass Spectrometry and X-Ray single crystal diffraction analysis. No polymorphs were identified. As discussed, the quality and chiral purity of exametazime is controlled by its specifications: Clarity of saline solution, identification by IR and HPLC, melting point (4°C), loss on drying (NMT 0.4%), pH of saline solution (7.4), assay (HPLC, 0.4%), impurities (total: NMT 0.4%), enantiomeric excess (chiral HPLC, NMT 0.4%), (NMT 0.4 ppm), residual solvents and bacterial endotoxins. Specified impurities are:

Any unspecified impurity is NMT 0.4%. Impurity A is a Reference standards have been developed by JDI.

The composition of the drug product (kit, one vial) is 0.5 mg of HMPAO per vial, 4.5 mg NaCl, 7.6 mcg SnCl$_2$.2H$_2$O as a reducing agent. The end user takes the vial containing the lyophilized and reconstitutes it with 5 mL of USP 0.9% NaCl for Injection, containing 10 mCi - 54 M Ci of Tc 99m Sodium Pertechnetate Injection, USP. Note, that the referenced approved drug, Ceretec™, consists of three vials. The additional vial 2 contains 0.003 M Na$_2$HPO$_4$ and NaH$_2$PO$_4$ in 0.9% NaCl and vial 3 contains 1 mL of 1% methylene blue.

The shelf life of Tc 99m exametazime complex is only 30 min and it is increased to 4 h by adding methylene blue as the stabilizer when used for cerebral imaging (GE product). Drug product and process review focused in ensuring quality of the reconstituted Tc 99m exametazime, and data to support execution of the radiolabeling procedure in the
radiopharmacy by the end-user. Quantitative composition of Tc 99m exametazime after reconstitution, details of the radiolabeling procedure, and the type of Tc 99m generator used was information requested by the drug product reviewer and amended to the application by the applicant. The final composition of Tc 99m exametazime is 0.5 mg HMPAO, 0.6 mg NaCl, 7.6 mcg SnCl₂·2H₂O, Tc 99m exametazime 7.3x10^6 (10 mCi) - 1.7x10^4 mg (54 mCi) and 0.4 ml WFI. Eluate from generators was used within 2h from elution. Critical quality attributes for the drug product are appearance, assay, impurity profile, stannous chloride content, radiolabeling efficiency and physicochemical properties such as osmolality, density, specific gravity and viscosity. The test results were comparable to the referenced drug and complied with the USP monograph for Tc 99m exametazime. The exametazime kit is glass vial with a rubber stopper sealed under N₂. No extractables were found from the stopper and no leachables study was performed. The pH of the solution is high (9.0-9.8) and there is a potential to leach from the vial. However, no interference(s) were noted for the radiolabeling reaction, except for SnCl₂. The applicant agreed to revise the limit for SnCl₂ in their release specification from mcg/mL to mcg/mL not to fail the stability test limit of mcg/mL. With respect to the radiochemical purity specification (RCP) for the reconstituted solution, the product complies with the USP specification, NLT % at release and NLT % after leukocyte labeling. After production of 10 batches the applicant agreed to revisit this specification. The stability specification limits are the same as the release specification limits except the impurity limits: NMT %, Impurity A NMT %, any unspecified impurity: NMT % (NMT %) and water content limit %. Stannous chloride content (NLT mcg/vial (expressed as Sn) is lower than the release specification limit as expected. A shelf life of 12 months was granted for the kit and a 30 minute expiry was granted for the reconstituted drug product Tc 99m exametazime. With respect to microbiological controls, the process and product quality attributes were reviewed by the microbiologist and found adequate.

**Facilities Review**

The manufacturing facilities are: Jubilant Draximage Inc., Kirkland, Canada (exametazime manufacture and drug product testing), Jubilant HollisterStier (JHS) in Kirkland Canada (drug product manufacture, packaging release and stability testing). Pre-approval inspections were conducted, 483 issued and the applicant responded adequately. are testing facilities and were evaluated by profile. Overall cGMP recommendation is “Acceptable”.

Overall, CMC reviewers found the purity and quality of the kit and reconstituted Tc 99m exametazime adequate. All deficiencies are resolved. Quality amendments triggered the review clock extension on 4/17/2017. In conclusion, the manufacturing process yields a product that is consistent and reproducible within the established product specifications, as well as current good manufacturing practices (cGMP) requirements. I concur with the conclusions of the CMC review team. See Integrated Quality Assessment (IQA) in Panorama.
2. **Non-clinical Pharmacology/Toxicology**

No new non-clinical data are submitted. The review team agrees with the applicant that their product is supported by the findings and labeling of Ceretec™.

3. **Clinical Pharmacology/Biopharmaceutics**

No BE/BA studies were conducted. The applicant submitted a biowaiver request per 21 CFR 320.22(b)(1)(i) and (ii). The biopharmaceutics review team determined that the biowaiver request was not applicable but rather the *in vitro* BE data submitted for demonstrating bioequivalence between the proposed and reference drug can be evaluated under 21 CFR 320.24(b)(6) which states: “Any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence”. As such, the comparative physicochemical properties and the *in vitro* studies in support of BE, % labeling efficiency (%LE) and % efflux radioactivity (%CER) for radiolabeled leukocytes for the proposed drug versus Ceretec™ were evaluated. Comparisons of formulations and critical physicochemical properties are evaluated in the biopharmaceutics review p. 7-9 by Dr. Poonam Delvadia (see Panorama). In the pre-IND meeting package dated 9/28/2015 and 10/15/2015, the applicant submitted the detailed *in vitro* BE protocol and proposed % labeling efficiency (%LE) and % cell efflux radioactivity (%CER) as the metrics to address bioequivalence. The Agency advised the applicant by written responses: (1) to collect %CER data over multiple time points to calculate and use area under the curve (AUC) as the endpoint for *in vitro* equivalence assessment; (2) to use two one-sided t-test (TOST) procedure with 90% confidence interval (CI) around the geometric mean ratio of products for each end point to conclude BE instead of the proposed paired t-test with null and alternative hypotheses to support the claim of bioequivalence; and (3) to provide power calculations (80% to 90%) and relevant sample sizes based on varied estimates of the variability in %LE and %CER. In the NDA submission, the applicant refined the *in vitro* equivalence study protocol and made the following minor technical adjustments to the original protocol proposed in the pre-IND meeting package: (1) sample size changed from 16 to 30 blood samples; (2) use of heparin as anticoagulant instead of acid citrate dextrose (ACD); and (3) addition of Hespan® or hetastarch [6% Hydroxyethyl starch (HES)] in the blood collection tube as a sedimentation agent. See the protocol steps for radiolabeling of leukocytes for the *in vitro* BE study in p. 11-12 of Dr. Delvadia’s review.

**Percent labeling efficiency (%LE)** was calculated by: %LE = \[\frac{A}{(A+B)}\]×100

Where A: Radioactivity of the cells (measured after leukocytes were treated with reconstituted Tc 99m exametazime centrifuged, precipitated and separated in tube A);
B: Radioactivity of the supernatant separated in tube B

The %LE data for the test and reference drug were subjected to equivalency test using one-tailed paired t-test at \(\alpha\) of 0.05.

The labeled leukocytes sample was tested for cell viability using the trypan blue dye method. The number of cells with blue color (C) and those which have excluded the dye (D) were counted in a hemocytometer.

**Percent cell viability** was calculated by \% cell viability = (D×100)/(C+D).
To measure Percent Cell Efflux Radioactivity, the precipitated leukocytes (button) were broken up and re-suspended in 3 ml of supernatant and subsequently divided in four samples centrifuged and separated from supernatant. Radioactivity was measured for the corresponding tubes containing leukocytes (E) and supernatant (F).

**Percent cell efflux radioactivity (%CER)** was calculated by: \( \%CER = \frac{F \times 100}{E+F} \). Based on the %CER versus time profile, Cmax and AUC (trapezoidal method) were calculated and used for statistical in vitro BE analysis comparing the test and the reference drug. Dr. Satish Misra (statistician, CDER/OTS) was consulted to assess the data pooling for both %LE and %CER (C\text{max} and AUC) across both reference and test drug. In the statistical review dated 3/31/2017 in DAARTS, Analysis of Variance (ANOVA) in SAS software determined that %LE and %CER (C\text{max} and AUC) can be pooled as there is not significant effect of the reference drug lot # and test lot # in fast and fed state. The same conclusion was reached by the biopharmaceutics reviewer by performing statistical analysis using Phoenix software. Refer to the biopharmaceutics review p. 24-26. In conclusion, the proposed product is bioequivalent to the reference drug, Ceretec™, with respect to two clinically relevant in vitro endpoints, % labeling efficiency (%LE) and % cell efflux radioactivity (%CER – C\text{max} and AUC).

I concur with the findings.

4. **Clinical Microbiology**
Not applicable.

5. **Statistical Analysis Evaluation of in vitro studies in support of bioequivalence.**
See 3 above. Statistical analysis evaluated data pooling across test and reference drug in support of the in vitro % labeling efficiency and % cell efflux radioactivity (C\text{max} and AUC). Analysis of Variance (ANOVA) in SAS software, determined that %LE and %CER (C\text{max} and AUC) can be pooled as there is not significant effect of the reference drug lot # and test lot # in fast and fed state. In conclusion, the proposed product is bioequivalent to the reference drug, Ceretec™, with respect to two clinically relevant in vitro endpoints, % labeling efficiency (%LE) and % cell efflux radioactivity (%CER – C\text{max} and AUC).

6. **Safety**
The safety of Tc 99m exametazime has been well established since the Ceretec™ approval and 29 years of clinical use. No new safety data has been submitted for review. However, the lactation section of the package insert (PI) has been updated for the current drug per USNRC guidelines and the Pregnancy and Lactation Labeling Rule (PLLR) requirements for labeling. See discussion in 8 and 10 below.

7. **Advisory Committee Meeting**
Not applicable.
8. Pediatrics

The Division of Pediatric and Maternal Health (DPMH) was consulted to review subsections 8.1 Pregnancy, 8.2 Lactation and 8.4 Pediatrics for the Kit for the Preparation of Technetium Tc 99m Exametazime Injection package insert.

Pregnancy

Dr. Carrie Ceresa, from the Division of Pediatric and Maternal Health, analyzed the risk from exposure of the pregnant mother to ionizing radiation and evaluated the applicant’s review of published literature (16 publications). Published literature suggests that risk of fetus to intellectual abnormalities occurs during exposure at 8-15 weeks gestation in the range of 60 - 310 mGy. Fetal anomalies or abortion have not been reported in radiation exposure <50 mGy which is higher than exposure from diagnostic procedures. American College of Radiology (ACR) and International Commission on Radiological Protection (ICRP) guidelines are outlined in the review. The ICRP summarizes that medical professionals ought to be familiar with the risk of radiation exposure to the embryo/fetus and that exposures in excess of 100-200 mGy can lead to nervous system abnormalities, malformations, childhood cancers, growth retardation and fetal death. DPMH conducted additional literature review of “Tc99m and pregnancy” and related terms and concluded: “The findings from the available data found in published literature with Tc-99m exametazime and use in pregnant women are insufficient to inform a drug associated risk for major birth defects and miscarriage. Limited published literature describes Tc-99m exametazime crossing the placental barrier and visualization of radioactivity in the fetal liver. No adverse fetal effects or radiation-related risks have been identified for diagnostic procedures involving less than 50 mGy, which represents less than 10 mGy fetal doses.”

Lactation

DPMH analyzed the applicant’s review of the literature and conducted additional literature search for “Tc99m and lactation”. The United States Nuclear Regulatory Commission (USNRC) has established guidelines for breast feeding after exposure to radiopharmaceuticals. USNRC guidelines are based on 10CFR 35.75(b) which require a licensee to provide instructions on the discontinuation or the interruption period of breast-feeding and the consequence of failing to following the recommendation. According to the USNRC guidelines table, exposures to Tc-99m pertechnetate labeled white blood cells, of 1100 MBq (30 mCi) the duration of interruption for breast-feeding is 24 hours and for exposures of 440 MBq (12 mCi) the duration of interruption for breastfeeding is 12 hours. Additionally, if a radiopharmaceutical is not listed in that table it is recommended to “assume that 50% of the administered activity is excreted in the breast milk.” After discussions with DMIP, DPMH agreed to adapt the duration of interruption of breastfeeding recommendations from the USNRC. For a typical labeled dose of Tc-99m exametazime where exposure is 259 MBq to 925 MBq (7 mCi to 25 mCi) the recommended interruption of breastfeeding will include advising the female to pump and discard breast milk for 12 to 24 hours after administration.

Pediatrics

No new pediatric clinical data or animal toxicology data was submitted for section 8.4 and DPMH – pediatrics recommends retaining the statement, “Safety and efficacy in pediatric patients have not been established”, in accordance with language specified in 21CFR 201.57 in situations where pediatric data are absent. DPMH-pediatrics also recommends deleting the statement,
In conclusion, DPMH revised sections 8.1, 8.2 and 17 of the PI for compliance with PLLR.

9. Other Relevant Regulatory Issues
The applicant identified one patent related to the approved drug Ceretec™ (Patent #4789736) that expired on December 6, 2005.
No financial disclosure information is submitted because no clinical studies were conducted.

10. Labeling
Major revisions were made to the labeling of the kit submitted by the applicant. Dr Michele Fedowitz revised labeling to conform to the current Physician Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLL) requirements for labeling (discussed above in 8 and in Dr. Stern’s review). Other major revisions included the Dosage and Administration section of the PI and the radiolabeling procedure by the end user. In the revised PI, the isolation and preparation procedure for the leukocytes precedes the reconstitution of the kit with sodium pertechnetate to form Tc 99m exametazime. This revision was made because in real life, the leukocytes need to be ready for radiolabeling with the short-lived Tc99m exametazime complex within 30 min of reconstitution of the kit. The non-proprietary name was revised to “Kit for the preparation of technetium Tc 99m exametazime for leukocyte labeling” since Tc 99m exametazime is not injected directly. In the Indication Statement, with respect to absorbed dose estimates, the applicant proposed by Dr. Stanley Stern based on values from literature specific to Tc 99m exametazime labeled WBC. (See review in DARRTS dated 3/24/2017).
There was concurrence from all disciplines involved in the review of Tc 99m exametazime regarding the edits to the labeling. At this time, OSE review of the proprietary name “DRAX Exametazime” is pending.

11. Recommendations/Risk Benefit Assessment
Recommended Regulatory Action
Approval.

Risk Benefit Assessment
The safety and clinical efficacy and utility of Tc 99m exametazime for leukocyte labeling have been established for the approved referenced drug Ceretec™. DRAX Exametazime is determined to be bioequivalent to Ceretec™ based on biopharmaceutics and statistical assessment of in vitro studies for % labeling efficiency and % cell efflux radioactivity of white blood cells. Product quality data support approval. This recommendation was derived independently from all reviewers involved in evaluating the application.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DANAE D CHRISTODOULOU
08/08/2017