Radiopharmaceutical Details: $^{11}$C-PIB

1. Name of Radiopharmaceutical (active ingredient)

$^{11}$C-PIB (also known as $^{11}$C-[6-OH-BTA-1])

2. Indicate the chemical structure for low molecular weight drug molecules

(not required for antibodies, proteins, or polymeric agents)

$^{11}$C-PIB: {N-methyl-$^{11}$C-}2-(4'-methylamino-phenyl)-6-hydroxy-benzothiazole; mw = 256

4. State specific details of techniques to analyze and quantify the compound

(ex: spectrophotometer – make, settings, sample dilutions, etc.)

The chemical analysis and radiochemical purity of each batch of the radiotracer PIB will be determined utilizing high performance liquid chromatography (HPLC), and compared to an authentic sample of PIB prepared using $^{12}$C-CH$_3$I and that has been characterized by NMR spectroscopy and high resolution (exact mass) mass spectroscopy. Analytical reverse phase HPLC will be done using a Phenomenex Luna 5u C8 100x2mm column, with a solvent mobile phase of 30/70 acetonitrile/ 20 mM NH$_4$OAc pH 4.5 at a flow rate of 0.6 mL/min (PIB RT~5 min). Approximately 15 microliters of sample are injected onto the column. Detection of mass is done using a flow UV detector operating at 350 nm and radioactivity using a flow radioactivity detector.

4b. Indicate the minimum detectable mass of the drug by HPLC analysis.

No detection limit has been determined for this compound using this system.

5. Radioisotopes

Carbon-11

6. Method of assaying radioisotope activity prior to administration

(ex: Capintec ion chamber, gamma counter, or liquid scintillation counter; include details of make, setting, type of standard, etc.)

The amount of radioactivity in each unit dose is assayed prior to administration using a calibrated Capintec 712M dose calibrator dialed into a setting of 457. A daily constancy test is performed using an NIST traceable Cs-137 source. Accuracy, linearity and geometry testing is performed as required by the NRC or equipment manufacturer.

7. Radionuclidic Purity

(in %)

>99%
8. Significant radionuclidic impurities and means of assay

Carbon-11 is obtained with very few radionuclidic impurities, as determined by observing the decay rate of the products of a typical carbon-11 yielding target irradiation.

9. Radiochemical Purity

(in %)

>95%

10. Significant radiochemical impurities and means of assay
(ex: Chromatographic techniques and procedure for analyzing radiochromatogram).

The radiochemical purity will be determined for each batch of PIB by analytical HPLC (from section 4) with a radioactivity (NaI) scintillation detector.

11. Provide evidence that the tracer will be stable over period of storage prior to administration.
(Give details of storage conditions and on-going quality assurance procedures for sterility, apyrogenicity, and radiochemical purity.)

Formal stability data has not been collected.

14. Provide detailed information on how the pharmaceutical quality of the radioactive drug will be assured at the time of administration.
Include the following:

• pH
• Sterility
• Apyrogenicity
• Identify (chemical and radiochemical purity)
• Concentration

a. pH

A small amount of each batch of the final radiotracer product will be spotted on Merck pH paper. The pH will be in the physiological range (4.5-7.5) and will be consistent from batch to batch.

b. Sterility

The product is delivered in a sterile multi-dose vial. No addition of liquid or aliquotting to another storage container is permitted. Individual doses are removed from this vial using aseptic techniques and only by trained pharmacy staff or nuclear medicine technicians.
During preclinical studies the final drug product was produced utilizing established synthesis procedures [See appended Master Formula Card]. When tested as described below the prepared batches were sterile. During clinical studies the radioactive drug product will be produced utilizing these established procedures and on a synthesis apparatus which will be appropriately maintained. Sterility tests will be routinely performed on batches of the drug product in an ex post facto manner utilizing residual samples.

An aliquot of the final drug products will be inoculated into each of the appropriate sterility test media and incubated according to USP recommendations:

i. Fluid Thioglycollate Media (BBL, Division of Becton-Dickinson Co., Cockeysville, MD): 14 days at 30-35° C.

ii. Soybean Casein Broth (BBL, Division of Becton-Dickinson Co., Cockeysville, MD): 14 days at 20-25° C.

Positive growth is indicated by cloudiness in the culture media. Results will be compared to positive and negative controls. The efficacy of a 0.22 µm membrane filter for terminal sterilization [See appended Master Formula Card] warrants release of the drug products for patient administration prior to results of sterility testing as stipulated by current USP.

c. Apyrogenicity

An aliquot of the final drug product will be tested for the presence of bacterial endotoxin utilizing a Limulus Amebocyte Lysate (LAL) Test. The test is performed using a Charles River Endosafe-PTS Portable Testing System which is based on a kinetic chromogenic BET. The established USP endotoxin limit is 175 EU per dose for radiopharmaceuticals and is not exceeded.

d. Identify (chemical & radiochemical purity)

Potential chemical precursor impurities, 6-MOMO-BTA-0 (precursor) and 6-HO-BTA-0 (de-protected precursor), are removed during the semi-preparative HPLC purification.

e. Concentration

i. Mass concentration (mass/volume)

Range: 1.0-10 µg/ml

Mass concentration will be determined using the HPLC system outlined in section 4 by comparison of UV absorbance intensity with a standard of known concentration.

ii. Activity concentration (activity/volume)

Range: 2-10 mCi/ml

iii. Specific activity (activity per mass of drug)
Specific activity is determined prior to release of the product however there is not a minimum acceptable specific activity for this tracer.

For questions or concerns, contact:

Brian Hockley
Division of Nuclear Medicine
(734) 615-2044
Fax: (734) 615-2557
Email: hockley@umich.edu