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***APPLICATION NUMBER:***

**203155Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type New Drug Application 505(b)(2)  
Application Number(s) NDA 203-155  
Priority or Standard Priority

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Reviewer Name(s) William Dickerson, M.D.  
Review Completion Date August 15, 2012

Established Name Choline C11 Injection  
(Proposed) Trade Name None  
Pharmacologic Class Positron Emission Tomography  
(PET) Radiopharmaceutical  
Applicant Mayo Clinic PET Radiochemistry  
Facility, Rochester, MN

Formulation(s) Glass vial with 40–331 mCi (1.48-  
12.247 GBq) of <sup>11</sup>C choline in  
aqueous 0.9% sodium chloride  
solution (approximately 10 mL)

Dosing Regimen One time dose of 10—20 mCi  
(370-740 MBq) for PET Imaging

Indication(s) Recurrence of Prostate Cancer  
Intended Population(s) Adult men

Template Version: March 6, 2009

## Table of Contents

|          |                                                                                           |           |
|----------|-------------------------------------------------------------------------------------------|-----------|
| <b>1</b> | <b>RECOMMENDATIONS/RISK BENEFIT ASSESSMENT .....</b>                                      | <b>6</b>  |
| 1.1      | Recommendation on Regulatory Action .....                                                 | 6         |
| 1.2      | Risk Benefit Assessment.....                                                              | 6         |
| 1.3      | Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...              | 7         |
|          | There is no recommendation for Postmarket Risk Evaluation and Mitigation Strategies. .... | 7         |
| 1.4      | Recommendations for Postmarket Requirements and Commitments .....                         | 7         |
|          | There is no recommendation for Postmarket Requirements and Commitments.....               | 7         |
| <b>2</b> | <b>INTRODUCTION AND REGULATORY BACKGROUND .....</b>                                       | <b>7</b>  |
| 2.1      | Product Information .....                                                                 | 8         |
| 2.3      | Availability of Proposed Active Ingredient in the United States .....                     | 10        |
| 2.4      | Important Safety Issues With Consideration to Related Drugs.....                          | 10        |
| 2.6      | Other Relevant Background Information .....                                               | 11        |
| <b>3</b> | <b>ETHICS AND GOOD CLINICAL PRACTICES.....</b>                                            | <b>11</b> |
| 3.1      | Submission Quality and Integrity .....                                                    | 11        |
| 3.2      | Compliance with Good Clinical Practices .....                                             | 12        |
| 3.3      | Financial Disclosures.....                                                                | 12        |
| <b>4</b> | <b>SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES .....</b>       | <b>13</b> |
| 4.1      | Chemistry Manufacturing and Controls .....                                                | 13        |
| 4.2      | Clinical Microbiology.....                                                                | 14        |
| 4.3      | Preclinical Pharmacology/Toxicology .....                                                 | 14        |
| 4.4      | Clinical Pharmacology .....                                                               | 14        |
|          | 4.4.1 Mechanism of Action.....                                                            | 15        |
|          | 4.4.2 Pharmacodynamics.....                                                               | 15        |
|          | 4.4.3 Pharmacokinetics.....                                                               | 15        |
| <b>5</b> | <b>SOURCES OF CLINICAL DATA.....</b>                                                      | <b>16</b> |
| 5.1      | Table of Studies/ Clinical Trials.....                                                    | 16        |
| 5.2      | Review Strategy.....                                                                      | 16        |
| 5.3      | Discussion of Individual Studies/ Clinical Trials .....                                   | 17        |
| <b>6</b> | <b>REVIEW OF EFFICACY .....</b>                                                           | <b>18</b> |
|          | Efficacy Summary.....                                                                     | 18        |
| 6.1      | Indication .....                                                                          | 18        |
| 6.2      | Sponsor's Clinical Study .....                                                            | 18        |
| 6.3      | Supportive Studies Submitted by Sponsor .....                                             | 20        |
| 6.4      | Additional Review of Literature by Rafael D. Rieves and This Reviewer.....                | 30        |
| <b>7</b> | <b>REVIEW OF SAFETY.....</b>                                                              | <b>36</b> |

|                                                                                                       |           |
|-------------------------------------------------------------------------------------------------------|-----------|
| Safety Summary .....                                                                                  | 36        |
| 7.1 Methods.....                                                                                      | 37        |
| 7.1.1 Studies/Clinical Trials Used to Evaluate Safety .....                                           | 37        |
| 7.1.2 Categorization of Adverse Events.....                                                           | 37        |
| 7.2 Adequacy of Safety Assessments .....                                                              | 37        |
| 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of<br>Target Populations ..... | 37        |
| 7.2.2 Explorations for Dose Response.....                                                             | 39        |
| 7.2.3 Special Animal and/or In Vitro Testing .....                                                    | 39        |
| 7.2.4 Routine Clinical Testing .....                                                                  | 39        |
| 7.2.5 Metabolic, Clearance, and Interaction Workup .....                                              | 39        |
| 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ..                      | 39        |
| 7.3 Major Safety Results .....                                                                        | 39        |
| 7.3.1 Deaths.....                                                                                     | 39        |
| 7.3.2 Nonfatal Serious Adverse Events .....                                                           | 39        |
| 7.3.3 Dropouts and/or Discontinuations .....                                                          | 39        |
| 7.3.4 Significant Adverse Events .....                                                                | 40        |
| 7.4 Supportive Safety Results .....                                                                   | 40        |
| 7.4.1 Common Adverse Events .....                                                                     | 40        |
| 7.4.2 Laboratory Findings .....                                                                       | 40        |
| 7.4.3 Vital Signs .....                                                                               | 40        |
| 7.4.4 Electrocardiograms (ECGs) .....                                                                 | 40        |
| 7.4.5 Special Safety Studies/Clinical Trials .....                                                    | 40        |
| 7.5 Other Safety Explorations.....                                                                    | 40        |
| 7.5.1 Dose Dependency for Adverse Events .....                                                        | 40        |
| 7.5.2 Time Dependency for Adverse Events.....                                                         | 40        |
| 7.5.3 Drug-Demographic Interactions .....                                                             | 40        |
| 7.5.4 Drug-Disease Interactions.....                                                                  | 41        |
| 7.5.5 Drug-Drug Interactions.....                                                                     | 41        |
| 7.6 Additional Safety Evaluations .....                                                               | 41        |
| 7.6.1 Human Carcinogenicity .....                                                                     | 41        |
| 7.6.2 Human Reproduction and Pregnancy Data.....                                                      | 41        |
| 7.6.3 Pediatrics and Assessment of Effects on Growth .....                                            | 41        |
| <b>8 POSTMARKET EXPERIENCE.....</b>                                                                   | <b>42</b> |
| <b>9 APPENDICES .....</b>                                                                             | <b>42</b> |
| 9.1 Literature Review/References .....                                                                | 42        |
| 9.2 Labeling Recommendations .....                                                                    | 45        |
| 9.3 Advisory Committee Meeting.....                                                                   | 45        |

## Table of Tables

|         |                                                                                                                   |    |
|---------|-------------------------------------------------------------------------------------------------------------------|----|
| Table 1 | Studies Reviewed.....                                                                                             | 16 |
| Table 2 | Sponsor's Submission Prospective Studies with Choline C11 PET .....                                               | 21 |
| Table 3 | PET Scan Results of Patients Classed by PSA Profiles (Breeuwsma) .....                                            | 22 |
| Table 4 | Choline C11 PET/CT Detection per PSA Level (Garcia) .....                                                         | 23 |
| Table 5 | Sponsor's Submission Prospective Studies with Choline F18 PET/CT .....                                            | 24 |
| Table 6 | Sponsor's Submission Retrospective Studies with Choline C11 or F18 PET/CT .....                                   | 25 |
| Table 7 | 18F-FCH Sensitivity (Detection) by PSA (Following Biochemical Relapse of Prostate Cancer) (Pelosi) .....          | 27 |
| Table 8 | <sup>11</sup> C Choline Absorbed Radiation Dose Per Unit Activity (rad/mCi) for Adults and Pediatric Groups ..... | 38 |

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

|       |                                                                                                |
|-------|------------------------------------------------------------------------------------------------|
| ADT   | androgen deprivation therapy                                                                   |
| AE    | adverse event                                                                                  |
| BCR   | biochemical recurrence (e.g. rising PSA after primary therapy)                                 |
| CFR   | Code of Federal Regulations                                                                    |
| CT    | computed tomography                                                                            |
| EBRT  | external beam radiation therapy                                                                |
| FU    | follow-up                                                                                      |
| HIFU  | high-intensity focused ultrasound                                                              |
| IRB   | Institutional Review Board                                                                     |
| ITT   | Intent to treat                                                                                |
| LR    | local recurrence (of prostate cancer)                                                          |
| MRI   | magnetic resonance imaging                                                                     |
| NPV   | negative predictive value                                                                      |
| PCa   | prostate cancer                                                                                |
| PET   | positron emission tomography                                                                   |
| PPV   | positive predictive value                                                                      |
| PSA   | prostate-specific antigen                                                                      |
| PSAdt | PSA doubling time                                                                              |
| RP    | Radical Prostatectomy                                                                          |
| RRP   | Radical retropubic prostatectomy (surgical removal of the prostate including seminal vesicles) |
| SD    | standard deviation                                                                             |
| SEER  | Surveillance Epidemiology and End Results                                                      |
| SUV   | standardized uptake value                                                                      |

## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

#### ***Recommend Approval.***

This FDA clinical reviewer recommends approval of Mayo Clinic's original New Drug Application (NDA) No. 203155 of Choline C 11 Injection for the proposed indication as a radioactive diagnostic agent for positron emission tomography (PET) imaging for the identification of site of recurrence of prostate cancer in men (b) (4)

This application was submitted in accordance with Section 505(b)(2) of the 1984 Federal Food, Drug and Cosmetic Act.

### 1.2 Risk Benefit Assessment

The overall assessment of risks and benefits of Choline C 11 injection favors approval. Per the Mayo Clinic's NDA, prostate cancer is the most common non-cutaneous malignancy in American and European men. Approximately 35,000 men in the US die yearly from prostate cancer. Most of these men who die from prostate cancer, were treated with primary surgery or primary radiation therapy for potential cure. Other types of primary treatment include cryoablation and occasionally androgen deprivation therapy. Despite primary therapy, approximately 35% of men have a biochemical recurrence (BCR) after surgery and up to 40% of men have a BCR after radiation therapy. BCR can be defined in different ways but is essentially a detectable prostate specific antigen (PSA) persisting after surgery, or a rise in PSA at least 2 ng/ml above nadir following radiation therapy. Per the Mayo Clinic report, up to 90,000-100,000 men have a BCR yearly and present a diagnostic and treatment dilemma. In the Mayo Clinic's Retrospective Study, they report that Choline C11 PET imaging led to a 30% improvement over conventional imaging in defining optimal "next step" therapy for their patients who had a BCR and underwent Choline C11 PET imaging. (Ref: Mayo Clinic New Drug Application (NDA) dated December 6, 2011, "Original NDA (NDA No. 203-155) Submission for Choline C 111 Injection", Section 5.3.5.4.1 Abbreviated Study Report, Paragraphs 7 and 13.)

**Reviewer's Comments:** I believe Choline C11 PET/CT imaging is a useful modality to aid in decision making for some patients with a biochemical recurrence (BCR) of prostate cancer (PCa) after definitive treatment. The Mayo retrospective study and other studies described in Section 6 of this Clinical Review describe a benefit for about 30% of patients to plan salvage or palliative therapy. The Choline C11 PET/CT detection rate varies with prostate specific antigen (PSA) level, and also appears to vary with PSA doubling time, and may

be affected by the use of hormone therapy. Local recurrence of PCa after radiation may be treated with surgery or cryoablation. Local recurrence after surgery may be treated with radiation. Although radiation oncologists frequently treat surgical recurrences blind, it would encourage treatment if there were a positive local recurrence on PET. A positive PET/CT would offer physicians and patients a clearer diagnosis than just BCR. A definite diagnosis would allow a more specific plan whether recurrence is local or distant.

**Allergic Reactions:** As with any injectable drug product, allergic reactions and anaphylaxis may occur. However, no allergic reactions were described in the retrospective study of 176 patients submitted by the Mayo Clinic, or in the 11 publications which the Mayo Clinic submitted to support its application. Also, since choline is a naturally occurring metabolite, it is unlikely that allergic reactions will be identified in the future.

**Radiation Risks:** Choline C 11 Injection is a radioactive isotope which may increase the risk of cancer. However no increased incidence of cancer has been described in the above publications. For an adult, the effective dose is 0.0161 rem/ mCi.

**Adverse Events:** The Mayo Clinic described only 1 adverse event in its retrospective study of 176 charts reviewed. The 1 adverse event was an injection site reaction which was mild, self-limiting, and resolved.

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There is no recommendation for Postmarket Risk Evaluation and Mitigation Strategies.

### 1.4 Recommendations for Postmarket Requirements and Commitments

There is no recommendation for Postmarket Requirements and Commitments.

## 2 Introduction and Regulatory Background (Reference Mayo NDA Section 1.6.3)

The subject of this clinical review is the New Drug Application (NDA 203-155) from the Mayo Clinic PET Radiochemistry Facility in Rochester, MN, to produce Choline C 11 Injection for the diagnostic PET imaging of men with recurrent

prostate cancer [REDACTED] (b) (4)

On February 8, 2011 a type B, pre-IND (PIND) meeting was held between Mayo Clinic and the FDA. PIND number 110,731 was assigned. FDA issued meeting minutes on February 28, 2011. The FDA stated that the sponsor needed to narrow the indication to focus on the specific clinical usefulness that they believed had been demonstrated to date as outlined by the sponsor's clinical representative. The FDA further stated that the preliminary responses cited a potential meta-analysis but, based upon a much narrower indication and smaller patient population, a meta-analysis of published data or other studies would likely not prove useful.

FDA stated that a 505(b)(2) submission which includes a systematic literature review with pre-specified study report selection criteria (and potentially a meta-analysis) would be a reasonable approach. The selection criteria would depend on their proposed indication for [11C] choline in terms of the intended patient population, and whether they proposed the drug be used to detect distant metastases, local metastases, and/or local recurrence.

Based on FDA recommendations, on September 23, 2011, Mayo Clinic PET Radiochemistry Facility submitted a request for a waiver of user fees to FDA. A response from FDA was sent on Nov 30, 2011 indicating that the waiver request was granted. Mayo Clinic PET Radiochemistry Facility submitted a request for [REDACTED] (b) (4)

## 2.1 Product Information (Reference NDA Section 2.4.1)

### 2.1.1 Description of the Product

Choline is a common dietary supplement. The compound Choline C 11 is identical in molecular structure to natural choline except that one carbon atom of Choline C 11 is a radioactive C11 atom. Choline C 11 has all of the pharmacologic effects of natural occurring choline. The amount intravenously injected in patients during a Choline C 11 PET scan is about 1/60 of a grain of salt, about 100,000 times less than the daily recommended intake of choline for nutritional needs. Choline as a dietary substance is important for the structural integrity of cell membranes, methylation metabolism, cholinergic neurotransmission, transmembrane signaling, and lipid and cholesterol transport and metabolism. Human cells grown in culture have an absolute requirement for choline. When cells are deprived of choline, they die by apoptosis.

Carbon 11 or  $^{11}\text{C}$  is a cyclotron-produced radionuclide that decays 99.76% to boron-11 by positron emission and has a physical half life of 20.4 minutes. The emission of radiation (960 keV) by the  $\beta$  particle does not change the activity, function, or characteristics of choline. Choline C 11, a radiolabeled analog of choline, is distributed to all organs of the body after intravenous administration.

Choline C 11 Injection, as described in the current application, is produced by the Mayo Clinic PET Radiochemistry Facility, Rochester, MN. It has also been produced at several other facilities worldwide.

### 2.1.2 Description of the Imaging Method

This product has been and will be used in a manner similar to other P.E.T. imaging products. However, due to the short radioactive half-life of Carbon-11 of only 20.4 minutes, time constraints must be followed.

### 2.1.3 Proposed Indication and Dosing Regimen of the Imaging Product

The initial proposed indication from the Mayo Clinic was

(b) (4)

The indication wording is being reevaluated.

The dosage for Choline C 11 Injection is 10-20 mCi (370-740 MBq) as a bolus through a catheter inserted into a patient's large peripheral vein (Ref: Pages 18-19 of 36 of Abbreviated Clinical Study Report).

## 2.2 Currently Available Products and Modalities for Proposed Indication

Currently available products for identifying sites of recurrence of prostate cancer in men with biochemical recurrence based on a rising prostate specific antigen (PSA) are:

- Conventional Imaging: Bone Scan, CT Scans of the chest, abdomen, and pelvis, MRI of the prostate or pelvis, and in some cases transrectal ultrasound with biopsy. These studies are usually negative until recurrent disease has progressed as evidenced by a significant increase in the PSA.

- Prostascint (Indium 111 Capromab Pendetide) Imaging: This type of imaging was approved by the FDA in 1996 as a diagnostic imaging agent in post-prostatectomy patients with a rising PSA and negative standard metastatic evaluation. It is also indicated as a diagnostic imaging agent in patients with newly diagnosed prostate cancer who are at high risk of lymph node metastasis.

This agent is not commonly used in medical practice because of its poor image resolution.

-Although PET imaging with F 18 FDG is widely used in oncology, it has not been shown to be useful for imaging prostate cancer because the radioisotope concentrates in the bladder and makes visualization of the prostate difficult. Choline C 11 injection does not concentrate in the bladder and therefore has a potential advantage in imaging prostate cancer.

## 2.3 Availability of Proposed Active Ingredient in the United States

Choline C 11 is a radioactive drug produced from C 11 in a cyclotron. Since C 11 has a physical half-life of only 20.4 minutes, it must be produced locally at a facility with a cyclotron. The precursor at the Mayo Clinic PET radiopharmacy cyclotron is carbon dioxide C 11. (Ref: NDA 5.3.5.4.1 section 9.2.2)

## 2.4 Important Safety Issues With Consideration to Related Drugs

### 2.4.1 Radiation Exposure

As acknowledged by the sponsor, radiation exposure from radiopharmaceuticals may increase the risk of cancer. However, no known radiation effects have been seen by using Choline C 11 or any other PET radiopharmaceutical. The sponsor cites an article by Tolvanen et al. where the levels of radiation absorbed were calculated to be low. The effective dose from a PET scan depends on the activity of the injected radiotracer and is the same whether a part of the body or the whole body is imaged. Tolvanen et al calculated the effective dose for Choline C 11 for a human adult of about 70 kg to be equivalent to 2.0 mSv from 460 MBq of Choline C 11 PET. In comparison with the most common radiotracer used in PET, 18F-fluorodeoxyglucose (18F-FDG), the effective dose of is typically 8 mSv for human adults using 400 MBq of 18F-FDG. The short half life of C 11 (20.4 min) results in less exposure than other radiotracers including F18-FDG (half life 110 min), Technetium 99m(half life 6 hours), or Thallium 201(half life 72 hours). (Ref: NDA 2.4.2.2.1)

Safety Section 7.2, Adequacy of Safety Assessments has a table describing organ doses for Choline C 11 PET imaging.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

In 1997, the Food and Drug Administration Modernization Act (FDAMA) was signed and required the FDA to develop procedures for approving PET agents. The FDA now regulates PET drugs. All PET drugs now require an Investigational New Drug Application (IND), or a New Drug Application (NDA). In August 2011 the FDA issued Guidance, "PET Drug Applications- Content and Format for NDAs

and ANDAs, Fludeoxyglucose F 18 Injection, Ammonia N 13 Injection and Sodium Fluoride F 18 Injection” (This Guidance is available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078738.pdf> )

As stated above in the introduction to this section, in February 2011 the Mayo Clinic initiated a pre-IND (PIND 110,731) for Choline C 11 as a PET tracer for prostate cancer. The Mayo Clinic had a type B meeting with the FDA on February 8, 2011. In general, the FDA recommended the Mayo Clinic limit the indication for their PIND to evaluation of recurrent prostate cancer, (b) (4)

The Mayo Clinic’s Choline C11 PET NDA has been submitted in accordance with the regulations that require FDA approval prior to use of a radioactive drug for PET imaging. The Mayo Clinic has applied for an NDA under the Section 505(b)(2) pathway of the 1984 Federal Food, Drug and Cosmetic Act which means that the application contains full reports of investigations of safety and effectiveness but at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference.

## 2.6 Other Relevant Background Information

To support its application, the Mayo Clinic submitted a review of 11 “main” articles, and it’s own Abbreviated Clinical Study Report. Its study is a retrospective chart review of patients at the Mayo Clinic who had Choline C 11 positron emission tomography (PET) scans between September 2007 and November 2010 to evaluate biochemical recurrence of prostate cancer, following failed initial treatment.

Change in PDUFA Goal Date and On-Site Inspection: The PDUFA Goal Date was originally June 12, 2012. However, the FDA added 3 months to this date after the sponsor submitted a major amendment on April 17, 2012. The FDA reviewers requested that the FDA perform an on-site Clinical Inspection to examine the data collection forms and medical records from a representative number of patients. It was requested that the inspection summary be completed one month prior to the new PDUFA Goal Date of September 12, 2012.

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

Overall quality of the submitted application is acceptable for a review.

The submission was made in the electronic Common Data Terminology (eCDT) format which simplifies finding information. Due to some detailed questions which the FDA reviewers had about the NDA, the FDA submitted several Information Requests to the sponsor. The sponsor replied to each one with amendments to its application.

### 3.2 Compliance with Good Clinical Practices

Although the submission is a 505(b)(2) relying mainly on a review of published articles, the sponsor also submitted a retrospective study of the the performance of Choline C 11 PET imaging at the Mayo Clinic. On January 17, 2012 the FDA sent the sponsor an Information Request for data analysis of the sponsor's pivotal study. On January 23, 2012 the FDA had a teleconference with the sponsor at which time the FDA also requested a Good Clinical Practice (GCP) statement. On February 6, 2012 the sponsor sent the FDA the sponsor's Efficacy Information Amendment (1.11.3) and Statistical Analysis Plan (5.3.5.4.12). The Efficacy Information Amendment included a GCP Statement that the data presented to support the NDA were collected in compliance with GCP standards to the extent that the institution and regulatory agencies required for a retrospective chart review. Data collection was done with institutional review board (IRB) oversight and approval in accordance with the approved research plan. Data were recorded in a manner to protect both confidentiality and quality.

On April 17, 2012 the FDA received from the sponsor a clinical response to an Information Request. Because the FDA considered this a major amendment and because the PDUFA goal date was less than 90 days away, the FDA extended the PDUFA goal date by 3 months. The FDA also requested the FDA's Division of Scientific Investigations (DSI) inspect the sponsor's site and audit data collection forms and medical records, especially for the sponsor's 75 patients in whom "conventional imaging" was negative. The inspection results are still pending.

### 3.3 Financial Disclosures

The applicant, Dr. Joseph Hung, provided adequate financial disclosures. He submitted Form FDA 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) in his amendment 0001 to the application and signed the following statement :

"As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of

compensation of the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2 (a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)."

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

The Chemistry Manufacturing and Controls (CMC) reviewer recommends approval provided that the sponsor satisfactorily addresses CMC concerns and provides acceptable labeling. The microbiology reviewer's conclusion and recommendation is still pending. CMC conclusions include the following:

- sufficient information is provided in this New Drug Application to ensure the identity, strength, quality and purity of the drug substance
- sufficient information is provided in this New Drug Application to ensure the identity, strength, quality and purity of the drug product
- the referenced drug master files (DMF) are adequate to support the product application
- there are no major issues with specifications, methods and impurities
- the stability of the product is demonstrated to support a 60 minute expiration dating period

#### **Description of Drug Product(s) and Drug Substance(s):**

Choline C11 chloride ([11C] Methyl-dimethyl-2-hydroxyethyl-ammonium) has a molecular weight of 138.63 g. The radionuclide 11C has a half-life of 20.4 minutes and is a cyclotron-produced radionuclide that decays to boron-11 by positron emission. The drug substance, [11C] choline, is produced in-situ during the production of Choline C 11 injection drug product (b) (4) (b) (4)

Choline C 11 Injection is supplied in a glass vial containing 4.0-33.1 mCi/mL (0.148-1.225 GBq/mL) of [11C] Choline in aqueous 0.9% sodium chloride solution (approximately 10 mL volume) in a 30 ml glass vial. The standard dosage is 20 mCi

(0.740 GBq). A range of  $\pm 10\%$  is applied to every dispensed standard dosage, which is within the  $\pm 20\%$  variance allowed by the Nuclear Regulatory Commission for the determination of dispensed dosages. Individual dose of Choline C 11 injection is intravenously administered through a catheter and PET imaging is initiated immediately after administration. The imaging data are acquired for up to 15 minutes.

Impurities: A known impurity (b) (4) the main chemical impurity in the Choline C11 (b) (4). It is present as an (b) (4) (b) (4) ingredient, and can be identified and quantified (b) (4). The acceptance criterion for (b) (4) concentration is (b) (4). According to the Mayo Clinic submission, the amount of (b) (4) in the final drug is between approximately (b) (4). The Mayo Clinic states "There are no known impurities or degradants in the imaging agent at sufficient concentrations to warrant any safety concerns in the clinical setting." (Ref: NDA 2.4.4.7, page 11 of 15)

**Reviewer's Comment:** Based on the above information, the safety and efficacy of Choline C 11 injection from the standpoint of chemistry manufacturing and controls (CMC) appears acceptable. Additional CMC details are provided in NDA section 3.2.S.2.2.

#### 4.2 Clinical Microbiology

The microbiology reviewer, Robert Mello, PhD, has described 2 deficiencies which are being communicated to the sponsor. These deficiencies relate to the Mayo Clinic's sampling frequency for viable monitoring of the (b) (4) production areas, and inadequate media fill procedures. Specific corrective action will be recommended to the sponsor.

#### 4.3 Preclinical Pharmacology/Toxicology

No critical issue has been identified.

#### 4.4 Clinical Pharmacology (Ref: Clin Pharm DARRTS entry 7/27/2012)

The Clinical Pharmacology Review performed by Christy John and Gene Williams stated in their Executive Summary that the application is acceptable from a clinical pharmacology standpoint, provided an agreement is reached on package insert language.

#### 4.4.1 Mechanism of Action

According to the sponsor, Choline C 11 Injection is a radiolabeled analog of choline, an endogenous substrate that is an essential component of phospholipids of the cell membrane, and as such is involved in synthesis of the structural components of cell membranes, as well as modulation of trans-membrane signaling. The activities of phospholipids (i.e., increased uptake of choline) have a role in aberrant cell proliferation and transformation that occurs in tumor cells.

#### 4.4.2 Pharmacodynamics

$^{11}\text{C}$  choline has shown high prostate tumor-specific uptake without the visual interference from the uptake in the bladder.

#### 4.4.3 Pharmacokinetics

Distribution: After intravenous administration in reported studies, the percentage of  $^{11}\text{C}$  choline in plasma declined rapidly in human arterial and venous plasma. In human arterial plasma, the amounts of  $^{11}\text{C}$  choline decreased from  $98\% \pm 2\%$  at 1 minute post injection to  $18\% \pm 9\%$  at 25 minutes after injection. In human venous plasma, the amounts of  $^{11}\text{C}$  choline at the same time points were  $100\% \pm 0\%$  and  $35\% \pm 11\%$ , respectively. The radionuclide C 11 has a physical half-life of 20.4 minutes.

In one study, the radioactivity distributed mainly to the kidneys, lungs, liver, and adrenal gland. The effective dose in a human adult of about 70 kg was 0.016 rem/mCi (0.0044 mSv/MBq), which is equivalent to 0.2 rem (2.0 mSv) from 12.43 mCi (460 MBq) of  $^{11}\text{C}$  choline. The highest absorbed doses in humans were 0.076 rad/mCi (0.021 mGy/MBq) in the kidneys, 0.074 rad/mCi (0.020 mGy/MBq) in the liver and 0.11 rad/mCi (0.029 mGy/MBq) in the pancreas. Only 2.0% of injected radioactivity was excreted in the urine during the 1.5 hours after the injection. The absorbed radiation doses after administration of 12.43 mCi (460 MBq) of Choline C 11 Injection were low. Except for the pancreas, biodistribution in the rat was in accordance with that in humans. Section 7.2.1 has a table of Choline C 11 radiation doses absorbed by different organs.

Metabolism: As stated by our Clinical Pharmacology Team, following intravenous administration,  $^{11}\text{C}$ -choline undergoes metabolism resulting in the detection of  $^{11}\text{C}$ -betaine as the major metabolite in blood. In a study of patients with prostate cancer or brain disorders, the fractional activities of  $^{11}\text{C}$ -choline and  $^{11}\text{C}$ -betaine in human arterial plasma appeared to reach a plateau within 25 minutes, with  $^{11}\text{C}$  betaine representing  $82\% \pm 9\%$  of the total  $^{11}\text{C}$  detected at

that time point. A small amount of unmetabolized  $^{11}\text{C}$ -choline was detected within the blood at the final sampling time point (40 minutes).

Elimination: Urinary excretion of  $^{11}\text{C}$  choline was below 2% of injected radioactivity up to 1.5 hours after injection. The rate of  $^{11}\text{C}$  choline excretion to the urine was  $0.014 \text{ ml min}^{-1}$ . The highest absorbed doses were found for the pancreas (0.108 rad/mCi or 0.0292 mGy/MBq), the kidneys (0.0763 rad/mCi or 0.0206 mGy/MBq), and the liver (0.0744 rad/mCi or 0.0201 mGy/MBq).

Plasma protein binding of Choline C 11 Injection or its  $^{11}\text{C}$  metabolites has not been studied. The pharmacokinetics of Choline C 11 Injection have not been studied in renally impaired, hepatically impaired, or pediatric patients.

## 5 Sources of Clinical Data

### 5.1 Table of Studies/Clinical Trials

**Table 1 Studies Reviewed**

| Source                                                                                                                        | Description                                                                                                                                                                                                                                                                                      |
|-------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Mayo Clinic's "Abbreviated Clinical Study Report"                                                                          | Retrospective review of 176 Choline C11 PET scans performed at the Mayo Clinic from September 2007 to November 2012 to identify sites of recurrent prostate cancer and impact on decision making in men with a history of prostate cancer and biochemical recurrence based on rising PSA values. |
| 2. Mayo Clinic's submission of 11 articles to support 505(b)(2) approval.                                                     | 5 prospective articles, and 6 retrospective articles plus a literature review were submitted by the Mayo Clinic to support their application.                                                                                                                                                    |
| 3. Additional articles from review of literature by our Division Director, Rafael D. Rieves, and my own review of literature. | Dr. Rieves did a PubMed search 5/8/2012 and found 5 prospective articles describing Choline C 11 PET imaging for recurrent prostate cancer. I also reviewed literature.                                                                                                                          |

### 5.2 Review Strategy

This clinical reviewer reviewed the above 3 sources. I also reviewed National Comprehensive Cancer Network (NCCN) guidelines, American Urological Association

(AUA) guidelines, and American Society for Radiation Oncology (ASTRO) guidelines for treatment of biochemical recurrence of prostate cancer.

### 5.3 Discussion of Individual Studies/ Clinical Trials

1. The **sponsor's retrospective study** of 176 Choline C 11 PET scans performed at the Mayo Clinic from September 2007 to November 2010. Each patient had a biochemical recurrence following failed initial treatment. Initial treatment had been a Radical Retropubic Prostatectomy (126), Radiation Therapy (41), Cryosurgery (3), Androgen Deprivation Therapy (5) or data missing (1). The **Summary of Results** stated that Choline C 11 PET showed a sensitivity of 93% and a specificity of 76% compared with a gold standard using biopsy and imaging for patients starting all types of treatments. The Choline C 11 PET diagnostic scan shows a sensitivity of 95% and a specificity of 86% when compared with a gold standard using biopsy and imaging for RRP patients only. **Conclusions** were: Choline C 11 PET performed well in identifying treatable lesions and helped in selection of optimal therapies in men with BCR following primary treatment failure. The optimum PSA value for lesion detection was determined to be between 1.7 and 2.0 ng/mL. Choline C 11 PET enhanced the rate of prostate cancer lesion detection by approximately 30% over conventional imaging and offers the ability to identify consolidated disease recurrences, which may be amenable to surgical resection. This reviewer will discuss in Section 6 his interpretation of these results.
2. **11 articles submitted by the Mayo Clinic** in support of their 505(b)(2) application. There were 5 prospective studies and 6 retrospective studies. All studies were from Europe, and are described in detail in the next sections.
3. **Additional reviews** by Dr. R. Dwaine Rieves, Director of our Division of Medical Imaging Products, and this clinical reviewer. Dr. Rieves widened the search criteria and this reviewer looked at articles describing salvage radiation therapy without positive imaging. .

Reviews of these 3 sources are provided in detail in the following sections.

## 6 Review of Efficacy

### **Efficacy Summary**

#### Indication

The sponsor seeks the following indication for Choline C 11 Injection:

[REDACTED] (b) (4)

The sponsor did not seek an indication for initial staging of prostate cancer since Choline C11 PET is nominally equivalent to conventional imaging for such staging, (NDA 2.5.4.1.1 "Rationale for Choice of Indication" )

#### Sponsor's Clinical Study

Method of Sponsor's Study: After IRB review and exemption, the sponsor performed a retrospective review of the records of all patients at the Mayo Clinic in Rochester, MN who had had a Choline C 11 PET scan for imaging of biochemical recurrence (BCR) of prostate cancer during the period September 2007 until November 2010.

Inclusion Criteria for the study: Men with documented BCR of prostate cancer, defined as at least 2 separate PSA measurements greater than zero acquired 3 months apart for radical prostatectomy (RRP) patients, nadir plus 2 ng/mL for patients treated with radiation or primary cryoablation, or a steady rise in prostate-specific antigen (PSA) for men treated with primary androgen deprivation therapy (ADT). 176 charts were identified for this study.

We disagree with the sponsor's approach to statistical definitions. The sponsor defined true positive and true negative as the following:

A PET scan was considered a "true positive" if any of the following was shown:

- histologic confirmation by targeted biopsy or surgical resection, or
- confirmation by conventional imaging, or
- a decrease in prostate-specific antigen (PSA) >50% after selective irradiation of choline- avid lesions.

A PET scan was considered a "true negative" if either of the following was shown:

- disease was absent on the biopsy results or surgical resection, or
- confirmation with negative conventional imaging.

We disagree with these terms because a “true negative” at one time, might become a “true positive” later due to progression of disease. As time passes, a greater amount of prostate cancer tissue would probably translate into a higher positive biopsy rate. For this reason we prefer only the term “detection rate” instead of the terms “sensitivity, specificity, positive and negative predictive value” which the sponsor used. The sponsor also used the term “clinical usefulness” which they calculated as the number of clinically useful PET scans / total number of PET scans. The sponsor defined “clinical usefulness” as the ability to detect lesions not identified using conventional imaging, and which thereby prompted a change in clinical management. (Mayo Amendment 0007, Section 1.11.3). Our disagreement reflects our different approaches to characterizing the data and not a challenge to the integrity of the sponsor. In fact, some of the articles reviewed also present data according to the same definitions used by the Mayo Clinic.

Since this was a retrospective review, there was no follow-up of most of the patients. This could impact the results as described above since an early biopsy of a PET-avid area might be negative due to sampling error, but a later biopsy might confirm a PET scan as accurately showing disease.

**Sponsor’s Endpoints:** We do not find the sponsor’s endpoints of sensitivity, specificity, positive predictive value, negative predictive value, and clinical usefulness useful. There is no real primary endpoint since this was a retrospective study. Also, there was lack of follow-up and missing data due to the retrospective nature of this study. For example, of 126 patients who had prostate surgery, 11 charts were missing data to confirm whether or not a positive PET scan was a true positive.

**Sponsor’s Conclusions:** -The Mayo Clinic described a sensitivity of 93% and a specificity of 76% compared with a gold standard using biopsy and imaging for patients starting all types of treatments, and a sensitivity of 95% and a specificity of 86% when compared with a gold standard using biopsy and imaging for RRP patients only. Per the sponsor, “Choline C 11 PET performed well in identifying treatable lesions and helped in selection of optimal therapies in men with BCR following primary treatment failure. The optimum PSA value for lesion detection was determined to be between 1.7 and 2.0 ng/mL. Choline C 11 PET enhanced the rate of prostate cancer lesion detection by approximately 30% over conventional imaging and offers the ability to identify consolidated disease recurrences, which may be amenable to surgical resection. Choline C11 PET encompasses a safe and effective clinical tool that can greatly improve the clinical assessment and treatment of a growing population of men who have previously failed one or more primary prostate cancer therapies, and a population that is currently underserved and at greatest need of potentially life-saving therapy.”

***Reviewer’s Comments:***

An Information Request to the Mayo Clinic in March 2012 resulted in the following additional information:

- Of 176 PET scans, 75 men had negative conventional imaging
- Of these 75 men, 35 were PET negative. 31 of these 35 had no recurrence, but 4 of 35 had recurrences confirmed by biopsy (False negative PET)
- Of these 75 men, 40 were PET positive. 24 of these 40 were confirmed by biopsy, 1 was confirmed positive on follow-up, 11 were un-confirmed, and 5 had no evidence of recurrence on biopsy- (False positive PET).
- As shown above, there is much unconfirmed data
- A so-called "true negative" might have been failure of a biopsy to obtain malignant cells when they are present but not identified on biopsy.
- There was no follow-up for most of these patients
- Since there is a different definition for BCR after a RRP or EBRT, it makes it difficult to give general guidelines for when to offer a PET scan.
- Having a mixture of primary treatments, e.g. RRP, EBRT, ADT, and Cryosurgery produce different results. The PSA's at recurrence were much earlier for the RRP patients, because their PSA should be 0 after a RRP.
- The statistical results can not be relied on because this was a retrospective review and some data is absent. There was no follow-up for most of the cases.
- There is some correlation between increase in PSA and detection ability of Choline C11 PET imaging. However, PSA is more sensitive to BCR than Choline C11 PET.
- Although additional information requests were made to the Mayo Clinic the last few months, the Mayo Clinic has been limited in what data it could provide, since they performed only a retrospective review. There was no protocol. Images were read in light of clinical data, and follow-up was limited or absent. Per Dr. Rieves, the sponsor had said at the pre-NDA meeting that the published literature alone should support their NDA.

### ***Reviewer's Conclusions:***

Despite the shortcomings of the Mayo Clinic's Retrospective Study on 176 patients who had Choline C11 PET/CT scans to evaluate biochemical failure following treatment for prostate cancer, I agree with the Mayo Clinic's conclusion that Choline C11 PET/CT may help guide further treatment on about 30 % of these patients.

### **Supportive Studies Submitted by Sponsor**

#### **Method of Obtaining Supportive Studies:**

Per NDA 5.4, literature searches were performed using the key words *choline*, *prostate* and *PET* for published papers from 1998 through October 2011. Three

major biomedical and scientific databases- PUBMED, National Library of Medicine, and MEDLINE were used. The initial search produced 183 peer-reviewed articles which the sponsor provided with their application. From these 183 articles, selection was then limited to articles with at least 30 patients, a focus on restaging of prostate cancer and some other criteria described in NDA 5.4, 3.0. Using criteria pertinent to the indication, 11 articles were found which focused on restaging prostate cancer after initial therapy in patients with suspected recurrence due to persistent or elevated PSA blood testing. These 11 articles are the main supportive studies provided by the sponsor. They are divided into 3 prospective studies with Choline C11, 2 prospective studies with Choline F18, and 6 retrospective studies with Choline C11 or F18. The sponsor stated that no individual controlled studies, randomized trials or case controlled studies were identified. (NDA 5.4, 4.0)

The sponsor did not do a meta-analysis on the articles they submitted because there was a significant variability in what was measured in the different studies. For example, some articles described carbon 11 choline imaging after radiation therapy, other articles described it after a radical prostatectomy, and some patients were on hormone therapy at the time of their PET scan.

**Table 2 Sponsor's Submission Prospective Studies with Choline C11 PET**  
(Ref: NDA 2.5.4.6.2, and 2.7.3.3.1.2)

| Primary Author    | Title                                                                                                                                                                |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Breeuwsma 2010 | Detection of local, regional, and distant recurrence in patients with PSA relapse after external-beam radiotherapy using (11)C-choline positron emission tomography. |
| 2. Garcia 2009    | PET/CT with 11C- choline and 18F-FDG in patients with elevated PSA after radical treatment of a prostate cancer.                                                     |
| 3. Richter 2010   | Dual tracer 11C-choline and FDG-PET in the diagnosis of biochemical prostate cancer relapse after radical treatment.                                                 |

**Details:**

**1. Breeuwsma et al:**

- prospectively studied 80 patients with prostate cancer who had received definitive primary therapy using EBRT.
- 70 had PSA elevation, and 10 were controls without elevation in PSA and thought not to have recurrence.
- None of 10 patients without BCR had a positive PET scan.

- 57 of 70 patients with biochemical recurrence (median PSA 10.7 ng/mL, range 0.6-54.7 ng/mL) showed an abnormal uptake pattern (sensitivity 81%). (See Table 3)
- Site of recurrence was local in 41 of 57 patients (mean PSA 11.1 ng/mL at scan)
- Proven by biopsy in 26 of 41 cases, and by clinical course and PSA response to local salvage treatment confirmed local recurrence locoregionally and/or distant in 16 of 57 patients (mean PSA 17.7 ng/mL).
- Overall, PPV and NPV for 11C choline scan were 100% and 44%, respectively; accuracy (67/80) was 84%.
- **Authors concluded:** 11C choline PET scan is a sensitive technique to identify the site of recurrence in patients with PSA relapse after EBRT for prostate cancer.
- **Reviewer's Comment:** This study only describes the use of PET scans at a single institution, but Figures 1 and 2 of the article show PET-CT fusion images for 2 patients who apparently were included in the study. Therefore it is not clear to me if all the patients received PET/CT imaging or if most of them received only PET imaging.

**Table 3 PET Scan Results of Patients Classed by PSA Profiles (Breeuwsma)**

| PSA  | No. of pts | Negative Scan | Local Recurrence | Regional/ distant metastases | Sensitivity |
|------|------------|---------------|------------------|------------------------------|-------------|
| 0-4  | 16         | 3             | 11               | 2                            | 80%         |
| 4-10 | 21         | 6             | 11               | 4                            | 73%         |
| > 10 | 33         | 4             | 19               | 10                           | 87%         |

Ref: Breeuwsma, Table 3

## 2. Garcia et al:

- Compared the diagnostic accuracy of 18F-FDG PET and 11C choline PET in 38 patients with increasing PSA (0.8-9.5 ng/ml) after definitive treatment (20 surgery, 18 radiation therapy).
- 11C choline PET/CT and 18F-FDG PET/CT performed on same day
- Focal uptake of 11C choline was detected in 26 patients (68%), and focal uptake of 18F-FDG was detected in 13 patients (34%).
- Local recurrence suggested by 11C choline uptake in 14 patients, but only 4 patients with 18F-FDG.
  - - Recurrence was confirmed by biopsy in 8 of 14 patients (57%), in 4 patients (28.5%) by a reduction in PSA following further radiotherapy, and definitive diagnosis was not reached in 2 patients (14%), since the presence of distant lesions contraindicated radical treatment."
- Pelvic lymph nodes detected with 11C choline PET/CT in 8 patients and only in 4 patients (50%) with 18F-FDG.
- Mediastinal involvement detected in 5 patients with 11C choline and 3 patients with 18F-FDG.
- Focal bone involvement detected in 3 patients with 11C choline and 18F-FDG.

- 11C choline able to detect 40% of recurrences in patients with PSA < 1 ng/mL, 50% of recurrences in patients with PSA 1-4 ng/ml and 87% of recurrences with PSA > 4 ng/mL.
- Sensitivity of 11C choline was higher for surgically treated patients, with no significant differences found between patients with and without hormone therapy.
  - 10 of 38 patients were on hormone therapy. 11C choline PET/CTs were positive in 70% of those on hormones, and 68% of those not on hormones.
- 11C choline PET/CT was useful for the detection of biochemical recurrence of prostate cancer, with higher sensitivity as compared to 18F-FDG.
- 11C choline was able to detect 40% of recurrences in patients with PSA < 1 ng/mL, 50% in patients with PSA 1-4 ng/ml, and 87% with PSA 4.1-9.5 ng/ml
- 11C choline PET was positive in 16 of 20 patients (80%) after primary surgery, and 10 of 18 patients (55.5%) after primary radiation therapy.
- Disease staging with 11C choline showed direct impact on the selection of the most appropriate therapeutic approach.
- **Authors concluded:** PET/CT with 11C choline may be useful to detect recurrence in patients following radical treatment of prostate cancer, and has a superior diagnostic performance to PET/CT with 18F-FDG.
- Sensitivity of 11C choline is related to PSA level (See Table 4)
- Higher detection after surgery than radiation therapy
- Does not seem to be modified by hormone therapy
- Staging with 11C choline has a direct impact on the selection of the most suitable therapy following recurrence
- Recommend include patients with PSA < 1 ng/mL in whom early diagnosis offers more therapeutic options.

**Table 4 Choline C11 PET/CT Detection per PSA Level (Garcia)**

| PSA     | Choline C11<br>Detection Rate |
|---------|-------------------------------|
| < 1     | 40%                           |
| 1-4     | 60%                           |
| 4.1-9.5 | 87%                           |

Ref: Garcia data

### 3. Richter et al

- 73 patients (49 surgery, 24 radiotherapy, 15 also had hormone therapy), median PSA 2.7 (range 1.1-5.4) after treatment
- Compared efficacy of FDG and 11C choline-PET (18 patients had PET only, and 55 patients had PET/CT)
- Imaging results were confirmed by positive biopsy or by an increase in PSA during follow-up or a decrease in PSA after the therapy

- Of 73 patients, 11C choline detected 43 (sensitivity 60.2%) and FDG detected 22 (sensitivity 30%). One patient was true positive for FDG and false negative for 11C choline.
- Detection of prostate cancer relapse by 11C choline-PET increased as PSA values increased.
- When patients with PSA values lower than 1.9 ng/mL were excluded, the sensitivity of 11C choline PET and FDG PET increased to 80% and 40%, respectively.
- Detection with 18F-FDG (but not 11C choline) was greater in the poorly differentiated Gleason score group than in the well/moderately differentiated group.
- Authors concluded:** Detection of prostate cancer relapse with 11C choline PET/CT is clearly dependent on PSA value. Cutoff value over 1.9 ng/ml was highly significant. Adjuvant hormone therapy does not influence PET results. 11C choline-PET/CT is clearly superior to conventional imaging techniques in the detection of distant recurrence.

**Reviewer's Comments:** Results support use of 11C Choline PET for imaging recurrent prostate cancer, especially if PSA > 1.9 ng/mL. One concern: in the abstract a PSA range of patients of 1.1 to 5.4 is specified. However on page 213 of the article, it appears that PSA ranged from <1 to 20 ng/mL.

**Table 5 Sponsor's Submission Prospective Studies with Choline F18 PET/CT**

| Primary Author  | Title                                                                                                                                    |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------|
| 4. Cimitan 2006 | [18F]fluorocholine PET/CT imaging for the detection of recurrent prostate cancer at PSA relapse: experience in 100 consecutive patients. |
| 5. Husarik 2008 | Evaluation of [(18F)-choline PET/CT for staging and restaging of prostate cancer.                                                        |

#### 4. Cimitan et al

- Prospective study of **18F-choline (18F-FCH)** in 100 patients with prostate cancer with suspected recurrence based on rising PSA levels.
  - -58 patients had surgery, 28 then also had hormone therapy
  - -21 patients had radiotherapy, 15 later also had hormone therapy
  - -21 patients had hormonal therapy alone
- Of 100 patients, 54 (PSA 0.22–511.79 ng/mL) had positive FCH PET/CT scans.
  - -37 patients had bone and/or abdominal lymph node uptake
  - -17 had pelvic uptake suspicious for recurrence.
  - -Malignant disease confirmed in all but one.
- 46 patients (PSA 0.12–14.3 ng/mL) had negative FCH PET/CT scans.
  - -Of negative scans, 89% were obtained in patients with serum PSA <4 ng/mL and 87% in patients with Gleason score <8.
  - -No recurrent tumor proven clinically during a 6 month followup

**-Authors concluded:** 18F-FCH PET/CT not likely to impact PCa patients with BCR until PSA increases above 4 ng/mL. In selected patients, FCH PET/CT helps exclude distant metastases when salvage local treatment is intended.

#### 5. Husarik et al

- studied use of 18F-choline (18F-FCH) in 43 patients for staging PCa patients and 68 patients (mean PSA 10.8) for restaging PCa after BCR.
  - -48 patients following surgery (including 14 with surgery and hormones), 17 patients following radiotherapy (including 13 with radiotherapy and hormones), 2 with hyperthermia only, 1 with hormones only. Surgery includes 15 who had both surgery and radiation therapy.
- Of 68 patients with BCR, 18F-FCH PET/CT scans revealed local recurrence in 36 patients.
- 23 patients had 18F-FCH-positive lymph nodes (LN)
  - - Twenty LN were surgically removed in 7 patients.
  - - Histopathology verified metastases in all LN, but revealed two additional metastatic lymph nodes with 18F-FCH-negative LN.
- 17 patients showed 18F-FCH-positive bone metastases, as proven by bone scan or MRI.
- No pathological 18F-FCH uptake was observed in 11 patients with BCR.
- Sensitivity to detect recurrent disease was 86%.
- **Authors concluded:** 18F-FCH PET/CT scans can reliably localize recurrent PCa in patients with PSA levels of >2 ng/mL.

**Table 6 Sponsor's Submission Retrospective Studies with Choline C11 or F18 PET/CT**

| Primary Author      | Title                                                                                                                                                                    |
|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 6. Castelluci 2010  | Is there a role for 11C-choline PET/CT in the early detection of metastatic disease in surgically treated prostate cancer patients with a mild PSA increase <1.5 ng/ml ? |
| 7. Giovacchini 2010 | [ <sup>11</sup> C]Choline uptake with PET/CT for the initial diagnosis of prostate cancer: relation to PSA levels, tumour stage and anti-androgenic therapy.             |
| 8. Pelosi 2008      | Role of whole-body 18F-choline PET/CT in disease detection in patients with biochemical relapse after radical treatment for prostate cancer                              |
| 9. Reske 2008       | [ <sup>11</sup> C]choline PET/CT imaging in occult local relapse of prostate cancer after radical prostatectomy.                                                         |
| 10. Rinnab 2007     | Evaluation of [ <sup>11</sup> C]-choline positron-emission/computed tomography in patients with increasing                                                               |

|           |      |                                                                                                            |
|-----------|------|------------------------------------------------------------------------------------------------------------|
|           |      | prostate-specific antigen levels after primary treatment for prostate cancer.                              |
| 11.Rinnab | 2009 | [(11)C]choline PET/CT in prostate cancer patients with biochemical recurrence after radical prostatectomy. |

## 6. Castellucci et al

- Evaluated 102 patients previously treated with RRP who showed a mild increase in PSA <1.5 ng/mL during follow up.
  - - 16 of the 102 patients were on hormone therapy
- Overall, Choline C 11 PET/CT showed positive findings in 29/102 patients (28%).
  - - Positive PET findings were validated by biopsy, lymphadenectomy, other imaging, or FU for at least 12 months.
- Mean PSA<sub>dt</sub> (PSA doubling time) in Choline C 11 PET/CT-positive and –negative patients was 4.34 months (SD 2.82) and 13.30 months (SD 9.75), respectively.
- Optimal threshold for PSA<sub>dt</sub> was calculated to be 7.25 months
- Age, time to BCR, initial tumor staging, Gleason score, and the PSA were not statistically significant in predicting a positive Choline C 11 PET/CT scan
- Only PSA<sub>dt</sub> and initial node status were significant and independent predictive factors from multivariate logistic regression analysis.
- An unexpected finding was that Choline C11 PET/CT detected distant metastases in 21% of the patient.
- **Authors concluded:** Data supports the use of Choline C 11 PET/CT in patients with a low PSA level (<1.5 ng/mL) and fast PSA kinetics. One of the advantages of Choline C11 PET/CT may be early detection of metastases, which may negate the value of radiation therapy to the pelvis.

## 7. Giovacchini et al:

- Of 2,124 patients with prostate cancer who received 11C choline PET/CT scans, data were retrospectively reviewed for 358 who had previous treatment by RP, and BCF, defined as at least 2 consecutive PSA measurements of >0.2 ng/mL.
- Mean PSA was 3.77 (range 0.23-45 ng/ml).
- PET/CT was positive for 161 of the 358 patients (45%)
- In multivariate analysis, high PSA levels, advanced pathological stage, previous biochemical failure and advanced age were significantly (P<0.05) associated with an increased risk of positive PET/CT findings.
- **Authors concluded:** In addition to PSA levels, advanced pathological stage, previous biochemical failure, and advanced age should be considered by physicians when referring prostate cancer patients with biochemical failure after radical prostatectomy to 11C choline PET/CT.

#### 8. Pelosi et al:

- 56 consecutive patients with BCR following RP were imaged with **18F-FCH** PET/CT.
  - - PSA mean 4.59 (range 0.1-39 ng/ml).
  - - No patient had received hormone therapy.
  - - Positive studies were confirmed with further imaging, biopsy and FU.
- Of 24 patients with positive PET studies, 4 were local recurrences, 20 were systemic disease (10 with lymph node metastasis, 2 with bone metastasis, and 8 with at least 2 of the following: local recurrence and/or metastases to lymph nodes and/or bone and/or lung and/or muscle).
- Among 4 patients with local recurrence, further studies did not identify distant metastases; prostate-bed biopsy confirmed the PET finding.
- Of the 32 remaining patients (of 56 total), PET showed 1 patient had a single bone uptake (left rib); but further studies showed it to be a posttraumatic fracture.
- In remaining 31 cases, PET study was negative. From study of the prostate bed, 5 false negative cases were found.
- Urinary excretion of tracer may have masked small areas of pathological uptake at prostate-bed level resulting in the false negative PET results.
  - -High rate of negative PET scans could be due to small lesion size (PET resolution limit is between 5 mm and 10 mm).
- PET sensitivity was as shown in Table 7 below.
- **Authors concluded:** 18F-FCH PET/CT detection rate was related to PSA levels.

**Table 7 18F-FCH Sensitivity (Detection) by PSA (Following Biochemical Relapse of Prostate Cancer) (Pelosi)**

| PSA       | Sensitivity |
|-----------|-------------|
| <1 ng/ml  | 20%         |
| 1-5 ng/ml | 44%         |
| > 5 ng/ml | 81.8%       |

Ref. Pelosi, from data

#### 9. Reske et al:

- 11C choline PET/CT in 49 patients with and without elevation of PSA after RRP to evaluate the test in detection of local relapse of PCa in the prostatic bed.
  - -Group A was 36 patients with BCR (PSA range 0.3 thru 12.1). All patients had Biopsy of suspected relapse site. 7 of 36 patients were on hormones.
  - -Group B (Controls) was 13 consecutive patients without BCR.
- 11C choline PET/CT was true positive in 23/33 (70%) of patients Group A, and true negative in 12/13 Group B (controls).
  - - 10 of 33 patients with biopsy proven LR had negative 11C choline PET/ CTs.
- 11C choline PET/CT identified 12/17 (71%) patients with a favorable biochemical response to local radiotherapy follow-up (2-year median, 0.8–3.2 year range).

- Focally increased 11C choline uptake in the prostatic bed, reliably predicted local low volume occult relapsing prostate adenocarcinoma after radical prostatectomy, and
  - - PET/CT identified 12/17 (71%) of patients with a favorable biochemical response to local radiotherapy.
- **Authors concluded:** 11C choline PET/CT can identify a subgroup of 70% of patients with biopsy proven low volume LR of PCa after RRP. Thirty percent of patients failed to exhibit increased 11C choline PET/CT uptake.

#### **10. Rinnab (2007), Mottaghy, Blurnstein, et al**

- Choline C 11 PET/CT in 50 patients with rising PSA after definitive initial therapy.
  - - Radical prostatectomy 40 patients, EBRT 3 patients, Brachytherapy 7 patients
  - - Mean range to BCF of 22 months (range 2-136 months)
  - - PSA level for positive PET/CTs of 3.62 (range 0.5-13.1)
  - - PSA level for negative PET/CTs of 0.90 (range 0.41-1.40)
- PET/CT was positive in 7/13 patients with a PSA level of <1.5 ng/mL and histology was positive in 9/13.
- PET/CT was positive in 17/17 patients with PSA levels of 1.5-2.5 ng/mL and histology was positive in 13.
- PET/CT was positive in 11/11 men with PSA level of 2.5–5 ng/mL and histology was positive in 10.
- PET/CT was positive in 9/9 men with PSA levels of > 5 ng/mL PET/CT and histology was positive in 8.
- The sensitivity of Choline C11 PET/CT for detecting recurrence at a PSA level of < 2.5 ng/mL was 91%, with a specificity of 50%.
- **Authors concluded:** Choline C11 PET/CT “seems to be useful” for re-staging men with prostate cancer and BCR. They recommended that it be used even at PSA levels of <2.5 ng/mL. The authors also state that this technique is complementary to conventional imaging techniques, but has the advantage of staging the disease in one step.

#### **11. Rinnab (2009), Simon, Hautmann, et al.**

- Choline C 11 PET/CT used to evaluate 41 PCa patients with BCR after RP.
- Choline C11 PET/CT positive patients mean PSA 3.1 ng/ml (range 0.5-11.6)
- Choline C11 PET/CT negative patients mean PSA 0.83 ng/ml (range 0.41-1.40)
- For PSA levels 1.5ng/ml to 2.5 ng/ml all 11C choline PET/CT findings were positive; histopathology confirmed findings in 75% of the patients.
- For detection of local recurrence or distant metastasis, overall sensitivity, PPV, and accuracy were 93%, 80%, and 78%, respectively.
- At PSA < 2.5 ng/ml, sensitivity, specificity, and PPV of 11C choline for the detection of recurrence was 89%, 40%, and 72%, respectively.
- PSA values < ng/ml had a detection rate of 36%.
- **Authors concluded:** 11C choline PET/CT had a high sensitivity for detection of local

or distant metastasis, and recommended it for restaging patients with rising PSA levels, even at levels below 1.5 ng/ml. "Once validated , this approach will have direct impact on clinical decision making, i.e. local versus systemic therapy."

**Reviewers Comments:** Articles #10 and #11 are by the same primary author. The main difference is that Article #10 not only included 40 patients who had RP, it also included 3 EBRT patients, and 7 brachytherapy (radioactive seeds) patients. Article #11 was limited to 41 RP patients. As expected the results of the 2 articles are quite similar.

### **Reviewer's Summary of Supportive Studies Submitted by Sponsor**

-It is interesting that all of the above studies (and most studies in the literature on Choline C11 PET imaging) are from Europe.

-The studies varied as to whether primary treatment had been surgery, radiation therapy, or either surgery or radiation therapy. Some studies also utilized hormone therapy alone or in combination with surgery or radiation therapy. This impacts the detection rate per PSA value, since BCR after surgery is defined differently than BCR after radiation therapy or hormone therapy.

-The 3 prospective studies using Choline C11 PET/CT (Breeuswsma, Garcia and Richter) concluded that Choline C11 is a sensitive technique for identifying the site of recurrence in these patients.

-Garcia stated that there was a higher detection rate after surgery than radiation therapy. Garcia also stated that Choline C11 has a superior diagnostic performance to PET/CT with 18F-FDG, the sensitivity of 11C choline is related to PSA level, does not seem to be modified by hormone therapy, staging with 11C choline has a direct impact on the selection of the most suitable therapy following recurrence, and recommend include patients with PSA < 1 ng/mL in whom early diagnosis offers more therapeutic options.

- Richter concluded that detection of site of recurrence with 11C choline PET/CT is clearly dependent on PSA value. Richter stated a cutoff value >1.9 ng/ml was highly significant. Richter also stated adjuvant hormone therapy does not influence PET results, and 11C choline-PET/CT is clearly superior to conventional imaging techniques in the detection of distant recurrence.

-Cimitan and Husarik described prospective studies with 18F-FCH PET/CT. Cimitan stated that 18F-FCH was not likely to impact PCa patients with BCR until PSA increases above 4 ng/mL. On the other hand, Husarik said he could reliably localize recurrent PCa in patients with PSA levels of >2 ng/mL.

-In the remaining 6 retrospective studies, Castelluci said the data supports the use of Choline C 11 PET/CT in patients with a PSA level <1.5 ng/mL and fast PSA kinetics. Reske stated that 11C choline PET/CT can identify a subgroup of 70% of patients with biopsy proven low volume LR of PCa after RRP. Rinnab describes results from 2007 which included 40 patients who had RP, 3 EBRT patients, and 7 brachytherapy patients, results from 2009 with 41 RP patients. As expected the results of the 2 articles are quite similar. In the 2007 article Rinnab stated that Choline C11 PET/CT "seems to

be useful” for re-staging men with prostate cancer and BCR. He recommended it be used even at PSA levels of <2.5 ng/mL. He also stated that this technique is complementary to conventional imaging techniques, but has the advantage of staging the disease in one step.

**Reviewer’s Conclusions on Supportive Studies:** All of the above authors describe a place for imaging recurrent prostate cancer with Choline C11 PET/CT.

**PSA level:** Including the Mayo Study, the sensitivity among the studies ranged from 20% (PSA ≤1 ng/mL) to 93% (PSA ≥1.7 ng/mL), and the specificity ranged from 50% (PSA <2.5 ng/mL) to 93% (across all PSA values). Garcia recommends Choline C11 for imaging even with a PSA <1, even though his detection rate was only 40% for PSA < 1 (His detection rate rose to 60% for PSA 1-4 and 87% for PSA 4.1-9.5). Richter states a cutoff value over 1.9 ng/ml was highly significant. Castellucci states that data supports a PSA < 1.5 ng/ml if there is a rapid PSA doubling time. Rinnab recommends levels below 1.5 ng/ml post prostatectomy, or levels below 2.5 ng/ml in general. My interpretation of the literature is that for biochemical failure after a prostatectomy, the literature overall supports waiting until a PSA > 1.0 ng/ml to have a reasonable Choline C11 PET/CT detection rate. For biochemical failure after radiation therapy, by definition, the PSA has already risen by at least 2 ng/ml above post treatment nadir, so Choline C11 PET/CT could be obtained once BCR is determined.

**Effect of Adjuvant hormone therapy:** Garcia and Richter both state that adjuvant hormone therapy does not seem to influence the detection rate. This is confounding to me, because hormone therapy would affect the PSA, so the PSA would naturally be higher if a patient is not on hormone therapy. The sponsor’s NDA section 2.7.2.3.7 warns that “hormone therapy” agents and anti-androgens may inhibit uptake of choline C11 and therefore should not be administered to patients who will undergo a Choline C11 PET scan unless the patient is being evaluated for “hormone-refractory” prostate cancer relapse or recurrence. Therefore, I recommend caution when dealing with patients on hormone therapy.

#### Additional Reviews of Literature by Rafel D. Rieves, M.D. and This Reviewer

##### 6.4.1 Review of Literature by Rafel D. Rieves, M.D.

###### Method of Reviewing Literature

On May 8, 2012 Dr. Rieves, Chief of the Division of Medical Imaging (DMIP), performed a PubMed Search of the terms *C11 choline*, and *prostate cancer*. Time line was 10 years. Dr. Rieves will present his findings in his Summary Review, but below are the highlights of his review of published literature.

###### Study Results

Five prospective study report publications were found.  
-231 patients total

- most post RP
- most had a PET/CT

There were also 13 retrospective medical record report publications (3 reports duplicate)

- 871 patients total
- most post RP
- all PET/CT

### **Prospective Study 1**

**Scatoni V, Picchio M, Suardi N, Messa C, Freschi M, Roscigno M, Da Posso L, Bocciardi A, Rigatti P, Fazio F. Detection of Lymph-Node Metastases with Integrated 11C Choline PET/CT in Patients with PSA Failure after Radical Retropubic Prostatectomy: Results Confirmed by Open Pelvic-Retroperitoneal Lymphadenectomy. European Urology. 2007;52: 423-429:**

- Prospective evaluation of BCR after surgery 2002-2005
- 25 patients with BCR (median PSA 1.98 ng/ml, range 0.2-23.1)
- Choline C11 PET/CT imaging of lymph node metastases positive in 21 patients and negative in 4 patients
  - 19 of 21 positive PET scans had positive pathology
  - Of 4 patients with negative PET and positive MRI, all had negative pathology
- Conventional imaging positive in 12 patients and negative in 13
  - Choline C11 positive in 9 patients with negative conventional imaging
- Exclusion: local recurrence by trans rectal ultrasound (TRUS) or metastatic disease by scans
- Images interpreted by two independent readers
- No safety results
- Authors' Conclusion:** Choline C11 PET/CT is an accurate diagnostic tool for the detection of lymph-node metastases of recurrent prostate cancer.
- Reviewer's Comment:** An editorial by Schoder and Bochner (See Appendix 9.1 Literature Review/ References) referring to the above article points out that the 25 patients with BCR had no evidence for local recurrence in the prostate bed or osseous metastases. When analyzed by nodal sites (63 total), the PET/CTs were true positive in 20 sites, false positive in 3, true negative in 29, and false negative in 11 for a sensitivity of 64% and specificity of 90%. Schoder and Bochner conclude that Scattoni et al provided promising data, but much work remains to determine the clinical utility of choline C11 PET/ CT for detecting lymph node recurrence in patients with early PSA relapse.

### **Prospective Study 2**

**Rinnab L, Mottaghy F, Simon J, Volkmer B, de Petriconi R, Hautmann R,**

**Wittbrodt M, Egghart G, Moeller P, Blumstein N, Reske S, Kuefer, R.  
11C Choline PET/CT for Targeted Salvage Lymph Node Dissection in  
Patients with Biochemical Recurrence after Primary Curative Therapy for  
Prostate Cancer. Urologia Internationalis. 2008;81:191-197.**

- Prospective study to investigate the diagnostic value of C11 choline PET/CT in patients with suspected lymph node metastases before salvage lymph node dissection
- 15 consecutive patients with rising PSA after primary therapy.
- Primary therapy was RP in all (15) but included EBRT in 4 and hormone therapy in 5
- Mean time from prostatectomy to BCR was 23.6 months (range 4-81 months).
- All had negative conventional imaging (ultrasound and/or CT and/or MRI and/or bone scintigraphy)
- All had PET/CT then salvage pelvic/ retroperitoneal extended lymph node dissection due to uptake of 11C Choline in at least 1 lymph node.
- PSA at time of PET/DC median 2.0 (range 1.0-8.0 ng/ml)
- Positive histology in 8/15 patients (7 false positives)
- Only 1 patient had PSA nadir of <0.1 ng/ml after salvage surgery. Another patient had stable disease with PSA of 0.5 ng/ml. Three patients developed bone metastases during follow-up.
- No safety outcomes

**Authors' Conclusion:** Interim analysis indicates that 11C choline PET/CT may be a useful technique in detection of lymph node metastases when PSA rises after definite PCa therapy. However, the clinical value of 11C choline PET/CT targeted salvage lymph node dissection is questionable since most patients had further progression within a limited period of time.

**Reviewer's Comment:** The C11 choline dose used in this study was 1,112 MBq +/- 131 MBq. This is a higher dose than what the Mayo Clinic used in its retrospective study and which it plans to use which is 370-740 MBq. This higher dose might have contributed to better imaging, but in this study, results appear comparable to other studies described.

**Other Prospective Studies:**

Dr. Rieves also reviewed the prospective studies by Breeuwsma, Garcia and Richter which were also submitted by the sponsor and which I have summarized above in Section 6.3.

**Significant Retrospective Studies:** Dr. Rieves identified 10 retrospective reviews of C11 choline PET/CT imaging for BCR of PCa, and described the following main points:

- Scan detection rates vary with PSA
- Most report a "cut point" of about 2 ng/mL
- One study of 10 patients with positive C11 choline scans noted that on surgical resection of nodes 3 of 10 patients had only inflammation in the nodes.
- Other retrospective articles are described above in Section 6.3

**Publication Review Main Points by Dr. Rieves:**

- Choline scanning detects cancer recurrence among men with negative conventional imaging and BCR about 50 to 67%, depending on PSA
- False Positive choline scans occur about 10 to 50 %
- False Negative choline scans occur about 10 to 30%, generally in men with a lower PSA
- C11 Choline appears to be about twice as sensitive as FDG for detecting recurrence of prostate cancer
- Limitation of Use: Choline C11 PET imaging does not replace histologic verification of sites of recurrent prostate cancer and does not assess the response to therapies.

***Reviewer's Conclusions:***

- As above, C11 Choline imaging does not rule out false positive or false negative results. The detection rate appears related to the PSA value, but early detection at a lower PSA value may offer a better probability of salvage than waiting for a higher detection rate from a higher PSA.

6.4.2 Review of Literature by this Reviewer

Method of Reviewing Literature

In February 2012 I requested the FDA Biosciences Library perform a literature review with the key words *choline*, *prostate* and *PET* from 1998 to the present time. A librarian searched MEDLINE, Cancerlit, Embase, and Pascal and found a total of 262 references (no duplicates). This compares with the sponsor who reported searching with the same 3 key words *choline*, *prostate*, and *PET* from 1998 through 2011 in 3 databases: PUBMED, and National Library of Medicine and MEDLINE through the ENDNOTE database search program. The sponsor reported obtaining 183 peer-reviewed articles. Other than the prospective articles described above by the sponsor, and by Dr. Rieves, I only have one additional prospective study and a review article to describe below.

I also reviewed National Comprehensive Cancer Network (NCCN) and American Urological Association (AUA) guidelines for treatment of biochemical recurrence of prostate cancer. The NCCN guidelines were updated for Prostate Cancer in March 2012. The AUA published "Guideline for the Management of Clinically Localized Prostate Cancer: 2007 Update" and a "PSA Best Practice Statement: 2009." Both of these AUA publications are available free on the internet, but do not describe detailed management of biochemical failure.

**Prospective Study**

**Rigatti P, Suardi N, Briganti A, Da Pozzo L, Tutolo M, Villa L, Gallina A, Capitanio U, et al. Pelvic/Retroperitoneal Salvage Lymph Node Dissection for Patients Treated With Radical Prostatectomy With Biochemical Recurrence and Nodal Recurrence Detected by (11C)Choline Positron Emission Tomography/Computed Tomography. European Urology, 2011, 60 (5) 935-943.**

- Prospective analysis of 72 patients with BCR after RP.
- All had choline C11 PET/CT with pathologic lymph nodes
  - Excluded patients with local recurrence based on conventional imaging
  - No one had hormone therapy prior to PET/CT
  - All had negative biopsies of the prostatic fossa and negative bone scans
- Intervention was salvage lymph node dissection
- Results: 57 % had biochemical response defined as PSA < 0.2 ng/ml 40 days after salvage lymph node dissection. However, with 39 month mean follow-up, 5 year BCR-free survival rate was 19%.

**Authors' Conclusion:** Salvage lymph node dissection is feasible in patients with BCR after RP

**Reviewer's Comments:** This large prospective series shows that there may be some benefit to the use of choline C11 PET/CT for imaging BCR after RP. 19 % of the 72 patients appear to have long term absence of PCa up to 5 years after a salvage lymph adenectomy. The authors stated that this study had a heterogeneous mix of patients, but those patients most likely to benefit from salvage surgery were those with a PSA < 4ng/ml at the time of salvage surgery.

### Review Article

Picchio M, Briganti A, Fanti S, Heidenreich A, Krause B, Messa C, Montorsi F, Reske S, Thalmann G. The Role of Choline Positron Emission Tomography/Computed Tomography in the Management of Patients with Prostate-Specific Antigen Progression After Radical Treatment of Prostate Cancer *European Urology*, 2011, 59 (1) 51-60.

- The authors state that choline PET/CT is currently used as a diagnostic tool in restaging PCa after BCR following either surgery or radiation therapy, but there are no guidelines on how to use this imaging for patient management.
- The authors reviewed articles choline PET/CT published 2003-2010
- Sensitivity rates varied from 38% to 98%
  - Detection rate improves with increasing PSA values
- This article states that it has been shown that nonsteroidal androgenic antagonists cause a significant decrease in choline uptake within the prostate gland if prostate cells are still in the androgen-dependent stage.
- A choline PET/CT for PSA value <1ng/ml is not recommended

**Authors Conclusions:** Choline PET/CT accuracy correlates with PSA value, PSA doubling time, and other pathologic features such as stage and histology. It may be proposed as a guide for individualized treatment of recurrence.

**Reviewer's Comments:** This article describes both C11 choline and F18 choline PET/CT. It provides an overview of many of the same articles submitted by the sponsor. Unlike most other articles described above, this article states that androgenic antagonists significantly decrease choline PET/CT detection.

## **National Comprehensive Cancer Network Guidelines (NCCN)**

NCCN Guidelines are a reputable resource for physicians to review clinical guidelines for the treatment of various malignancies. The guidelines are available at [www.nccn.org](http://www.nccn.org). The NCCN Guidelines for Prostate Cancer, version 3.2012, have different algorithms for post surgical or post radiation therapy recurrence of prostate cancer.

### **Following Surgery**

The guidelines for Post-Radical Prostatectomy Recurrence describe the following: “Recurrence” is defined as either PSA rising on 2 or more determinations after surgery, or failure of PSA to fall to undetectable levels.

Guidelines recommend:

- + or – Bone Scan
- + or – CT/MRI
- + or – PSAdt
- + or – Prostate bed biopsy

If studies are negative for distant metastases, the algorithm recommends radiation therapy + or – androgen deprivation therapy (ADT).

If studies are positive for distant metastases, the algorithm recommends ADT + or - radiation therapy to site of metastases or observation.

### **Following Radiation Therapy (RT)**

The guidelines for Post-Radiation Therapy Recurrence describe the following: “Recurrence” is defined as Post-RT positive digital rectal exam or rising PSA (RTOG-ASTRO Phoenix Consensus definition is a PSA rise by 2 ng/ml or more above the nadir PSA with or without hormone therapy).

Guidelines recommend:

If the patient is a candidate for local therapy and life expectancy > 10 years and PSA < 10 ng/mL:

- Prostate biopsy
- Bone scan
- + or – Abdominal/pelvic CT/MR
- + or – Endorectal MRI
- + or - PSAdt

If prostate biopsy is positive, and studies negative for distant metastases, observation or radical prostatectomy or cryosurgery or brachytherapy are recommended.

## **NCCN Guidelines for Adjuvant or Salvage Therapy after Radical Prostatectomy**

The NCCN website provides detailed discussion of adjuvant or salvage therapy after radical prostatectomy. NCCN describes the results of the SWOG 8794 trial which enrolled 425 men with extraprostatic cancer treated with RP. Patients were randomized to receive either adjuvant RT or usual care. 10 year biochemical failure-free survival for high risk patients (seminal vesicle positive) receiving post RP adjuvant radiation compared to observation was 36% vs 12%. The NCCN recommends that if adjuvant RT is being considered, it should be started before the PSA exceeds 1.5 ng/ml.

The NCCN summary of a study published in 2004 describes a retrospective review of 501 patients who received salvage radiotherapy for detectable and increasing PSA after prostatectomy. The study showed that the predictors of progression were Gleason score 8-10, pre-RT PSA level greater than 2 ng/mL, seminal vesicle invasion, surgical margin status, and a PSAdt of 10 months or less.

The value of salvage therapy following radiation is less clear.

**Reviewer's Comments:** The above NCCN guidelines show the heterogeneity of Prostate Cancer. There is a different definition for recurrence if a patient had primary surgery or primary radiation therapy. The PSA is going to be higher for the patient who had radiation therapy. The algorithms describe more options for salvage of the post radiation therapy patient, than the post radical prostatectomy patient. The NCCN provides a discussion of salvage treatment following BCR after a radical prostatectomy and recommends that salvage radiation therapy is more effective if started when the PSA is less than 2 ng/ml. This presents a dilemma that salvage therapy is most effective when given early (< 2 ng/ml), but a choline C11 PET/CT may not detect recurrence unless the PSA is higher (> 2ng/ml).

## 7 Review of Safety

### Safety Summary

Choline C11 PET/CT appears to offer safe imaging. The Mayo Clinic's retrospective study of 176 patient charts found only 1 adverse event which was an injection site reaction that was mild, self-limiting, and resolved.

As with any radiopharmaceutical, radiation safety precautions should be followed.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

As part of its submission, the Mayo Clinic reported on safety in the 176 charts it reviewed. Vital signs, physical examinations, and other safety observations were not collected as part of their retrospective study. The Mayo Clinic also performed a literature search through October 2011. The words "safety" or "toxicity" or "tox" or "side effect" or "serious adverse event" or "allergy" were searched with its search for efficacy. The articles were then extensively reviewed for safety parameters such as any references to adverse events, documentation of vital signs or physical examination findings, and any safety laboratory evaluations. (See NDA 2.7.4.1.1 and 5.4, 4.4) The Mayo Clinic submitted 13 articles (NDA 2.7.4 Table 1) to support the Safety of its application. The sponsor stated that they had extensively reviewed safety parameters such as any reference to adverse events, documentation of vital signs or physical examination findings, and any safety laboratory evaluations. None was reported in any of these published articles with the exception of DeGrado (Pharmacokinetics and Radiation Dosimetry of 18F-Fluorocholine) and Pelosi (Role of Whole-Body 18F-Choline PET/CT in Disease Detection in Patients with Biochemical Relapse after Radical Treatment for Prostate Cancer). No relevant issues were found in either article that would adversely affect the conclusions about the safety profile of choline.

**Reviewer's Comments:** Note that the sponsor's literature search for safety issues did not identify any safety issues. There were only 2 articles which even described safety with the search terms above and both articles involved 18F-choline, not 11C-choline. "No adverse events were reported" per DeGrado and "No adverse events were observed in any of the patients after administration of 18F fluorocholine (18F choline) or the oral contrast medium" per Pelosi.

### 7.1.2 Categorization of Adverse Events

Of 176 patient charts reviewed for their retrospective study, the sponsor found only 1 adverse event which was an injection site reaction that was mild, self-limiting,

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 8 has organ doses for Choline C11 PET imaging.

**Table 8  $^{11}\text{C}$  Choline Absorbed Radiation Dose Per Unit Activity (rad/mCi) for Adults and Pediatric Groups**

| Organ                               | Age (years) |              |         |         |        |        |         |
|-------------------------------------|-------------|--------------|---------|---------|--------|--------|---------|
|                                     | Adult       | Adult Female | 15      | 10      | 5      | 1      | Newborn |
| Adrenals                            | 0.0133      | 0.0166       | 0.0164  | 0.0246  | 0.0363 | 0.0611 | 0.129   |
| Bladder wall                        | 0.0126      | 0.0155       | 0.0154  | 0.0238  | 0.0386 | 0.0688 | 0.175   |
| Bone surfaces                       | 0.0178      | 0.0233       | 0.0229  | 0.0353  | 0.0570 | 0.128  | 0.379   |
| Brain                               | 0.00431     | 0.00507      | 0.00501 | 0.00795 | 0.0125 | 0.0231 | 0.0563  |
| Breast                              | 0.00516     | 0.00636      | 0.00634 | 0.0103  | 0.0162 | 0.0305 | 0.0700  |
| Gallbladder Wall                    | 0.0162      | 0.0200       | 0.0194  | 0.0279  | 0.0430 | 0.0817 | 0.172   |
| Stomach wall                        | 0.0222      | 0.0264       | 0.0281  | 0.0415  | 0.0688 | 0.135  | 0.387   |
| Small intestine                     | 0.00869     | 0.0102       | 0.0107  | 0.0168  | 0.0267 | 0.0480 | 0.105   |
| *ULI                                | 0.0237      | 0.0274       | 0.0299  | 0.0511  | 0.0836 | 0.162  | 0.393   |
| **LLI                               | 0.00668     | 0.00815      | 0.00766 | 0.0123  | 0.0195 | 0.0345 | 0.0840  |
| Heart                               | 0.0127      | 0.0164       | 0.0165  | 0.0250  | 0.0381 | 0.0667 | 0.132   |
| Kidneys                             | 0.0763      | 0.0836       | 0.0916  | 0.129   | 0.191  | 0.340  | 0.883   |
| Liver                               | 0.0744      | 0.0982       | 0.0989  | 0.149   | 0.220  | 0.418  | 0.952   |
| Lungs                               | 0.0170      | 0.0218       | 0.0246  | 0.0349  | 0.0532 | 0.103  | 0.265   |
| Muscle                              | 0.00939     | 0.0134       | 0.0141  | 0.0267  | 0.0756 | 0.149  | 0.213   |
| Ovaries                             | 0.00746     | 0.00912      | 0.00927 | 0.0145  | 0.0230 | 0.0420 | 0.0920  |
| Pancreas                            | 0.108       | 0.121        | 0.153   | 0.316   | 0.402  | 0.885  | 3.08    |
| Red marrow                          | 0.00704     | 0.00843      | 0.00850 | 0.0124  | 0.0184 | 0.0381 | 0.123   |
| Skin                                | 0.00453     | 0.00575      | 0.00549 | 0.00858 | 0.0137 | 0.0260 | 0.0625  |
| Spleen                              | 0.0339      | 0.0412       | 0.0480  | 0.0738  | 0.115  | 0.211  | 0.543   |
| Testes                              | 0.00503     |              | 0.00629 | 0.00983 | 0.0156 | 0.0293 | 0.0680  |
| Thymus                              | 0.00626     | 0.00794      | 0.00797 | 0.0118  | 0.0185 | 0.0335 | 0.0750  |
| Thyroid                             | 0.00551     | 0.00632      | 0.00705 | 0.0114  | 0.0186 | 0.0344 | 0.0765  |
| Uterus                              | 0.00726     | 0.00888      | 0.00905 | 0.0144  | 0.0230 | 0.0414 | 0.0911  |
| Total body                          | 0.0110      | 0.0138       | 0.0139  | 0.0221  | 0.0355 | 0.0681 | 0.167   |
| Effective Dose Equivalent (rem/mCi) | 0.0252      | 0.0301       | 0.0334  | 0.0554  | 0.0798 | 0.158  | 0.445   |
| Effective Dose (rem/mCi)            | 0.0161      | 0.0198       | 0.0212  | 0.0340  | 0.0507 | 0.0996 | 0.273   |

\*Upper large intestine, \*\* Lower large intestine  
(Ref: NDA 5.3.5.4.1 Abbreviated Clinical Study Report, page 15)

**Reviewer's Comment:** Review of this table does not reveal any organ to be at excessive risk of radiation exposure. The main column of interest is the "Adult" column since prostate cancer does not occur in women or children.

#### 7.2.2 Explorations for Dose Response

There were no explorations for dose response.

#### 7.2.3 Special Animal and/or In Vitro Testing

There was no special animal and/or in vitro testing.

#### 7.2.4 Routine Clinical Testing

Clinical testing was performed as described in the publications that the sponsor submitted to support its application. Studies ranged from IRB approved prospective studies, to IRB exempted retrospective studies.

#### 7.2.5 Metabolic, Clearance, and Interaction Workup

This is described in the FDA's Clinical Pharmacology Review

#### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Choline C11 injection is a short-acting radiopharmaceutical which may be compared with other radiopharmaceutical drugs such as FDG and Ammonia N-13. These other drugs have been FDA approved for several years and have an excellent safety record. It may also be compared with Indium 111 ProstaScint (capromab pendetide) which is the only medical imaging drug currently approved for use in the imaging of patients with prostate cancer. ProstaScint is a murine monoclonal antibody which contains 0.5 mg protein, much larger than the weight of Choline C11 which is about .005 mg. Radiation dose from ProstaScint is about 27 mSv per study, compared with choline C11 PET/CT which has a dose estimate of about 5 mSv per study.

### 7.3 Major Safety Results

#### 7.3.1 Deaths

There were no reported deaths.

#### 7.3.2 Nonfatal Serious Adverse Events

There were no nonfatal serious adverse events.

#### 7.3.3 Dropouts and/or Discontinuations

There were no dropouts and/or discontinuations.

#### 7.3.4 Significant Adverse Events

There were no significant adverse events.

### 7.4 Supportive Safety Results

#### 7.4.1 Common Adverse Events

There have been no common adverse events.

#### 7.4.2 Laboratory Findings

Laboratory studies are not ordered for Choline C11 injection.

#### 7.4.3 Vital Signs

Vital signs were not collected as part of the retrospective study conducted by the Mayo Clinic and were not noted in any of the articles.

#### 7.4.4 Electrocardiograms (ECGs)

ECGs are not routinely ordered with choline C11 injection.

#### 7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies or clinical trials for safety.

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

No dose dependency for adverse events has been noted.

#### 7.5.2 Time Dependency for Adverse Events

No time dependency for adverse events has been noted.

#### 7.5.3 Drug-Demographic Interactions

No drug-demographic interactions have been noted.

#### 7.5.4 Drug-Disease Interactions

No drug-disease interactions have been noted. The sponsor described in NDA 2.7.4.5.1.2 that many studies of choline have been done treating disease states, such as liver disease, and no drug-disease interaction has been found.

#### 7.5.5 Drug-Drug Interactions

Metabolism of colchicine has been shown to interfere with  $^{18}\text{F}$  methylcholine uptake. Therefore the sponsor recommended discontinuing colchicine 48 hours prior to PET/CT scanning with Choline C 11 Injection. (Ref: Roef M, et al, "Colchicine must be stopped before imaging with [ $^{18}\text{F}$ ]-methylcholine")

The sponsor recommends that drugs that inhibit uptake of  $^{11}\text{C}$  choline by prostate tumors cells, termed as "hormone therapy" agents, should not be administered to patients who will undergo a PET/CT scan with Choline C 11 Injection, unless the patient is being specifically evaluated for "hormone-refractory" prostate cancer relapse or recurrence. The same applies to anti-androgens. (Ref. NDA 2.7.4.5.2)

**Reviewer's Comments:** Although the sponsor provides the above warning, none of the studies submitted by the sponsor described a drug interaction as a safety concern, and some of the studies described above in Section 6 did not note any impact of hormone therapy on choline C11 PET/CT detection. An article by Picchio et al (Ref. Picchio 2011) does state that in patients with PCa following treatment with a nonsteroidal androgenic antagonist, a significant decrease in choline uptake within the prostate gland has been shown if prostate cells are still in the androgen-dependent stage. I agree with the sponsor's recommendation not to start hormone therapy until after a PET/CT is performed. If a patient is already on hormone therapy, then he should continue on it if needed. Patients often receive depot injections of hormone therapy which last up to 4 or more months. It would be impractical to wait 4 months for the effects of hormone therapy to abate.

### 7.6 Additional Safety Evaluations

#### 7.6.1 Human Carcinogenicity

Human carcinogenicity was not evaluated.

#### 7.6.2 Human Reproduction and Pregnancy Data

Human Reproduction and Pregnancy Data was not evaluated.

#### 7.6.3 Pediatrics and Assessment of Effects on Growth

Pediatrics and Assessment of Effects on Growth were not evaluated.

## 8 Postmarket Experience

At the present time there is no plan for a postmarketing requirement.

## 9 Appendices

### 9.1 Literature Review/References

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## 9.2 Labeling Recommendations

The Label for Choline C11 Injection is being reviewed.

## 9.3 Advisory Committee Meeting

There is no plan for an Advisory Committee Meeting.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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WILLIAM E DICKERSON

08/15/2012

ALEXANDER GOROVETS

08/15/2012

The primary clinical review is complete.

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA Number: 203155**

**Applicant: Mayo Clinic**

**Stamp Date: Dec 12, 2011**

**Drug Name: Choline C11  
injection**

**NDA/BLA Type: NDA**

**Checklist filed Feb 9, 2012**

On initial overview of the NDA/BLA application for filing:

|                                       | Content Parameter                                                                                                                                                                                                                                             | Yes         | No | NA | Comment                                                                      |
|---------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|----|----|------------------------------------------------------------------------------|
| <b>FORMAT/ORGANIZATION/LEGIBILITY</b> |                                                                                                                                                                                                                                                               |             |    |    |                                                                              |
| 1.                                    | Identify the general format that has been used for this application, e.g. electronic CTD.                                                                                                                                                                     | X           |    |    | Hybrid, eCTD format and .pdf                                                 |
| 2.                                    | On its face, is the clinical section organized in a manner to allow substantive review to begin?                                                                                                                                                              | X           |    |    | 1.14 Labeling, 2.5 Clinical overview, 2.7 Clin Summary, 5 Clin Study Reports |
| 3.                                    | Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?                                                                                                                                   | X           |    |    | 2.5, 2.7 and 5.2                                                             |
| 4.                                    | For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?                                                                                                  | X           |    |    |                                                                              |
| 5.                                    | Are all documents submitted in English or are English translations provided when necessary?                                                                                                                                                                   | X           |    |    |                                                                              |
| 6.                                    | Is the clinical section legible so that substantive review can begin?                                                                                                                                                                                         | X           |    |    |                                                                              |
| <b>LABELING</b>                       |                                                                                                                                                                                                                                                               |             |    |    |                                                                              |
| 7.                                    | Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?                                                                                | X           |    |    |                                                                              |
| <b>SUMMARIES</b>                      |                                                                                                                                                                                                                                                               |             |    |    |                                                                              |
| 8.                                    | Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?                                                                                                                                                                 | X           |    |    |                                                                              |
| 9.                                    | Has the applicant submitted the integrated summary of safety (ISS)?                                                                                                                                                                                           |             |    | X  | Not a true eCTD. Per Dr. Rieves there is no need for ISS or ISE.             |
| 10.                                   | Has the applicant submitted the integrated summary of efficacy (ISE)?                                                                                                                                                                                         |             |    | X  | Same as #9 above.                                                            |
| 11.                                   | Has the applicant submitted a benefit-risk analysis for the product?                                                                                                                                                                                          | X           |    |    | See 2.5.6 on p.47 of 2.5 & comments at end.                                  |
| 12.                                   | Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?                                                                                                                      | 505<br>b(2) |    |    | No Reference Drug.                                                           |
| <b>DOSE</b>                           |                                                                                                                                                                                                                                                               |             |    |    |                                                                              |
| 13.                                   | If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?<br>Study Number:<br>Study Title:<br>Sample Size: Arms:<br>Location in submission: |             |    | X  | Microdose, discussed by Clin Pharm.                                          |
| <b>EFFICACY</b>                       |                                                                                                                                                                                                                                                               |             |    |    |                                                                              |
| 14.                                   | Do there appear to be the requisite number of adequate and well-controlled studies in the application?                                                                                                                                                        |             |    | X  | 505b2                                                                        |

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

|               | Content Parameter                                                                                                                                                                                                                                           | Yes | No | NA | Comment                                                                                                                                                                                        |
|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|----|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|               | Pivotal Study #1<br>Indication:                                                                                                                                                                                                                             |     |    |    |                                                                                                                                                                                                |
| 15.           | Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? |     |    | X  |                                                                                                                                                                                                |
| 16.           | Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.                                                                     |     |    | X  | No previous Agency request.                                                                                                                                                                    |
| 17.           | Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?                                                                                                         |     |    | X  | The main study is from the Mayo Clinic of USA patients.                                                                                                                                        |
| <b>SAFETY</b> |                                                                                                                                                                                                                                                             |     |    |    |                                                                                                                                                                                                |
| 18.           | Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?                                                                                                          | X   |    |    | See 2.5.5 and 2.7.4. Retrospective study from USA & review of other studies.                                                                                                                   |
| 19.           | Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?                                                                                                              |     |    | X  | Single admin. Per 2.7.2.5 has not been evaluated, but per 2.6.2.3.1.2 there may be some cardio-protection from choline. 5.3.5.4.1 Retrospective Report p.15 dose is about 0.005mg Choline C11. |
| 20.           | Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?                                                                                                                                            | X   |    |    | This will be supported by an additional literature search by the Reviewer.                                                                                                                     |
| 21.           | For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?                                                           |     |    | X  | Single administration, not short course                                                                                                                                                        |
| 22.           | For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?                                                                                                     |     |    | X  | Single administration, not short course.                                                                                                                                                       |
| 23.           | Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?                                                                                                                             |     |    | X  | 505b2                                                                                                                                                                                          |
| 24.           | Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?                                                                                                                 |     |    | X  |                                                                                                                                                                                                |

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

|                               | Content Parameter                                                                                                                                                                   | Yes | No | NA | Comment                                                                                    |
|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|----|----|--------------------------------------------------------------------------------------------|
| 25.                           | Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?                                              |     |    | X  | No deaths or dropouts. See 2.5.5.4                                                         |
| <b>OTHER STUDIES</b>          |                                                                                                                                                                                     |     |    |    |                                                                                            |
| 26.                           | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?                                                                   |     |    | X  |                                                                                            |
| 27.                           | For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self selection and/or actual use)? |     |    | X  |                                                                                            |
| <b>PEDIATRIC USE</b>          |                                                                                                                                                                                     |     |    |    |                                                                                            |
| 28.                           | Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?                                                                       | X   |    |    |                                                                                            |
| <b>ABUSE LIABILITY</b>        |                                                                                                                                                                                     |     |    |    |                                                                                            |
| 29.                           | If relevant, has the applicant submitted information to assess the abuse liability of the product?                                                                                  |     |    | X  |                                                                                            |
| <b>FOREIGN STUDIES</b>        |                                                                                                                                                                                     |     |    |    |                                                                                            |
| 30.                           | Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?                                                    |     |    | X  | There are some foreign references. See #17 above. Retrospective review. No data submitted. |
| <b>DATASETS</b>               |                                                                                                                                                                                     |     |    |    |                                                                                            |
| 31.                           | Has the applicant submitted datasets in a format to allow reasonable review of the patient data?                                                                                    | X   |    |    | Statistics Section Fileable Feb 3, 2012                                                    |
| 32.                           | Has the applicant submitted datasets in the format agreed to previously by the Division?                                                                                            | X   |    |    |                                                                                            |
| 33.                           | Are all datasets for pivotal efficacy studies available and complete for all indications requested?                                                                                 | X   |    |    | Statistics Section Fileable Feb 3, 2012                                                    |
| 34.                           | Are all datasets to support the critical safety analyses available and complete?                                                                                                    |     |    | X  |                                                                                            |
| 35.                           | For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?                                                                    |     |    | X  | 505b2                                                                                      |
| <b>CASE REPORT FORMS</b>      |                                                                                                                                                                                     |     |    |    |                                                                                            |
| 36.                           | Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?                                              |     |    | X  | 505b2                                                                                      |
| 37.                           | Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?                |     |    | X  | 505b2                                                                                      |
| <b>FINANCIAL DISCLOSURE</b>   |                                                                                                                                                                                     |     |    |    |                                                                                            |
| 38.                           | Has the applicant submitted the required Financial Disclosure information?                                                                                                          | X   |    |    | Included in amendment submitted by Mayo Feb 6, 2012.                                       |
| <b>GOOD CLINICAL PRACTICE</b> |                                                                                                                                                                                     |     |    |    |                                                                                            |
| 39.                           | Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?             | X   |    |    | Included in amendment submitted by Mayo Feb 6, 2012.                                       |

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? \_\_ YES \_\_**

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

-NONE

|                           |                  |
|---------------------------|------------------|
| WILLIAM DICKERSON, M.D.   | February 9, 2012 |
| Reviewing Medical Officer | Date             |
| ALEXANDER GOROVETS, M.D.  | February 9, 2012 |
| Clinical Team Leader      | Date             |

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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WILLIAM E DICKERSON  
02/09/2012

ALEXANDER GOROVETS  
02/10/2012