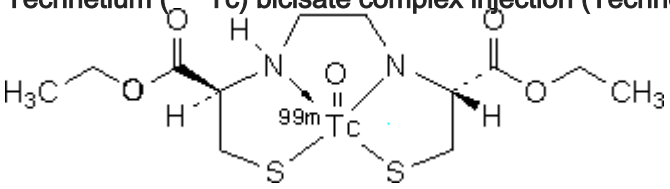
Technetium (^{99m}Tc) bicisate complex injection (Technetii (^{99m}Tc) bicisati multiplex injectio)



$C_{12}H_{21}N_2O_5S_2{}^{99m}Tc$

Chemical name. (*SP-5-35*)-[[1,1'-diethyl *N*,*N*'-ethylenebis(L-cysteinato-κ*N*,κ*S*)](3-)]oxo-[^{99m}Tc]technetium.

Other names. (^{99m}Tc)-Ethylene dicysteine diester complex injection, (^{99m}Tc)-ECD injection.

Description. Technetium (^{99m}Tc) bicisate complex injection is a clear, colourless aqueous solution.

Technetium-99m has a half-life of 6.02 hours.

Category. Diagnostic.

Storage. Technetium (^{99m}Tc) bicisate complex injection should be kept at a temperature between 2°C to 8°C.

Additional information. Wherever V is used within the tests of this monograph, V is the maximum recommended dose, in millilitres.

Requirements

Complies with the monograph for "Parenteral Preparations" and with that for "Radiopharmaceuticals".

Definition. Technetium (^{99m}Tc) bicisate complex injection is a sterile solution of bicisate dihydrochloride complexed with technetium-99m. The injection is suitable for intravenous administration and contains sufficient sodium chloride to make the solution isotonic with blood. The content of technetium-99m is not less than 90% and not more than 110% of the content of technetium-99m stated on the label at the reference date and time stated on the label. Not less than 90% of the total technetium-99m radioactivity is present as (^{99m}Tc) bicisate complex.

Manufacture

Radionuclide production. Technetium-99m is a radioactive nuclide formed by the radioactive decay of molybdenum-99. Molybdenum-99 is a radioactive isotope of molybdenum and may be produced by neutron irradiation of natural molybdenum or of molybdenum enriched in molybdenum-98 or it may be produced by uranium fission.

Radioformulation. Technetium (^{99m}Tc) bicisate complex injection is prepared aseptically from sterile starting materials such as a sterile kit containing bicisate dihydrochloride and a stannous salt with sodium pertechnetate (^{99m}Tc) injection (fission or non-fission). The injection may have the pH adjusted and may contain reducing, chelating, stabilizing, filling and antioxidizing agents as well as antimicrobial preservatives and buffers. The injection may also be prepared under aseptic processing combined with sterilization by Filtration (see 5.8 Methods of sterilization).

Identity tests

• Either tests A and C or tests B and C may be applied.

A. Record the gamma-ray spectrum using a suitable instrument with a sample of technetium-99m, suitably diluted if needed. The spectrum is concordant with the *reference spectrum* of a specimen of technetium-99m in that it exhibits a major peak of 140 keV.

Standardized technetium-99m solutions are available from laboratories recognized by the relevant national or regional authority.

B. The half-life determined using a suitable detector system is between 5.72 and 6.32 hours.

C. Examine the radiochromatograms obtained in the test for Radiochemical purity. The distribution of the radioactivity contributes to the identification of the preparation.

pH value. Carry out the test as described in the monograph for "Radiopharmaceuticals". pH of the injection, 4.0 to 8.0.

Sterility. The injection complies with 3.2 Test for sterility, modified as described in the monograph for "Radiopharmaceuticals". Test for sterility will be initiated on the day of manufacture. The injection may be released for use before completion of the test.

Bacterial endotoxins. Carry out the test as described under 3.4 Test for bacterial endotoxins, modified as described in the monograph for "Radiopharmaceuticals". The injection contains not more than 175/V I.U of endotoxins per millilitre. The injection

may be released for use before completion of the test.

Radionuclidic purity. Record the gamma-ray spectrum using a suitable instrument and measure the half-life using a suitable method. Determine the relative amounts of technetium-99m and radionuclidic impurities that may be present.

Radiochemical purity. Prepare fresh solutions. The injection to be examined should be incubated for at least 30 minutes after preparation.

Carry out two separate tests as described under *1.14.1 Chromatography*, Thin-layer chromatography, using a suitable silica gel plate with ethyl acetate R as the mobile phase (system A); a suitable silica gel reverse-phase plate with a mixture of 60 volumes of acetone R and 40 volumes of ammonium acetate 0.5M as the mobile phase (system B).

For system A, mark the plate with pencil lines at 2 cm, 4.5 cm and 7 cm from the origin. Apply to the plate 5 µl of the injection to be examined on the 2 cm line and allow the spot to dry for 5 to 10 minutes. Place the plate in a pre-equilibrated TLC tank for 30 minutes and develop the plate until the 7 cm line is reached. Remove the plate and allow it to dry in a current of air.

Cut the plate at the 4.5 cm line and determine the radioactivity distribution of each piece using a suitable method. In this system, the top portion of the plate contains the technetium (^{99m}Tc) bicisate complex and the bottom portion contains all radiochemical impurities.

Determine the radiochemical purity using the following equation:

$$100U / (U + L)$$

where:
U = activity of the upper piece of plate
L = activity of the lower piece of the plate

Not less than 90% of the total technetium-99m radioactivity is found as technetium (^{99m}Tc) bicisate complex. The sum of the percentages of radioactivity corresponding to the impurities is not more than 10%.

Determine the composition of the impurities using system B. Apply to the plate 2 µl of the injection to be examined and develop for a distance of 6 cm. Allow the plate to dry in air and determine the radioactivity distribution by a suitable method.

In this system, reduced hydrolysed technetium-99m has an Rf value of 0.00 to 0.14, the pertechnetate ion and the technetium (^{99m}Tc) ethylene cisteinate monomer have an Rf value of 0.70 to 0.84, the technetium (^{99m}Tc) EDTA complex has an Rf value of 0.95 to 1.0 and the technetium (^{99m}Tc) (IV) bicisate complex has an Rf value of 0.3 to 0.4; the technetium (^{99m}Tc) bicisate complex elutes in two spots at an Rf value of 0.15 to 0.44: one spot corresponding to technetium (^{99m}Tc) bicisate complex and another spot corresponding to technetium (^{99m}Tc) bicisate complex combined with the technetium (^{99m}Tc) (IV) bicisate complex.

Calculate the quantity of technetium (^{99m}Tc) (IV) bicisate complex by subtracting the percentage of technetium (^{99m}Tc) bicisate complex obtained in system A from the percentage of combined technetium (^{99m}Tc) bicisate complex and technetium (^{99m}Tc) (IV) bicisate complex obtained in system B. The sum of the impurities is not more than 10% of the total radioactivity.

Radioactivity. Measure the radioactivity as described under R.1.1 Detection and measurement of radioactivity in a suitable calibrated counting equipment by comparison with a standardized technetium-99m solution or by measurement in an instrument calibrated with the aid of such a solution (a good approximation may be obtained using an ionization chamber and employing a standardized solution of cobalt-57 provided that correction for the differences in the radiations emitted are made).

Standardized technetium-99m and cobalt-57 solutions are available from laboratories recognized by the relevant national or regional authority.

Biodistribution. Carry out the test as described under R3.1 Biological distribution using a set of three mice as described. At 5 to 10 minutes post injection, the following percentages of the injected radioactivity should be found: not less than 1.5 % in the brain, not less than 20% in the intestine and not more than 15% in the liver.