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RESEARCH**

APPLICATION NUMBER:

203155Orig1s000

PHARMACOLOGY REVIEW(S)

Supervisory Pharmacologist Memo
NDA: 203-155
Drug: Choline C 11 Injection
Sponsor: Mayo Clinic PET Radiochemistry Facility

This memo to file is in respect of NDA 203-155 application for Choline C 11 Injection proposed for

(b) (4)

There were no sponsor-conducted nonclinical studies submitted with this 505(b)2 application. The Sponsor relied on data from publicly available literature for evaluating the safety of Choline C 11 Injection. Dr. Honchel conducted the Pharmacology/Toxicology primary review of the NDA. His comments and observations on the strength and limitation of these studies were consistent with those typically encountered when such studies are used to support regulatory decisions.

He noted that (b) (4) 11C-choline is present in the drug product as an impurity. He observed that (b) (4) levels were lower when described in clinical studies not performed by Mayo Clinic compared to the Mayo Clinic drug product. He concluded that there were no apparent safety concerns with the proposed dose level for the (b) (4) impurity. On this issue, he recommended to consider asking the Sponsor to lower (b) (4) impurity levels in the drug product. However, he stated that “nonclinical will defer to clinical and CMC as to whether or not the Agency should follow the proposal.”

Overall, he recommended approval from pharmacology/Toxicology perspectives. He suggested changes in the label that would reflect findings from nonclinical studies or absence of data for sections of label that are typically waived for radioactive diagnostic agents.

I concur.

Adebayo Lanionu, Ph.D.
Supervisory Pharmacologist

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/s/

ADEBAYO A LANIYONU
08/09/2012

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 203-155
Supporting document/s: 001
Applicant's letter date: December 12, 2011
CDER stamp date: December 12, 2011
Product: Choline C 11 Injection
Indication: [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
Applicant: Mayo Clinic PET Radiochemistry Facility
Review Division: Medical Imaging
Reviewer: Ronald Honchel, Ph.D.
Supervisor/Team Leader: Adebayo Lanionu, Ph.D.
Division Director: Dwaine Rieves, M.D.
Project Manager: Alberta Davis-Warren

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 203-155 are owned by Mayo Clinic or are data for which Mayo Clinic has obtained a written right of reference. Any information or data necessary for approval of NDA 203-155 that Mayo Clinic does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 203-155.

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1 Executive Summary

1.1 Introduction

Many tumors, including prostate tumors, have increased choline uptake in order to meet the demand for increased membrane phospholipid synthesis. PET imaging with choline radiolabeled with ^{11}C or ^{18}F has been reported to be capable of visualizing such tumors. In this application, the Sponsor is seeking FDA approval for the use of Choline C 11 Injection for the identification of (b) (4) prostate cancer recurrence in patients (b) (4)

1.2 Brief Discussion of Nonclinical Findings

There were no nonclinical studies submitted with this 505(b)2 application. The Sponsor is relying on data from the publicly available literature for evaluating the safety of Choline C 11 Injection. The mass dose of choline (labeled and unlabeled) will be up to 2 μg /patient. Choline is synthesized in the body. Additionally, choline is an essential nutrient and the recommended daily intake of dietary choline is 550 and 425 mg/day for men and women, respectively. (b) (4)

(b) (4) ^{11}C -choline (b) (4) and is present in the Mayo Clinic drug product as an impurity at much higher concentrations than choline. The publicly available literature in regards to the safety of intravenous (b) (4) administration is limited. However, it is noted that: 1) (b) (4); 2) the available nonclinical data suggests that the relatively low dose of (b) (4) in the Mayo clinic drug product (b) (4) is unlikely to be toxic; and 3) (b) (4)

The relatively small mass dose of choline in Choline C 11 Injection is safe from a nonclinical perspective. The limited publicly available data and the Mayo Clinic clinical data suggest that the (b) (4) impurity in the Mayo Clinic drug product is not likely to be associated with safety-related issues.

1.3 Recommendations

1.3.1 Approvability

Approval is recommended.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

Sponsor's Proposed Version:

8.1 Pregnancy

Pregnancy Category C

(b) (4) It is (b) (4) not known whether Choline C 11 Injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Choline C 11 Injection should be given to a pregnant woman only if clearly needed.

Recommended Version:

8.1 Pregnancy

Pregnancy Category C

It is not known whether Choline C 11 Injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Animal reproduction studies have not been conducted with Choline C 11 Injection. All radiopharmaceutical, including Choline C 11 Injection, have a potential to cause fetal harm. The likelihood of fetal harm depends on the stage of fetal development and the magnitude of the radiopharmaceutical dose. Assess pregnancy status before administering Choline C 11 Injection to a female of child bearing potential.

Sponsor's Proposed Version:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility



Recommended Version:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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.

2 Drug Information

2.1 Drug

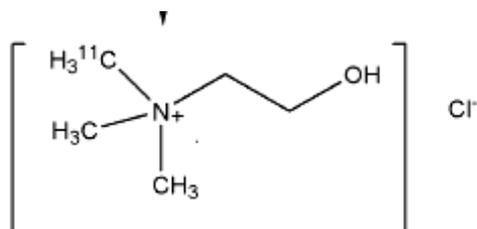
Generic Name: N/A

Code Name: N/A

Chemical Name: N-Methyl ^{11}C Choline Chloride

Molecular Formula/Molecular Weight: $[\text{C}_5\text{H}_{14}\text{NO}] \cdot \text{Cl}^- / 139.63$

Structure:



Pharmacologic Class: Radioactive Diagnostic Agent

2.2 Relevant INDs, NDAs, BLAs and DMFs

None.

2.3 Drug Formulation

Sterile saline solution

2.4 Comments on Novel Excipients

None.

2.5 Comments on Impurities/Degradants of Concern

See the Integrated Summary section.

2.6 Proposed Clinical Population and Dosing Regimen

A single intravenous dose of 10-20 mCi ^{11}C choline chloride (up to 2 μg mass dose of combined labeled and unlabeled choline) will be administered to patients in order to identify (b) (4) prostate cancer recurrence in

patients

(b) (4)

2.7 Regulatory Background

Choline PET has not previously been approved. The Sponsor did not submit an IND prior to conducting clinical studies.

3 Studies Submitted

3.1 Studies Reviewed

The Sponsor did not submit nonclinical study reports.

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

None.

4 Pharmacology

Pharmacology study reports were not submitted.

5 Pharmacokinetics/ADME/Toxicokinetics

PK/ADME/TK study reports were not submitted.

6 General Toxicology

Toxicology study reports were not submitted.

7 Genetic Toxicology

Genetic toxicology study reports were not submitted.

8 Carcinogenicity

Carcinogenicity study reports were not submitted.

9 Reproductive and Developmental Toxicology

Reproductive and developmental toxicology studies were not submitted.

10 Special Toxicology Studies

Special toxicology studies were not submitted.

11 Integrated Summary and Safety Evaluation

PET imaging with FDG is not considered useful for the detection of original and recurrent prostate cancer at the organ site due to a number of reasons including that the urinary excretion of FDG interferes with imaging tumors of the pelvis. Choline (trimethylethanolamine) is an essential nutrient that plays important roles in cell membrane structural integrity, methylmetabolism, cholinergic neurotransmission, transmembrane signaling, and lipid/cholesterol transport and metabolism. Many tumors, including prostate tumors, have increased choline uptake in order to meet the demand for increased membrane phospholipid synthesis and PET imaging with choline radiolabeled with ^{11}C or ^{18}F has been reported to be capable visualizing such tumors. The proposed indication for this application is for the (b) (4)



There were no nonclinical studies submitted with this 505(b)2 application. The Sponsor is relying on data from publicly available literature for evaluating the safety of Choline C 11 Injection.

GLP safety pharmacology studies have not been reported on choline. The Sponsor cited single-dose studies in mouse, rabbit and cat. However, these studies were not adequately designed to evaluate safety pharmacology based on current guidelines. Marked effects on blood pressure and respiration along with copious salivation and tears were noted in rabbit following the intravenous administration of 100 or 300 $\mu\text{mole/kg}$ (~10 and 31 mg/kg, respectively) choline (Gardiner & Gwee, 1974). Marked effects on blood pressure and respiration were also noted in cats following the intravenous administration of 100, but not 10, $\mu\text{mole/kg}$ choline (Gardiner & Patton, 1972). These results suggest that intravenous injection of choline at high enough doses would likely produce cholinergic-like cardiovascular and respiratory effects in humans. However, there are no safety pharmacology concerns for the choline dose levels in Choline C 11 Injection.

Tissue uptake is rapid after intravenous administration of ^{11}C choline (the plasma half-life is minutes) with the highest uptake observed in the kidney and liver with tissue radioactivity constant (taking into account decay) between 5 and 40 min after injection (Comar et al., 1976). Choline is readily transported across the blood:brain barrier. Once choline enters a cell it is immediately phosphorylated by choline kinase to phosphocholine or irreversibly oxidized to betaine in some cell types such as hepatocytes (Li & Vance, 2008; Zeisel et al., 2003). Phosphocholine then can be used to reversibly synthesize other membrane phospholipids. Betaine is the major methyl donor for synthesis of methionine from homocysteine. Choline can also be converted to acetylcholine.

Adequate GLP intravenous toxicology studies have not been performed using choline. No deaths (the only parameter evaluated) were observed following intravenous administration of 1 mg/kg choline to 4 mice (DeGrado et al., 2001).

In non-GLP studies, choline chloride was not genotoxic in the Ames assay or the Chinese Hamster Ovary Cell Chromosomal aberration assay (results cited in United Nations Environment Programme Publication. ID: 67-48-1, October 19-22, 2004). In addition to not being GLP, the adequacy of the studies in regards to meeting current OECD guidelines is questionable. Since choline is an essential nutrient that will be administered as a very low single (or infrequent) dose, GLP genotoxicity as well as carcinogenicity studies are not required.

Numerous studies have suggested that choline is essential for the mother and fetus during pregnancy and that choline supplementation may be beneficial to both. The FDA requires that infant milk not made using cow's milk be supplemented with choline. Thus nonclinical reproductive toxicology studies are not required for choline due to the reasons cited above plus the relatively low dose of choline that will be administered. There is the standard risk for injecting any radiolabel product during pregnancy; however, this risk is not relevant for the indicated patient population (prostate cancer patients). Adequate nonclinical studies evaluating the effects of choline on fertility have not been performed. However, choline is widely used as an animal dietary supplement with no apparent adverse effects on fertility reported (results cited in United Nations Environment Programme Publication. ID: 67-48-1, October 19-22, 2004).

The mass dose of choline (labeled and unlabeled) will be up to 2 µg/patient. Choline is synthesized in the body. Additionally, choline is an essential nutrient. The recommended daily intake of dietary choline is 550 and 425 mg/day for men and women, respectively. Therefore, the relatively small mass dose of choline in Choline C 11 Injection is safe from a nonclinical perspective.

(b) (4) ¹¹C-choline (b) (4) and is present in the drug product as an impurity. In Section 3.2.P.5.1 of the application, the acceptance criteria for (b) (4) in the drug product is (b) (4). Theoretically the Mayo Clinic drug product could contain up to (b) (4). In the limited batch data provided, (b) (4) levels ranged from (b) (4).

The publicly available literature in regards to the safety of intravenous (b) (4) administration is limited. (b) (4) was nominated by the (b) (4) for toxicological characterization and a review of the toxicological literature on (b) (4) was submitted. The review was prepared by a (b) (4) and can be found at (b) (4). Unless otherwise indicated, the information below was cited in (b) (4) review.

(b) (4). Regardless of route of administration, (b) (4) is rapidly transported to the liver where it is primarily metabolized into (b) (4). A small percentage of (b) (4) was (b) (4) and excreted in the urine in rats intravenously administered (b) (4). In a study designed to evaluate whether pretreatment with (b) (4) affects (b) (4), there were no deaths or evidence of liver injury in rats administered via intravenous infusion (b) (4). Intravenous administration of (b) (4) induced a transient hypotension in cats. (b) (4) was not genotoxic in the Ames test, a number of *in vitro* cytogenetic assays, and the *in vivo* (i.p. route of administration) micronucleus assay. Nonclinical studies suggest that (b) (4) exposure to the eyes, skin, and mucous membranes is likely extremely irritating. Adequate reproductive toxicology studies have not been performed on (b) (4). However, there is literature to suggest (b) (4) is potentially capable of producing developmental abnormalities, probably via choline uptake inhibition.

Adequate GLP studies for assessing (b) (4) toxicity could not be identified in the publicly available literature. However, it is noted that: 1) (b) (4) 2) the nonclinical data suggests that the relatively low dose of (b) (4) in the Mayo clinic drug product (b) (4) is unlikely to be toxic: and 3) (b) (4)

Although one cannot fully assess the safety of the (b) (4) impurity in the Mayo Clinic drug product from a nonclinical perspective, overall the application is still approvable based on the nonclinical literature review and the Mayo Clinic clinical data suggesting that (b) (4) at such relatively low doses is not toxic.

Two interesting (b) (4) findings were identified while researching the publicly available literature. (b) (4) levels when described in clinical studies not performed by Mayo Clinic were much lower (i.e. (b) (4) levels typically similar to or lower than choline levels) for their ¹¹C-choline drug product compared to the Mayo Clinic drug product (examples include (b) (4)). The other finding was that (b) (4) is an inhibitor of choline uptake (via competitive transporter binding). The Review Team was made aware of the above findings at the March 6, 2012 midcycle meeting. Although there is no apparent safety concern with the proposed dose level for the (b) (4) impurity from a nonclinical perspective, the Mayo Clinic drug product is different (b) (4) in regards to the (b) (4) impurity compared to non-Mayo Clinic drug product and it was recommended at the midcycle meeting to consider evaluating the Mayo Clinic data as "stand alone" data and the non-Mayo ¹¹C-choline data as "ancillary". It was also recommended to consider asking the Sponsor to lower (b) (4) impurity levels in the drug product. However, nonclinical will defer to clinical and CMC as to whether or not the Agency should follow the proposed recommendations.

12 Appendix/Attachments

REFERENCES

[REDACTED] (b) (4)

Comar D, Catron JC, Maziere M, Marazano C. Labeling and metabolism of methionine-methyl-¹¹C. *Eur J Nucl Med* 1:11-14, 1976.

DeGardo TR, Baldwin SW, Wang W, et al. Synthesis and evaluation of ¹⁸F-Labeled Choline Analogs as Oncologic PET Tracers. *J Nucl Med* 42:1805-14, 2001.

Gardiner JE, Patton WDM. The control of plasma choline concentration in the cat. *J Physiol* 227:71-86, 1972.

Gardiner JE, Gwee MCE. The distribution in the rabbit of choline administered by infusion or injection. *J Physiol* 239:459-76, 1974.

Hara T, Kosaka N, Shinoura N, and Kondo T. PET imaging of brain tumor with [methyl-¹¹C]choline. *J Nucl Med* 38:842-7, 1997.

Li Z, Vance D. Phosphatidylcholine and choline homeostasis. *J Lipid Res* 49:1187-94, 2008.

[REDACTED] (b) (4)

[REDACTED] (b) (4)

Zeisel S, Mar MH, Howe J, Holden J. Concentrations of choline-containing compounds and betaine in common foods. *J Nutr* 133:1302-1307, 2003.

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/s/

RONALD HONCHEL
03/20/2012

ADEBAYO A LANIYONU
03/20/2012

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 203-155

Applicant: Mayo Clinic PET
Radiochemistry Facility

Stamp Date: December 12,
2011

Drug Name: [11C] Choline
Injection

NDA Type: 505(b)2

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

| | Content Parameter | Yes | No | Comment |
|---|--|-----|----|--|
| 1 | Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin? | | | N/A. As a 505(b)2 application the Sponsor is relying on publically available literature (which they have provided) and previous findings by FDA that injection of [11C] Choline is safe and effective. |
| 2 | Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin? | | | N/A (see above). |
| 3 | Is the pharmacology/toxicology section legible so that substantive review can begin? | | | N/A (see above). |
| 4 | Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)? | X | | |
| 5 | If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA). | | | N/A. |
| 6 | Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route? | | | N/A. |
| 7 | Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations? | | | N/A. |
| 8 | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions? | | | N/A. |

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

| | Content Parameter | Yes | No | Comment |
|----|---|------------|-----------|---|
| 9 | Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57? | | X | The nonclinical portion of the labeling requires minor editing. |
| 10 | Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.) | | X | Information on potential impurities was not provided in the submission. Nonclinical will be relying on CMC to identify any potential impurity issues. |
| 11 | Has the applicant addressed any abuse potential issues in the submission? | | | N/A. |
| 12 | If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted? | | | N/A. |

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology 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.

Reviewing Pharmacologist

Date

Team Leader/Supervisor

Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

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/s/

RONALD HONCHEL
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