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APPLICATION NUMBER:

203155Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

NDA: 203-155

Type/Category: New NDA, Original-1 (Type 1- New Molecular Entity), 1P

Brand name: Choline C 11 Injection

Generic name: Choline C 11 Injection

Proposed indication: Choline C 11 Injection is a radioactive diagnostic agent for positron emission tomography (PET) for (b) (4)
(b) (4) recurrence of prostate cancer in patients (b) (4)
(b) (4)
(b) (4)
(b) (4)

Formulation: Single dose glass vial containing between 40 mCi to 331 mCi (1.48 GBq to 12.247 GBq) of C 11 choline in aqueous 0.9% sodium chloride solution in approximately 10 mL volume

Route of Administration: Intravenous

Applicant: Joseph C. Hung, Ph.D., Mayo Clinic PET Radiochemistry Facility

Reviewing Division: Division of Clinical Pharmacology V (DCP 5)

Medical Division: Division of Medical Imaging Products (DMIP)

Submission Dates: December 12, 2011, SDN 1
February 23, 2012, SDN 5
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Primary Reviewer: Christy S. John, Ph.D.

Secondary Reviewer: Gene Williams, Ph.D.

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1. Executive Summary

The applicant, Joseph C. Hung, Ph.D., Mayo Clinic PET Radiochemistry Facility (Mayo, MCPRF) has submitted a 505(b)(2) new drug application NDA 203-155 for Choline C 11 Injection as a diagnostic PET (positron emission tomography) imaging agent for identification of (b) (4) recurrence of prostate cancer in patients (b) (4)

(b) (4). The submission is based on literature findings and a retrospective study Mayo conducted of their experience using choline C 11 PET.

The clinical pharmacology information in this submission is from published literature; no clinical pharmacology studies were conducted by Mayo. The dose used by Mayo, 10-20 mCi (370-740 MBq), was justified based upon published literature by other investigators.

After intravenous administration, the estimated amounts of ^{11}C choline in venous plasma decreased from $100\% \pm 0\%$ of dose at 1 minute post injection to $35\% \pm 11\%$ of dose at 25 minutes after injection. The highest radiation absorbed doses were to the pancreas, kidneys, and liver. Less than 2.0% of injected radioactivity was excreted in the urine during a 1.5 hour post-dose collection period. ^{11}C betaine was the only metabolite quantitated, and constituted the majority of plasma radioactivity beginning at 10 minutes post-dosing.

A drug interaction with the anti-mitotic drug colchicine has been reported. A patient taking colchicine underwent C-11 choline PET imaging. Altered biodistribution was reported on the imaging. Similar interactions would be expected with other anti-mitotic drugs. (b) (4) (b) (4). We instead recommend that patients not receiving therapy delay initiation of therapy until after imaging, but that patients already on therapy continue with therapy prior to imaging.

Mayo does not require or recommend that patients fast prior to imaging. However, a literature report referenced in the NDA describes that imaging “soon after food intake” resulted in “the appearance of an artifact in the PET images.” No details of the type of food or timing of eating are provided in the literature report. Based on the literature results, we recommend that Choline C 11 imaging be performed in the fasted state.

Relevant *in vivo* and *in vitro* data are limited, but there is potential that drugs used to treat prostate cancer could interfere with imaging. Mayo proposes that patients not receiving therapies delay initiation of therapy until after imaging, but that patients already on therapy not have therapy washed out prior to imaging. We agree with this proposal.

1.1. Recommendations

The Office of Clinical Pharmacology, Division of Clinical Pharmacology V has reviewed the submission NDA 203-155. The application is acceptable from a clinical pharmacology standpoint, provided an agreement is reached on package insert language

1.2. Phase 4 Requirements and Commitments

We have no recommendations for post-marketing requirements or commitments.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The submission is based on literature findings and a retrospective study Mayo conducted of their experience using choline C 11 PET. Mayo has not conducted clinical pharmacology studies to support the NDA application. The dose used by Mayo, 10-20 mCi (370-740 MBq), was justified based upon published literature by other investigators.

After intravenous administration, the estimated amounts of ^{11}C choline in human plasma decreased from $100\% \pm 0\%$ of dose at 1 minute post injection to $35\% \pm 11\%$ of dose at 25 minutes after injection. The highest radiation absorbed doses were to the pancreas, kidneys, and liver. Only 2.0% of injected radioactivity was excreted in the urine during a 1.5 hour post-dose collection period. ^{11}C betaine was the only metabolite quantitated, and constituted the majority of plasma radioactivity beginning at 10 minutes post-dosing.

Colchicine has been found to impair the biodistribution of ^{18}F -methylcholine (Roef MJ, et al., Nucl. Med. Com. 2010; 31:1075-7). Based on the colchicine result, other antimitotic agents such as docetaxel and paclitaxel may also interfere with Choline C 11 imaging. (b) (4)

We instead recommend that patients not receiving therapy delay initiation of therapy until after imaging, but that patients already on therapy continue with therapy prior to imaging.

Mayo does not require or recommend that patients fast prior to imaging. However, a literature report referenced in the NDA describes that imaging “soon after food intake” resulted in “the appearance of an artifact in the PET images.” (Hara T, et al. J. Nucl. Med. 1998;39; 990-5). No details of the type of food or timing of eating are provided in the literature report. Based on the literature results, we recommend that Choline C 11 imaging be performed in the fasting state.

Data showing that choline C 11 imaging is less successful following prostate cancer therapy is available in the literature. This is an expected result – as tumor burden is reduced, imaging success is expected to decline. *In vivo* data on the effect of acute co-administration of drugs used to treat prostate cancer, i.e., data from studies designed to answer acute drug interaction questions, are not available. The limited *in vitro* data that is available was not designed to answer questions regarding acute drug interactions, and is difficult to interpret. Mayo proposes that patients not receiving therapies delay initiation of therapy until after imaging, but that patients already on therapy not have therapy washed out prior to imaging. We agree with this proposal.

2. Question Based Review

2.1. What *In Vitro* and *In Vivo* Clinical Pharmacology and Biopharmaceutics studies and Clinical Studies contributed PK and/or PD information to the application?

The Mayo Clinic Positron Emission Tomography (PET) Radiochemistry Facility (Mayo, MCPRF) has not conducted clinical pharmacology studies to support the Choline C 11 Injection NDA application. The information presented the application is drawn from a search of the literature. A total of six studies were cited that included data for choline C 11 (^{11}C -choline), ^{18}F -fluorocholine, ^{18}F -fluorodeoxyglucose, ^{18}F -fluoroacetate, or ^{11}C -acetate. Only three articles out of six had data relevant to Choline C 11 (**Table 1**). These articles contain information relevant, or potentially relevant, to the biodistribution or dosimetry of Choline C 11:

Tolvanen et al. (2010) – Compared biodistribution and dosimetry data in rats and humans (Eur. J. Nucl. Med. Mol. Imaging 2010; 37, 874-83),

Sutinen et al. (2004) – Evaluated uptake kinetics of Choline C 11 in patients with prostate cancer and BPH (Eur. J. Nuc. Med. Mol. Imaging 2004; 31, 317-24),

Kato et al. (2009) – Evaluated pattern of Choline C 11 uptake and calcification in aortic and common carotid arterial walls in patients with prostate cancer after a whole-body Choline C 11 PET/CT scan. (Eur. J. Nucl. Med. Mol. Imaging 2009; 36, 1622-28),

Hara et al. (1998) Evaluation of Choline C-11 in prostate cancer patient and food effect on imaging (J. Nucl. Med. 1998;39; 990-95),

Roivainen et al (2010) – Described the blood metabolism of C-11 choline and its implication for imaging prostate cancer (Eur. J. Nucl. Med. 2000; 27, 25-32), and

Giovacchini et al.– Reported “[^{11}C]choline uptake after bicalutamide therapy (Eur. J. Nucl. Med. Mol. Imaging 2008;35:1065–73).

Table 1. Studies with relevant choline C-11 biodistribution/dosimetry data

Reference and Location	Study Design, Description	Dose/ Dosage Form/Route	Number of Animals or Subjects/ Other Info	Results
Tolvanen et al. ¹⁴ (2010) 5.4.1	Investigational: Comparison of biodistribution and radiation dosimetry between rat and human data.	- Choline C 11 17±6 MBq (0.5±0.2 mCi) IV - Choline C 11 17±6 MBq (0.5±0.2 mCi) IV - Choline C 11 423±11 MBq (11.4±0.3mCi) IV	- 9 healthy rats (mean wt. 289 ±40 g) - 4 rats with tumors (mean wt. 340±50g). - 6 patients with RA (4M/2F; 60±10 years; wt 78±19 kg)	Distribution: - In rats: mainly to kidneys, lungs, liver, adrenal gland - In patients with RA: renal cortex, salivary glands, liver, spleen, pancreas, blood, muscle Urinary excretion: - <2% of radioactivity up to 1.5 h after injection - Rate = 0.014 mL min ⁻¹ Effective dose in humans: - 0.0044 mSv/MBq (in agreement with other [^{11}C]-labeled tracers) - Highest absorbed dose: 0.021 mGy/MBq in kidneys; 0.020 mGy/MBq in liver; 0.029 mGy/MBq in pancreas Conclusions: (1) Supports use of Choline C 11 within range of 400-500 MBq in clinical studies; (2) Distribution similar for the most part in rats and humans, except for pancreas, where tracer uptake was ~6-fold higher in humans
Sutinen et al. ¹⁶ (2004) 5.4.1	Investigational: Evaluated kinetics of [^{11}C] choline uptake in prostate cancer and BPH	- Mean dose Choline C 11 430±31 MBq (11.6±0.8 mCi) Single dose/IV	- 14 pts with prostate cancer; - 5 patients with BPH - Mean age of all pts: 66±8 yrs (range 50–84 yrs) - Mean BMI: 26.9±2.3 (range 23.5–32.0)	Methods: - ^{11}C choline standardized uptake value (SUV) measured and kinetic influx constant (K_i) obtained via graphic analysis - Tracer uptake in ROI measured using SUV (radioactive conc. in ROI/dose [corrected for body weight]) Results: - After injection, activity in plasma decreased rapidly and uptake in prostate was rapid - Activity leveled out in prostate in both cancer or BPH prostates - Cancer and BPH prostates well visualized with low to moderate accumulation in bladder and rectal wall - Activity in urine low - Mean K_i of untreated tumor = 0.205±0.089 min ⁻¹ (range 0.128–0.351; n=7); mean SUV = 5.6±3.2 (range 1.9–15.5; n=15) Conclusions: - SUVs may be difficult to compare due to differences in tracer biodistribution;

Reference and Location	Study Design, Description	Dose/ Dosage Form/Route	Number of Animals or Subjects/ Other Info	Results
				however, high correlation between K_i values and SUVs ($r=0.964$, $P=0.0005$) supports use of SUV in measuring uptake.
Kato et al. ¹⁷ (2009) 5.4.1	Retrospective review: Evaluated pattern of Choline C 11 uptake and calcification in aortic and common carotid arterial walls in patients with prostate cancer who had whole-body Choline C 11 PET/CT	Choline C 11 600±200 MBq (16.2±5.4mCi) /Single-dose /IV	93M patients/ ages 60-80 yrs (mean = 68 yrs); mean BMI 26.3 kg/m ³	Distribution and uptake kinetics: - Mean SUV max ranged 1.8 to 3.0 across 6 segments (right and left carotid arteries, thoracic ascending and descending aorta, aortic arch, and abdominal aorta) - Correspondence of radiotracer uptake and calcification was rare - Uptake of Choline C 11 in brain and myocardium lower when compared with ¹⁸ F-FDG - Elevated uptake seen in all segments of aorta and common carotid arteries - 88/93 (95%) patients showed Choline C 11 uptake in at least 1 location in aortic or common carotid arterial walls - Conclusions: - Choline C 11 may be more effective than ¹⁸ F-FDG for imaging cerebral and coronary arteries - Not clear if PET imaging of atherosclerotic plaques with Choline C 11 provides superior prognostic information compared to conventional imaging.

2.2. General Attributes of the Drug

2.2.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

The *in situ* drug product Choline C 11 Injection is produced in-house at the Mayo Clinic PET Radiochemistry Facility under current CGMP (21 CFR 212; USP <823>) guidelines. Choline C 11 Injection is supplied in a glass vial containing 4.0-33.1 mCi/mL (0.148-1.225 GBq/mL) of the drug product in aqueous 0.9% sodium chloride solution (approximately 10 mL volume). The standard dosage is 10-20 mCi (0.740 GBq). Choline C 11 Injection has a molecular weight of 139.63 g. The radionuclide C 11 has a physical half-life of 20.4 minutes. Choline C 11 Injection usually exhibits specific activity of approximately (b) (4)

injection. The reviewer estimates the mass of a 20 mCi dose as approximately one-third of a ug (310 ng). In a year 2000 report by the American Institute of Medicine, adequate daily intake of choline for an adult was 400 mg/day, and the upper limit of intake was 3500 mg/day. While those are values for oral administration, the 400 mg value is more than one million-fold 310 ng, and the 3500 mg value more than 10 million-fold 310 ng.

2.2.2. What are the proposed mechanism of action and therapeutic indications?

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 mechanism of preferential uptake of choline C 11 into tumor cells is not understood.

2.2.3. What are the proposed dosages and routes of administration?

The recommended dose is 10-20 mCi (370-740 MBq) as an intravenous injection. In the Mayo study, 10-20 mCi (370-740 MBq) of Choline C 11 was administered as a single-dose, bolus injection immediately before PET scanning, as stated in the imaging guidelines. Based on a review

of the literature included with the NDA, dose administered range from 370 MBq to 1300 MBq (10 to 35.1 mCi).

2.2.4. What drugs (substances, products) indicated for the same indication are approved in the US?

Prostascint (Indium In 111 capromab pendetide) is indicated for use in immunoscintigraphy in patients with biopsy-proven prostate carcinoma who are at high risk for pelvic lymph node metastases. Prostascint is also indicated in patients who have undergone a prostatectomy and have rising prostate-specific antigen (PSA) values and equivocal or no evidence of metastatic disease on standard metastatic evaluation, but in whom there is a high clinical suspicion of occult metastatic disease.

2.3. General Clinical Pharmacology

2.3.1. What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

No clinical pharmacology studies were designed by the sponsor to support the dosing claim. The dose selected by Mayo was based on literature reports of what dose gives optimal PET images.

2.3.2. What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Study endpoints in the study by Mayo included sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and “clinical usefulness.” Studies in the literature were designed to determine the accuracy of imaging with 11 C choline for the detection of prostate cancer.

A PET scan was considered a “true positive” if any of the following were shown:

- histologic confirmation by targeted biopsy or surgical resection,
- confirmation by conventional imaging, or
- a decrease in 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.

2.3.3. Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The active moieties in plasma and clinically relevant tissues were not identified and measured to assess pharmacokinetic parameters and no exposure-response relationship was studied. Only one dose was used for clinical studies.

2.4. Exposure-Response

2.4.1. What are the characteristics of the exposure-response relationship for effectiveness?

2.4.2. What are the characteristics of the exposure-response relationships for safety?

No exposure-response relationships were reported for this single administration drug given as a microdose for imaging.

2.4.3. Does this drug prolong QT/QTc Interval?

Regarding their own experience, Mayo writes,

One patient with an injection-site reaction.

No other safety findings noted.

The NDA's integrated summary of safety (ISS) includes thirteen literature studies. For twelve of the studies Mayo writes,

No pre-specified safety endpoints were identified in the study.

Mayo Clinic reviewed the publication for safety data (adverse event documentation, clinical laboratory parameters, vital signs, and physical examinations, and ECG findings) and none was found.

For the thirteenth study, Mayo writes,

No pre-specified safety endpoints were identified in the study.

Mayo Clinic reviewed the publication for safety data; reported that no adverse events were observed in any of the patients after administration of 18 F Choline

Choline is a circulating endogenous substance, and Choline C 11 Injection is administered once as a microdose. There is no expectation that Choline C 11 dosing will alter QT-interval and the reviewer finds the lack of rigorous assessment of the effect of dosing on QT-interval acceptable.

2.4.4. Is the dose and dosing regimen selected consistent with the known E-R relationship?

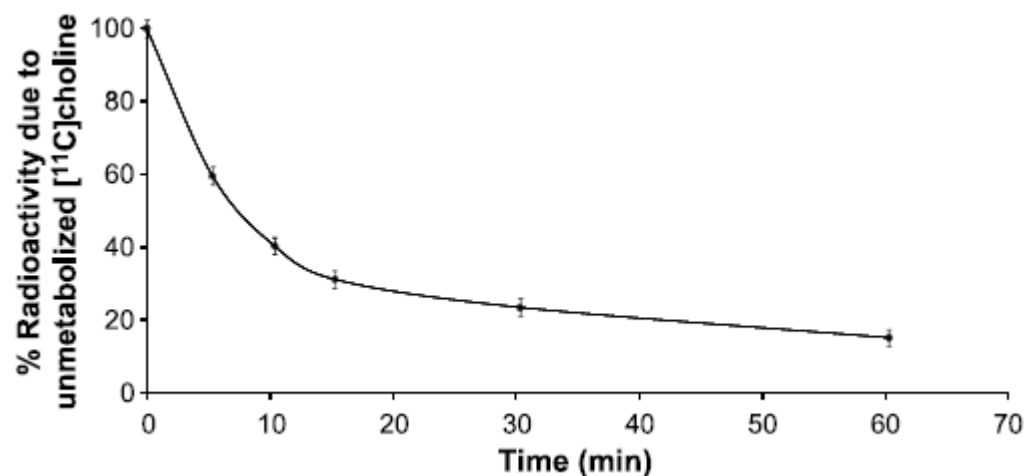
No exposure-response relationship was determined for this single administration drug given as a microdose.

2.5. Pharmacokinetics

2.5.1. What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

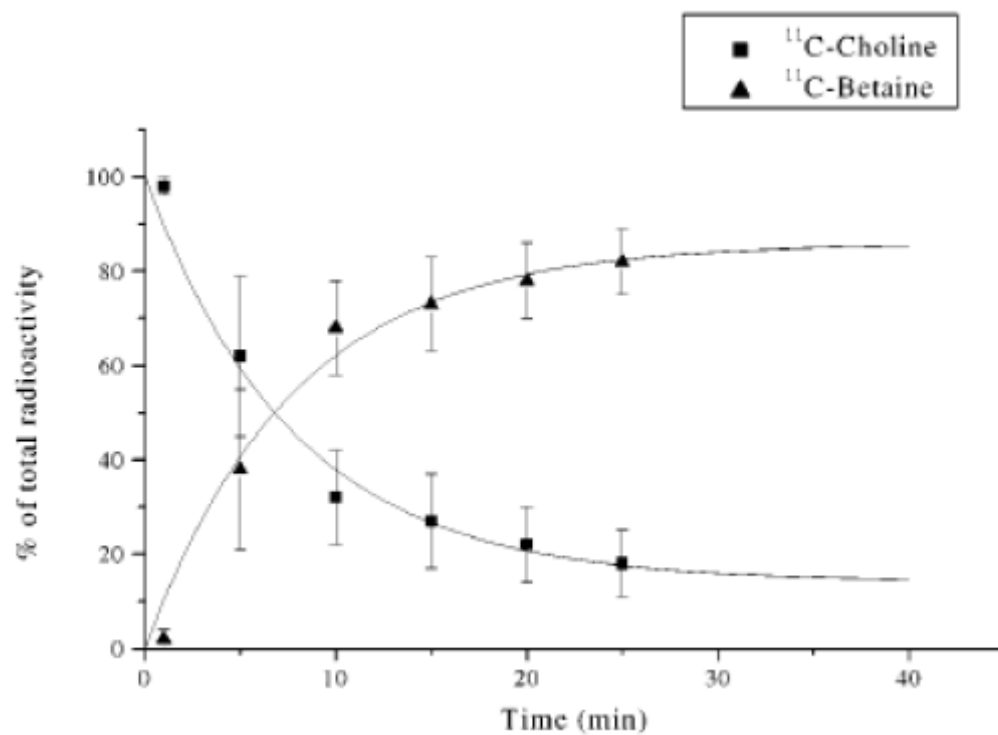
In a study to quantify the arterial plasma input function, arterial plasma samples were collected from 20 patients diagnosed with breast cancer after a single intravenous (IV) bolus injection of choline C 11 [Kenny LM, et al. Reproducibility of [C 11]choline- positron emission tomography and effect of trastuzumab. *Clin Cancer Res.* 2010;16;4236-45]. The target dose for radioactivity was 10.0 mCi (370 MBq = 1.036 mSv) for each scan. Analysis of metabolites showed that the fraction of radioactivity in plasma due to choline C 11 decreased rapidly after injection such that at 60 minutes, the mean ($\pm$ SE) radioactivity fraction in arterial plasma due to choline C 11 was 15.15 $\pm$ 2.17% (range 7.98-41.99%). **Figure 1.** shows the decline of parent choline C 11 relative to total C 11 over time.

Figure 1. Decline of choline C 11 (parent drug) relative to total C 11 over time



C 11 betaine was the only metabolite reported in human plasma. The time courses of plasma concentrations of ^{11}C -choline and ^{11}C -betaine are shown in **Figure 2**. (Roivainen A et al. Eur. J. Nucl. Med. 2000; 27, 25-32).

Figure 2. Plasma concentrations of ^{11}C -choline and ^{11}C -betaine versus time



2.5.2. How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

PK of the drug and its relevant metabolites were not reported for healthy adults.

2.5.3. What are the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

Only limited concentration-time data were reported (see 2.5.1.). The inter- and intra-subject variability of the PK parameters in volunteers and patients with target disease were not reported.

2.5.4. What are the characteristics of drug absorption?

Choline C 11 is administered as a single-time intravenous injection. The characteristics of drug absorption from alternate routes are not reported.

2.5.5. What are the characteristics of drug distribution?

The highest absorbed doses were found in 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). The effective dose in a human adult of about 70 kg was 0.0044 mSv/MBq, which is equivalent to 2.0 mSv from 460 MBq of [¹¹C] choline (Tolvanen T. et al, Eur. J. Nucl. Med. Mol. Imaging 2010; 37, 874-83). There was additional literature report on dosimetry using ¹⁸F-fluorocholine (DeGrado T. et al. J. Nucl. Med. 2002, 43; 92-96), however this data is not directly relevant (fluorocholine is a different molecular entity than C 11 choline). Plasma protein binding of C 11 choline or its ¹¹C metabolites has not been reported, presumably because it has not been investigated.

2.5.6. Does the mass balance study suggest renal or hepatic as the major route of elimination?

Mass balance study results are not reported.

2.5.7. What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?

2.5.8. What are the characteristics of drug metabolism?

In vitro investigation of drug metabolism is not reported. The metabolite betaine was quantitated in plasma samples (see **Figure 2.** for concentration-time data), further profiling of plasma moieties is not reported. **Figure 1.** shows the decline of choline C 11 (parent drug) relative to total C 11 over time

2.5.9. Is there evidence for excretion of parent drug and/or metabolites into bile?

There is not evidence for excretion of parent drug and/or metabolites into bile, but studies examining excretion into bile or feces are not reported.

2.5.10. Is there evidence for enterohepatic recirculation for parent and/or metabolites?

There is not evidence for enterohepatic recirculation for parent and/or metabolites, but only limited concentration-time data are reported, and data following non-IV administration is not reported.

2.5.11. What are the characteristics of drug excretion in urine?

In one literature report (Sutinen, et al. Eur. J. Nuc. Med. Mol Imaging 2004; 31, 317-24) the measured radioactivity in voided urine was low, $0.6\% \pm 0.3\%$ of injected activity after 60 min post-injection. In a second report, less than 2.0% of injected radioactivity was excreted in the urine over the 1.5 hour period of data collection (Tolvanen T et al, Eur. J. Nucl. Med. Mol. Imaging 2010; 37, 874-83).

2.5.12. Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Dose proportionality results are not reported.

2.5.13. How do the PK parameters change with time following chronic dosing?

Choline C 11 is administered only one time for diagnostic imaging. Repeat dosing results are not reported.

2.5.14. Is there evidence for a circadian rhythm of the PK?

There is not evidence for a circadian rhythm of the PK, but only limited concentration-time data are reported, and data are not reported by time-of-day.

2.6. Intrinsic Factors

2.6.1. What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, C_{max}, C_{min}) in patients with the target disease and how much of the variability is explained by the identified covariates?

The inter-subject variability in exposure (AUC, C_{max}, C_{min}) is not reported.

2.6.2. Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

2.6.2.1. Severity of Disease State

No exposure-response relationships were reported for this single administration drug given as a microdose for imaging.

The correlation between imaging results (positive or negative scan) and PSA concentrations (a potential biomarker for severity of disease) was analyzed by the applicant at the request of medical reviewer. Entry to the study from which the analysis was performed required meeting one of the

following three criteria.

- 1) documented biochemical recurrence (BCR), defined as at least 2 separate prostate-specific antigen (PSA) measurements acquired 3 months apart for patients who had received radical prostatectomy (RP),
- 2) PSA nadir plus 2 ng/mL for patients treated with radiation or primary cryoablation, or
- 3) a steady rise in PSA for men treated with primary ADT.

The results of the applicant's analysis are shown in **Table 2**. High correlation would be demonstrated if the percentage values within each cell of the table increased (or decreased) greatly by row. This does not occur; the results show that imaging outcomes do not correlate highly with PSA concentrations.

Table 2. Correlation of PSA to imaging outcome

Left most column is PSA Concentration (ng/ml)

	Total n=75	Pos PET N=40	Neg PET N=35
Tercile (ng/ml):			
0.0 - 1.4	25 (33.3%)	6 (15.0%)	19 (54.3%)
1.4 - 4.5	26 (34.7%)	17 (42.5%)	9 (25.7%)
> 4.5	24 (32.0%)	17 (42.5%)	7 (20.0%)
Quartile (ng/ml):			
0.0 - 1.1	20 (26.7%)	4 (10.0%)	16 (45.7%)
1.1 - 3.0	18 (24.0%)	8 (20.0%)	10 (28.6%)
3.0 - 6.1	19 (25.3%)	15 (37.5%)	4 (11.4%)
> 6.1	18 (24.0%)	13 (32.5%)	5 (14.3%)
Quintile (ng/ml):			
0.00 - 0.94	15 (20%)	2 (5.0%)	13 (37.1%)
0.94 - 1.75	15 (20%)	7 (17.5%)	8 (22.9%)
1.75 - 4.05	15 (20%)	8 (20.0%)	7 (20.0%)
4.05 - 7.00	15 (20%)	12 (30.0%)	3 (8.6%)
> 7.00	15 (20%)	11 (27.5%)	4 (11.4%)

2.6.2.2. Body Weight

The effect of body weight on imaging or PK is not reported. In the study conducted by Mayo, body weight was not recorded on the data collection form. Body weight was also not consistently reported in the literature reports submitted.

2.6.2.3. Elderly

The effect of age on imaging or PK is not reported. In the study conducted by the Mayo Clinic, of the 176 men, the mean ($\pm$ SD) age was 60.6 ($\pm$ 7) years, with a range from 42 to 78 years.

2.6.2.4. Pediatric Patients

Data from pediatric patients are not reported. A pediatric waiver was granted for the NDA

2.6.2.5. Race/Ethnicity

The effect of race/ethnicity on imaging or PK is not reported.

2.6.2.6. Renal Impairment

The effect of renal impairment on imaging or PK is not reported.

2.6.2.7. Hepatic Impairment

The effect of hepatic impairment on imaging or PK is not reported.

2.6.2.8. What pregnancy and lactation use information is available?

No pregnancy or lactation use information is available.

2.6.3. Does genetic variation impact exposure and/or response?

The effect of genetic variation impact on exposure and/or response is not reported.

2.7. Extrinsic Factors

2.7.1. Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

In vitro investigation of drug metabolism is not reported. The mass dose is approximately 30 ug – dosing is unlikely to perpetrate drug interactions.

2.7.2. Is the drug a substrate of CYP enzymes?

In vitro investigation of drug metabolism is not reported.

2.7.3. Is the drug an inhibitor and/or an inducer of enzymes?

2.7.4. Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

In vitro investigation of drug metabolism is not reported. The mass dose is approximately 30 ug – dosing is unlikely to perpetrate drug interactions.

2.7.5. Are there other metabolic/transporter pathways that may be important?

Choline transporters are present at the blood-brain barrier, in the central nervous system, and in the breast. The reviewer judges that the presence of transporters is unlikely to alter imaging success for prostate cancer or safety.

2.7.6. What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

The effect of extrinsic factors influence on exposure and/or response is not reported.

2.7.7. What are the drug-drug interactions?

The first paragraph of section 7 **DRUG INTERACTIONS** of the proposed package insert is reproduced (indented)

(b) (4)

The basis for the colchicine language is a literature report (Roef MJ, et al., Nucl. Med. Com. 2010;31:1075-7). During the review process we made an information request to Mayo regarding the paper. Our request and Mayo's response are reproduced (indented).

FDA Request:

We did not find any references to drug-drug interaction for [11-C]Choline except for colchicine (Roef MJ, et al., Nucl Med Com. 2010;31:1075-7) . The authors of this article discuss that other antimitotic therapies using agents such as paclitaxel or docetaxel may also produce compromised [11-C]choline PET images. Do you agree with this conclusion? If not, please explain.

Mayo's Response:

We agree. It is reasonable that any antimitotic therapeutic agent to which a particular patient's prostate cancer is sensitive would reduce the uptake of choline as the normal uptake pathways for cell membrane synthesis, lipid metabolism, and other cellular processes using choline would likely be suppressed.

Based on the paper and after consideration of Mayo's response, we have extended the colchicine recommendation to include the class "antimitotic agents." However, we have changed the recommendation from (b) (4) to "neither initiate nor discontinue" (see **3. Detailed Labeling Recommendations**). A short delay in initiation of therapy to improve imaging seems reasonable to us, but discontinuing an ongoing (presumably efficacious) therapy for the purpose of obtaining a choline C 11 image does not.

The second paragraph of section 7 **DRUG INTERACTIONS** of the proposed package insert is reproduced (indented)

(b) (4)

During the review process we made an information request to Mayo regarding the use of hormonal therapy and anti-androgens. Our request and Mayo's response are reproduced (indented).

FDA Request:

In addition to colchicine, NDA section 2.7.2.3.7 Drug-Drug Interaction Studies identifies a number of other potential interactions. Please provide references in support of these drug-drug interactions.

Mayo's Response:

The drugs described in this section do not encompass drugs associated with a classic drug-drug interaction. The drugs listed in Section 2.7.2.3.7 will likely modulate tumor cell metabolism in such a way that they could alter the performance of scanning with Choline C 11 PET, but it is not known, nor do we suspect that they pose a safety risk in terms of drug potentiation, etc., when used with Choline C 11 Injection. As such, the hormone drug sensitivity of prostate tumors to be imaged with Choline C 11 PET must always be considered.

All the drugs listed in Section 2.7.2.3.7 could likely compromise choline uptake, as cancer cells are either down-regulated or killed. We know of no literature references that document that all of these drugs (Section 5.4) suppress choline uptake. However, some limited literature does exist for a few of these drugs.

Consistent with the ability of these drugs to inhibit choline uptake in patients with hormone sensitive cancers, change in SUV values after bicalutamide therapy and in an article by Giovacchini et al. (Eur. J. Nucl. Med. Mol. Imaging 2008;35:1065–73), the authors report that “[¹¹C]choline uptake after bicalutamide therapy significantly ($P < 0.05$) decreased compared to baseline (6.4 ± 4.6 SUV and 11.8 ± 5.3 SUV, respectively).” Animal prostate cancer xenograft model and prostate cancer in vitro cell work both support the suppression of choline uptake by using docetaxel and/or bicalutamide.

On the basis of these data, we believe that there is a high likelihood that the concomitant use of these or the other drugs in the list could affect choline uptake by prostate cancer. We do not intend to infer that patients who have ever been exposed to these drugs are at risk for reduction of Choline C 11 uptake but that only those currently on the drugs may be at risk of alteration of the scan findings if their tumor is sensitive to the particular drug used.

Following the above response, FDA made an additional information request. Our request and Mayo's response are reproduced (indented).

FDA Request:

We note that you propose to (b) (4). The instructions regarding hormonal therapies are not similarly specific -- no time frame for "avoid" is given. Was there consistency in the length of time (prior to imaging) for discontinuation of hormonal therapies? If there was not consistency, how was the timing of pre-dose discontinuation determined, and do you have data on each patient's concomitant hormonal therapy and timing of discontinuation?

Mayo's Response:

MCPRF does not recommend that hormone therapies be stopped pre-imaging for the following two reasons:

For patients who are not on hormone therapy and who are about to be evaluated for recurrent prostate cancer due to rising PSA, our recommendation is that these patients should not start hormone therapy prior to Choline C 11 PET/CT evaluation. For patients who are currently on hormone therapy and, despite this, are experiencing rising PSA (due to emergence of hormone-refractory prostate cancer), our recommendation is that these patients should be imaged without need for stopping ongoing hormone therapy treatment.

The instructions regarding "hormonal therapy" agents as stated in our proposed labeling are in line with the rationales as described above.

After consideration of Mayo's responses, we have made modifications to improve the clarity of the package insert language (see **3. Detailed Labeling Recommendations**).

2.7.8. Does the label specify co-administration of another drug?

The package insert does not specify co-administration of another drug.

2.7.9. What other co-medications are likely to be administered to the target population?

As noted above (2.7.7.), and addressed in the package insert, many prostate cancer patients are on hormonal therapy and anti-androgens.

2.7.10. Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

No mechanistic basis for PD drug-drug interactions is reported. Due to the low dose, 1) (approximately 310 ng), choline is unlikely to perpetrate PD interactions, and 2) the drug is unlikely to have non-imaging PD effects.

2.8 General Biopharmaceutics

2.8.1. Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

2.8.2. How is the proposed to-be-marketed formulation linked to the clinical service formulation?

2.8.2.1. What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

2.8.2.2. If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?

Choline C 11 is an intravenously administered simple aqueous solution, the above biopharmaceutics questions are not applicable.

2.8.3. What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

Choline C 11 is administered intravenously, so bioavailability to the systemic circulation is not an issue. However, there is potential that ingestion of food could contribute choline to the systemic circulation and thus interfere with imaging. During the review process we made an information request to Mayo regarding food effect. Our request and Mayo's response are reproduced (indented).

FDA Request:

Can it readily be ruled out that a meal rich in choline, or other lipids that are constituents of cell membranes, would alter image quality? At your institution, is imaging always performed in a fasted state?

Mayo's Response:

While theoretically possible, we do not think that a meal rich in choline, or other lipids that are constituents of cell membranes, would alter image quality. In fact, we think that the prevalence of choline in common foods along with the body's apparent ability to maintain relatively steady-state choline plasma levels makes it unlikely that a meal rich in choline would alter the quality of the PET image after a Choline C 11 injection. We theorize that this is because the human body apparently attempts to maintain a constant supply of choline and that to do this it can store/synthesize choline for some time if choline is plentiful or if choline is not in the diet. Notably, in Section 2.7.2.3.5 we describe a study where an extreme 7-day fast only minimally reduced plasma levels of choline.

We also described in Section 2.7.2.1.1 results from a study that used an extreme constant 12-hour infusion protocol with hyper-elevated IV choline administration showed that only a doubling of plasma choline [sic]. These data are interesting in that the plasma changes appear muted with respect to the protocols and we think this supports the idea of body maintenance of plasma steady state levels. We think that any choline-rich foods patients would eat or a short fast prior to PET imaging would have little chance of changing choline plasma levels significantly or affecting Choline C 11 uptake. We have no rigorous data to support this; however, the experience at the Mayo Clinic PET imaging facility is that without any patient fasting or instruction on avoiding choline-rich foods, PET scan quality has been consistent with other data in the literature and with our other tumor imaging drugs used for PET imaging. We therefore do not request fasting nor do the patients undergoing Choline C 11 scans receive instruction on avoiding foods high in choline.

Subsequent to making the information request and receiving Mayo's response, the reviewer noted a literature report referenced in the NDA that described an effect of food on choline C 11 imaging (T. Hara, et al. J. Nucl. Med. 1998;39: 990-95). The authors report that if choline C 11 PET was performed "soon after food intake", the radioactivity incorporated into the pancreas came into pancreatic juice and then migrated into small intestines. The result was the "appearance of an artifact in the PET images." No details of the type of food or timing of eating are provided. Based on these results, we recommend that Choline C 11 imaging should be performed in the fasted state (see **3. Detailed Labeling Recommendations**).

2.8.4. Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were they bioequivalent or not?

2.8.5. If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?

Choline C 11 is an intravenously administered simple aqueous solution, the above biopharmaceutics questions are not applicable.

2.9. Analytical Section

2.9.1. How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

2.9.2. Which metabolites have been selected for analysis and why?

2.9.3. For all moieties measured, is free, bound, or total measured?

2.9.4. What bioanalytical methods are used to assess concentrations of the measured moieties?

2.9.5. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

2.9.5.1. What are the lower and upper limits of quantitation?

2.9.5.2. What are the accuracy, precision, and selectivity at these limits?

2.9.5.3. What is the sample stability under conditions used in the study?

2.9.5.4. What is the plan for the QC samples and for the reanalysis of the incurred samples?

The clinical pharmacology section of this application is based exclusively on literature references, Mayo performed no PK. We have no details of the analytical methods used. The reviewer finds the lack of assay validation acceptable for the current NDA, as the pharmacokinetics data has limited impact on dosing and the package insert.

3. Detailed Labeling Recommendations

The reviewer's recommendations for changes to sections **HIGHLIGHTS OF PRESCRIBING INFORMATION**, **2 DOSAGE AND ADMINISTRATION**, **7 DRUG INTERACTIONS**, and **12 CLINICAL PHARMACOLOGY** of Mayo's proposed package insert begin on the next page as "track changes." Copy-pasting this from Mayo's hyperlinked original, followed by the deleting of sections other than four sections we've edited, resulted in the message "**Error! Reference source not found.**" This message is not contained in the original.

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	203-155	Brand Name	Choline C 11 Injection
OCP Division V	V	Generic Name	Choline C 11 Injection
Medical Division	Division of Medical Imaging Products	Drug Class	Prostate imaging agent. Substrate for choline transporter
OCP Reviewer	Christy S. John, Ph.D.	Indication(s)	Choline C 11 Injection is a radioactive diagnostic agent for positron emission tomography (PET) for the identification of local lymph node and distant recurrence of prostate cancer in patients following primary treatment failure and/or in patients and those who have failed one or more conventional imaging modalities for localization of recurrent prostate cancer
OCP Team Leader	Gene Williams, Ph.D.	Dosage Form	Clear Solution
		Dosing Regimen	10-20 mCi
Date of Submission	12/12/2011	Route of Administration	Intravenous Injection
Estimated Due Date of OCP Review	4/12/2012	Sponsor	Mayo Clinic
PDUFA Due Date	06/12/2012	Priority Classification	P
Division Due Date	05/05/2012		

Clin. Pharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				

Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
<i>Patients-</i>				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				

Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X	5		
Total Number of Studies	X	5		

Filability and QBR comments		
	“X” if yes	Comments
Application fileable ?	X	This application is being submitted to fulfill recent FDA changes to the regulation of PET imaging agents. The applicant has submitted literature data in support of use of [C-11]choline at Mayo clinic. The applicant has provided five literature articles in support of clinical pharmacology. The rationale for dose justification is poor. According to the applicant, there is no data in literature for intrinsic or extrinsic factors effect on kinetics of [C-11]choline. Dosimetry data is available from literature (De Grado et al. J. Nuc. Med 43, 2002, 92-96).
Comments sent to firm ?	None	
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer signature	Christy S. John, Ph.D.	
Secondary reviewer Signature and date	Gene Williams, Ph.D.	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTY S JOHN
01/25/2012

GENE M WILLIAMS
01/25/2012

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/s/

CHRISTY S JOHN
07/27/2012

GENE M WILLIAMS
07/27/2012

I concur with Dr. John's recommendations.

Office of Clinical Pharmacology and Biopharmaceutics
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In-vivo effects of primary drug:				
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Subpopulation studies -				
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gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
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Phase 3 clinical trial:				
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Pediatric development plan				
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Secondary reviewer Signature and date	Gene Williams, Ph.D.	

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01/25/2012

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