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APPLICATION NUMBER:

203155Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	August 24, 2012
From	Alex Gorovets, MD
Subject	Cross-Discipline Team Leader Review
NDA#	203155
Applicant	Mayo Clinic
Date of Submission	12-12-2011
PDUFA Goal Date	09-12-2012 (includes major amendment)
Proprietary Name / Established (USAN) names	Choline C11 Injection
Dosage forms / Strength	370-740 MBq (10-20 mCi) / approximately 5 mcg
Proposed Indication(s)	(b) (4)
Recommended:	Approval

1. Introduction

This Cross Disciplinary Team Leader (CDTL) review document addresses the New Drug Application (NDA) 203155 for C-11 Choline produced at Mayo Clinic. It is a radioactive diagnostic drug for use with Positron Computer Tomography (PET) in patients with prostate cancer. Specifically, it is proposed for use in patients with suspected recurrence to help localize the site of recurrence.

This imaging drug has been in clinical use for over ten years but never approved by the FDA. This particular drug produced and used by the Mayo Clinic has also never been studied under an Investigational New Drug (IND) application. This all has been consistent with the history of PET drug regulations stemming from the 1997 Food and Drug Administration Modernization Act (FDAMA). FDAMA directed FDA to develop current Good Manufacturing Practice (cGMP) regulations and required that all PET drugs used for patient care in this country start complying with the drug regulations, as any other drug, two years after the cGMPs are published. These were published in December 2009. Mayo Clinic submitted their application in December 2011. The application was given a Priority review timeline as there is an unmet medical need for diagnostic agents in patients with recurrent prostate cancer.

The submitted NDA is a 505(b)(2) application relying on two sources of data: the results of a systematic review of published literature and a retrospective review based on the Mayo Clinic medical records. This reviewer has examined the review documents generated by the primary

reviewers and reviewed the appropriate portions of the application. No disagreements among the reviewers from different disciplines were encountered during the review process.

Of note, in addition to the primary and secondary reviewers reviewing the materials submitted in the application, Dr. Dwaine Rieves, the Division Director of the Division of Medical Imaging Products, has conducted an independent review of the published C11 Choline literature based on the earlier precedent for the approval process of F18 fluorodeoxyglucose (FDG) in oncology indication, a widely used PET imaging drug, also subject to the same PET regulations. This CDTL review does not include the review of Dr. Rieves' findings.

2. Background

Choline is a naturally occurring substance involved in multiple aspects of human metabolism, primarily important for structural integrity of cell membranes, and is commonly used as a dietary supplement. C11 Choline is identical in molecular structure to choline except that one of the carbon atoms is radioactive (C11 atom). According to the sponsor, the amount of C11 choline injected during a PET scan is about 100,000 times less than the daily recommended intake of choline for nutritional needs. There is apparently a preferential uptake of choline into the prostate cancer cells although an exact mechanism is unknown. Choline, unlike glucose, does not get concentrated in the urinary bladder, with the latter then not causing an interference with prostate imaging.

Carbon 11 (C 11) is cyclotron-produced and decays to boron-11 by positron emission, having a physical half life of 20.4 minutes; hence the imaging drug has to be locally produced. C11 Choline is distributed to all organs of the body after intravenous administration.

Prostate cancer is a common malignancy, especially in older men, and it recurs not infrequently after the initial surgical resection or radiation therapy. The recurrence is usually manifested by the rising blood levels of Prostate Specific Antigen (PSA), a so called biochemical recurrence. Following a complete prostatectomy, PSA falls to zero and any rise is considered significant. After radiotherapy, a defined rise of a PSA level from the post-surgical baseline is also considered significant.

The imaging work-up of a patient with a biochemical recurrence and, therefore, a suspected cancer recurrence usually consists of Magnetic Resonance Imaging (MRI) and/or Computed Tomography (CT) and bone scan (gamma-scintigraphy), in addition possibly to a local ultrasound. In the context of re-staging of prostate cancer, MRI, CT and bone scintigraphy are often referred to as "conventional" imaging. MRI and CT scans identify or rule out a recurrence in the prostatic fossa, local or distant lymph nodes as well as some distal metastases. Bone scans are for ruling out bone metastases. There are elaborate recommendations made by the professional societies for treatment of prostate cancer recurrence. In deciding on the type and timing of treatment, localizing the recurrence and obtaining histologic confirmation, if possible, are quite important.

There is currently one radioactive drug approved for imaging patients with prostate cancer and specifically patients with inconclusive conventional imaging. It is an Indium-111 labeled

murine monoclonal antibody, capromab pentetide (ProstaScint), for gamma-scintigraphy. ProstaScint imaging is known to result in high numbers of false positives and false negatives and confirmatory studies are always recommended. It has safety concerns as a biologic and it is not commonly used in clinical practice. ProstaScint is also associated with a relatively high radiation absorbed dose of 27 mSv (as compared to 5 mSv estimated for C11 Choline).

C11 Choline PET imaging in patients with prostate cancer has been used by multiple, primarily academic institutions around the world. Unfortunately, there are no reports of large prospective clinical trials that can be found in clinical or scientific literature.

3. CMC/Device

Based on the information provided by the applicant and reviewed by the Product Quality reviewer, C11 Choline Injection is formulated as a ready to use sterile, clear and colorless solution and supplied in a glass vial (~ 10 mL). Each milliliter contains 148 MBq to 1225 MBq (4 mCi to 33.1 mCi) of choline C 11 at the end of synthesis (EOS) calibration in aqueous 0.9% sodium chloride solution. Carbon 11 is produced in a cyclotron and decays to Boron 11 by positron emission. It has a physical half life of 20.4 minutes. Choline C11 chloride ([11C] Methyl-dimethyl-2-hydroxyethyl-ammonium) has a molecular weight of 138.63 g.

(b) (4)
As choline is a naturally occurring nutrient, specific activity is not considered to be a critical parameter in PET imaging with C11 Choline.

The standard patient dose is 370-740 MBq (10-20 mCi). Individual dose of Choline C 11 injection is intravenously administered by bolus through a catheter and PET imaging is initiated immediately after administration. The imaging data are acquired for up to 15 minutes.

Although there are apparently no product quality issues from a chemistry perspective there are two potentially serious deficiencies which have been identified by the Product Microbiology reviewer and communicated to the Applicant. These deficiencies relate to sampling frequency for monitoring (b) (4) production areas and to inadequate media fill procedures. As both are procedural, both are expected to be corrected by the Applicant.

4. Nonclinical Pharmacology/Toxicology

As noted in the primary and secondary Pharmacology/Toxicology reviews, there were no sponsor-conducted nonclinical studies submitted with this 505(b) (2) application. The reviewers point out that (b) (4) 11C-choline, is present in the drug product as an impurity. (b) (4) levels appear to be lower for

drug products used in published clinical studies than in the Mayo Clinic drug product. However, at the given dose level there are no apparent safety concerns.

The following will be noted in the labeling: Long term studies have not been performed to evaluate the carcinogenic potential of Choline C 11 Injection. The mutagenic potential of Choline C 11 Injection has not been adequately evaluated; however, any radiopharmaceutical, including Choline C 11 Injection, has the potential to be mutagenic. The effect of Choline C 11 Injection on fertility has not been evaluated.

5. Clinical Pharmacology/Biopharmaceutics

Choline C 11 Injection is a radiolabeled analog of choline, a precursor molecule essential for the biosynthesis of cell membrane phospholipids. Choline is known to be involved in synthesis of the structural components of cell membranes. Increased uptake of choline can be related to increased phospholipid synthesis with the latter being associated with tumor cell transformation and proliferation.

As outlined in the Clinical Pharmacology review, in men with prostatic hyperplasia or primary prostate cancer, PET imaging shows 11C-choline radioactivity accumulating rapidly within the prostate; uptake appeared to peak by five minutes following injection of the drug and the activity is retained over the subsequent 30 minute scanning period. Little uptake is observed in the bladder and rectum.

Following intravenous administration, 11C-choline undergoes metabolism resulting in the detection of 11C-betaine as the major metabolite in blood. 11C-choline distributes mainly to the pancreas, kidneys, liver, spleen and colon. Based upon the relatively low urinary excretion of radioactivity, renal distribution is predominantly to the organ itself, rather than via formation of urine. Urinary excretion of 11C-choline was < 2% of the injected radioactivity at 1.5 hours after injection of the drug.

6. Clinical Microbiology

C11 Choline is not an antibiotic.

7. Clinical/Statistical- Efficacy

The applicant has relied on two sources of information for demonstrating the clinical efficacy of C11 Choline: a retrospective review of clinical experience at Mayo and a systematic literature review. None of the cited studies were designed to address the use of this imaging drug in patients with negative conventional imaging however most if not all were the studies of patients with biochemical recurrence of prostate cancer. FDA reviewers then analyzed the provided data to explore the effectiveness of C11 Choline in localizing the sites of recurrence in patients where other imaging tests were unrevealing.

The clinical reviewer reviewed the Mayo retrospective study as well as the eleven articles provided by the applicant based on the pre-specified criteria for systematic review of published

data. No meta-analysis of these data has been performed. The reviewer also examined other studies cited in the literature. The statistical reviewer, in addition to verifying data from the main retrospective study, reviewed in more depth three out of the eleven literature based studies. These studies were prospective and used C11 (rather than F18) Choline.

The Mayo retrospective study included 176 male patients who developed biochemical recurrence (BCR) after primary treatment failure of prostate cancer. Each patient received 10-20 mCi (370-740 MBq) of C11 Choline Injection before undergoing a PET/CT. BCR for radical prostatectomy (RRP) patients was defined as at least two separate PSA measurements >0.2 ng/mL acquired 3 months apart. For patients treated with radiation therapy or primary cryoablation, BCR was defined as a PSA of nadir plus a certain value (≥ 2 ng/mL). Out of 176 patients with BCR, available imaging studies (CT, MR, and/or bone scintigraphy) were negative in 75 patients. In 35 out of these 75 patients, C11Choline PET scan (PET/CT) was also negative. Four out of these 35 were false negative as the cancer recurrence in these patients was shown on random biopsy of prostatic fossa. In the remaining 31 with negative C11 Choline PET scan, no recurrence was demonstrated although this has not been verified by histopathology or clinical follow up. In 40 out of 75 patients with negative other imaging tests, C11 Choline PET scan was positive. Out of these, 35 had shown recurrences, confirmed by histopathology in 24. Five patients were false positive. Overall, in almost half of patients with biochemical recurrence of prostate cancer and negative imaging work-up, C11 Choline PET scan was able to localize the site of cancer recurrence. To examine the validity of these imaging results one can also look at the 96 patients (out of 176) with positive conventional imaging tests. In these, 88 had positive C11 Choline PET scans and 83 out of these were found to have recurrences.

The applicant conducted a systematic review of published literature with the pre-specified data selection criteria which included prospective studies with more than 30 patients. The studies turned out to be too heterogeneous to be submitted to a meta-analysis. However, certain findings could be generalized to allow an assessment of the test's clinical benefit.

In study A [Garcia JR, et al: PET/CT with 11C- choline and 18F-FDG in patients with elevated PSA after radical treatment of a prostate cancer. *Rev Esp Med Nucl.* 2009; 28(3): 95-100], the site of recurrence (prostate, regional lymph nodes, or distant metastases) was identified by C11 Choline PET scan in 26 out of 38 patients. In 24 of these 26 patients, the recurrence was confirmed by histopathology or clinical follow up. In study B [Richter JA, et al: Dual tracer 11C-choline and FDG-PET in the diagnosis of biochemical prostate cancer relapse after radical treatment. *Mol Imaging Biol.* 2010 Apr; 12(2): 210-7], the site of cancer recurrence (local or distant) was identified by C11 Choline PET/CT in 43 out of 73 patients, all confirmed by histopathology or clinical follow up. The use of C11 Choline PET/CT was successful in identifying the site of recurrence in 15 patients with negative conventional imaging. In study C [Breeuwsma AJ, et al: Detection of local, regional, and distant recurrence in patients with PSA relapse after external-beam radiotherapy using (11) C- choline positron emission tomography. *Int J Radiat Oncol Biol Phys.* 2010; 77(1): 160-4], the site of recurrence (local, regional or distant) was identified in 57 out of 70 patients with suspected cancer recurrence following radiation, with 56 out of 57 patients having the site of recurrence confirmed by histopathology or clinical follow up. In all 10 patients who

underwent radiation therapy but had no biochemical evidence of cancer recurrence, C11Choline PET/CT was negative.

Many studies of C11 Choline PET imaging attempt to establish a relationship between the imaging results and the laboratory values for PSA. Although there is a clear general trend for higher numbers of positive scans in patients with higher PSA, the proposed cut-off values vary from study to study, usually measuring around 1.5 to 2.

8. Safety

The only safety finding consists of a single occurrence of an injection site reaction reported in the Mayo retrospective study. No adverse reactions were reported in published literature. Although a risk of radiation exposure exists like with any other radiopharmaceutical it is fairly minimal because of the very short half life of C11 radionuclide.

9. Advisory Committee Meeting

The drug has been in clinical use for some time. No Advisory Committee meeting has been planned.

10. Pediatrics

The drug is for use in adult men of older age. Pediatric waiver has been granted.

11. Other Relevant Regulatory Issues

A Good Clinical Practice (GCP) inspection was requested and conducted. Although this was a retrospective study not requiring an Institutional Review Board (IRB) approval, the verification was sought of data coming out of medical charts and being entered into the study analyses. Such verification was obtained. No inspectional issues were identified.

12. Labeling

Labeling is still being developed. Indication statement will emphasize the use of this imaging drug is a select patient population.

13. Recommendations/Risk Benefit Assessment

- This reviewer recommends approving C11 Choline produced by Mayo Clinic for use with PET or PET/CT in patients with suspected post-operative or post-radiation recurrence of prostate cancer where other, “conventional” imaging tests fail to identify a site of recurrence. Positive findings on C11Choline PET or PET/CT Scan have to be confirmed by histopathology prior to proceeding with patient management based on such findings.

- Although no prospectively designed efficacy trials have been performed by the applicant there are published reports that appear to provide substantial evidence of efficacy for a fairly narrow indication as stated above. Here lies a currently unique feature of this imaging drug in that it could be helpful in identifying the recurrence sites in the very important group of patients undergoing cancer re-staging. Of course, there is a concern about a publication bias but given the multitude of the reports such a concern is somewhat minimized. The Mayo retrospective study while limited by its retrospective nature provides additional supportive evidence of clinical benefit. Of note, most of the available information is related to local or lymph node recurrence rather than to distal metastases. Given that the risks of this drug are minimal, if any, the assessment of risk and benefit favors approval. No need for postmarketing studies is anticipated.

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ALEXANDER GOROVETS

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