

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203155Orig1s000**

**OFFICE DIRECTOR MEMO**

## Office Director Action Memo

<b>Date</b>	September 11, 2012
<b>From</b>	Charles J. Ganley, MD
<b>Subject</b>	Office Director Summary Review
<b>NDA/BLA #</b>	203-155
<b>Applicant Name</b>	Mayo Clinic PET Radiochemistry Facility (MCPRF)
<b>Date of Submission</b>	December 12, 2011
<b>PDUFA Goal Date</b>	September 12, 2012 (based on a major amendment extension)
<b>Proprietary Name / Established (USAN) Name</b>	Choline C 11 Injection
<b>Dosage Forms / Strength</b>	Supplied as a glass vial containing 40 – 331 mCi (1.48 – (b)(4) of <sup>11</sup> C choline in aqueous 0.9% sodium chloride (approximately 10 mL volume); the mass dose of choline is estimated at no more than 5 mcg per dose
<b>Proposed Indication(s)</b>	“for positron emission tomography (PET) imaging of patients with suspected prostate cancer recurrence and non-informative bone scintigraphy, computerized tomography (CT) or magnetic resonance imaging (MRI). In these patients, <sup>11</sup> C choline PET imaging may help identify potential sites of prostate cancer recurrence for subsequent histologic confirmation. Suspected prostate recurrence is based upon elevated blood prostatic specific antigen (PSA) levels following initial therapy. In clinical studies, images were produced with PET/CT co-registration. Limitation of Use: <sup>11</sup> C-choline PET imaging is not a replacement for histologic verification of recurrent prostate cancer.”
<b>Recommended Action:</b>	Approval

### Introduction

Choline C11 is a PET imaging agent that has been in use for many years without NDA approval. As noted in Dr. Rieves summary, The Food and Drug Modernization Act of 1997 outlined a process for regulation of PET drugs. He also provides a summary of the use of the medical literature to support the efficacy of PET drugs. This application is submitted by the Mayo Clinic in Rochester, Minnesota and they will be the sole manufacturing facility for this application. The application had two sources of data to support the efficacy and safety of the drug. These included a review summary of the literature for the use of detecting recurrent prostate cancer and a retrospective review of their experiences with the drug.<sup>1</sup>

### Recommended Action

Approval

The support for this approval is based on a literature review and the experience of the Mayo Clinic. Source data is not available for FDA review. It is difficult to define performance characteristics because of the nature of this data. The preponderance of the data, however, indicates that this test is able to locate areas of recurrent prostate cancer in patients where conventional testing (bone scintigraphy, computerized tomography or magnetic resonance imaging) is negative. Histologic confirmation is recommended in the labeling. Although it is difficult to identify an exact PSA level where the test may be

<sup>1</sup> Note this review was done without the collection of source documents for later validation.

less sensitive, the evidence in several of the data sets suggest lower levels may impact on the imaging performance. The labeling notes that blood PSA levels < 2 ng/ml have been associated with poor imaging performance.

### **Clinical Pharmacology**

The clinical pharmacology information in this application is based solely on information from the published literature. The following recommendations were made:

- A drug interaction with colchicine has been reported. Altered biodistribution was noted. The Mayo clinic proposed that anti-mitotic drugs be discontinued prior to imaging. The clinical pharmacology recommendation is to allow patients on this therapy to continue therapy but those who have not started on it, delay initiation until after the imaging procedure.
- Imaging be performed in the fasting state because of a literature report suggested that food may result in the appearance of artifact. There were no details provided in the literature reference. The labeling recommends that the patients be fasted for at least 6 hours prior to imaging to minimize the potential for dietary choline interference.
- Drugs to treat prostate cancer may interfere with the scans. For patients not receiving any therapies for prostate cancer, delay initiation of therapy until after imaging.

### **Chemistry**

There are no outstanding chemistry issues.

### **Microbiology**

There were two microbiology deficiencies identified in the primary review. The media fill program was deemed inadequate and the environmental monitoring was deficient. The sponsor responded to both deficiencies and the reviewer found the response adequate. The reviewer recommended approval.

### **Pharmacology / Toxicology**

The sponsor depended on the literature to support the non-clinical safety. Choline C11 was determined to be safe from a non-clinical perspective.

### **DSI**

An inspection of the Mayo Clinic data was limited because the data collected was not done under IRB and informed consent approval. As such, there was no source data available to compare to the submitted data from the Mayo Clinic.

### **Medical / Statistical Reviews**

The efficacy of choline C11 is based on the two sets of information, the Mayo Clinic experience from 2007 to 2010 and a review of relevant studies from the medical literature. The clinical, statistical, CDTL and Division Director memos summarize the prospective and retrospective reports in the medical literature in detail. I will not restate the details in this summary but refer to the reviews. It is clear that choline C11 is able to detect recurrent prostate cancer in patients with rising PSA but it is difficult to clearly characterize the performance characteristics for the test.

The statistical reviewer summarizes the Mayo Clinic data in Table 6 of their review. The table breaks down the data based on whether the patient had negative or positive conventional scanning.

- 79 patients had negative conventional scans. 44 of these patients had positive choline C11 scans. 25 / 44 had positive histology on biopsy. 14 / 44 had no histology. 5 / 44 had negative histology. This data supports the ability of the scan to detect areas of cancer where conventional imaging was negative. The median PSA for patients with positive scans was greater than 3 whereas the PSA for patients with negative scans was less than 2.

- 86 of 94 patients with positive conventional imaging had a positive choline C11 scan. The majority of patients did not undergo histological confirmation.

No allergic reactions were observed in the Mayo clinical experience or from the medical literature sources. The only adverse event observed in the Mayo Clinic experience was a single case of a local skin reaction at the site of infusion.

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CHARLES J GANLEY  
09/11/2012