Radiopharmaceutical Details: $^{18}$F-AV133

1. Name of Radiopharmaceutical (active ingredient)

$^{18}$F-AV133, fluoropropyl-dihydrotetrabenazine, (2R,3R,11bR)-9-(3-fluoropropoxy)-3-isobutyl-10-methoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1a]isoquinolin-2-ol

2. Indicate the chemical structure for low molecular weight drug molecules
(not required for antibodies, proteins, or polymeric agents)

\[ \text{Chemical structure image} \]

Mol. Wt.: 364.5

Components of Drug Product

$^{18}$F-AV-133 (API)

0.5mL Ethanol, USP

9.5mL 0.9% Sodium Chloride, USP

4. State specific details of techniques to analyze and quantify the compound
(ex: spectrophotometer – make, settings, sample dilutions, etc.)

Radiochemical purity, mass concentration, radiochemical identity, pH, radionuclidian identity, visual inspection, residual solvent analysis, filter membrane integrity testing and pyrogen testing will be performed prior to release of each batch of $^{18}$F-AV133. Liquid Chromatography (HPLC) will be performed using a Luna 5u C8(2) 100A reverse phase column (Phenomenex, Torrance, CA; 100x2.0mm) eluted with 20 mM ammonium acetate:acetonitrile (75:25) pH 4.5 at 0.3 mL/min. The HPLC system will be equipped with a bioscan flow count radioactivity detector. Residual solvent analysis of AV-133 will be performed using a Shimadzu GC-2010 equipped with a Restek Stabilwax column (35mx0.25mm), split/splitless inlet and flame ionization detector. The dose will be compared to a reference standard.

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

The detection limit has not been determined for this compound on this system.

5. Radioisotopes
Fluorine-18

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 439. 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

The radionuclide fluorine-18 is prepared using a cyclotron irradiation of oxygen-18 enriched water. Potential radionuclidic impurities are the very short half-life radionuclides oxygen-15 (half-life 2 minutes) and nitrogen-13 (half-life 10 minutes). The combination of the ion exchange and chromatographic columns used in the synthesis of $^{18}$F-AV-133, together with the time used in the synthesis (> 1 hour), result in effectively no contamination of the final product with either of these radionuclides. The radionuclidic identity is determined by calculating the half-life prior to release of the final product. The $t_{1/2}$ must calculate to between 105 and 115min.

9. Radiochemical Purity
(in %)
>90%

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

The potential radiochemical impurities in $^{18}$F-AV-133 are free $^{18}$F and the hydrolyzed precursor. The product, precursor and the free $^{18}$F are individually distinguishable in the QC HPLC system.

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.)
Stability studies indicate this compound is stable with respect to radiochemical purity for six hours from end of synthesis.

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
- Identity (chemical and radiochemical purity)
- Concentration

a. pH

A small amount of each batch of the final drug products will be spotted on pH paper (range 2-9). 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 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 and radiochemical purity)

The identity of AV133 in the dose will be determined using the same HPLC system as in section 4. The dose will be compared to a standard of known identity. The chemical purity of the dose will not be determined.

e. Concentration

The concentration of AV133 in the dose shall be determined using the same HPLC system as in section 4. The detector response to the dose will be compared to that of a standard of known concentration.

f. Filter integrity Testing

The bubble point of the sterilizing filter used to filter the AV133 dose will be determined according to the procedure described in USP<823>. This test will be performed prior to release of the final product.

For questions or concerns, contact:

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