PRODUCT MONOGRAPH

DRAXIMAGE® GLUCEPTATE

Kit for the Preparation of Technetium Tc 99m Gluceptate Injection /
Stannous Gluceptate Injection

Diagnostic

For Intravenous Use

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DRAXIMAGE® GLUCEPTATE

Kit for the Preparation of Technetium Tc 99m Gluceptate Injection
(Brain and Kidney Imaging Agent)
or
Stannous Gluceptate Injection
(Cardiac Blood Pool Imaging Agent)

DIAGNOSTIC - For Intravenous Use

DESCRIPTION

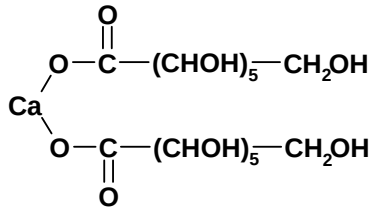
The kit consists of reaction vials which contain the sterile, non-pyrogenic, non-radioactive ingredients necessary to produce either Technetium Tc 99m Gluceptate Injection for diagnostic use in kidney and brain imaging or Stannous Gluceptate Injection for diagnostic use in cardiac blood pool imaging. Both diagnostic products are administered by intravenous injection.

Each 10 mL reaction vial contains 25 mg of calcium gluceptate† complexed with 3 mg of stannous chloride dihydrate in lyophilized form under an atmosphere of nitrogen. The pH has been adjusted with sodium hydroxide and/or hydrochloric acid.

Technetium Tc 99m Gluceptate Injection for Brain and Kidney Imaging

The addition of Sodium Pertechnetate Tc 99m Injection to produce Technetium Tc 99m Gluceptate Injection results in the rapid labeling of calcium gluceptate which is essentially quantitative and which remains stable throughout the useful life of the preparation. No bacteriostatic preservative is present.

The precise structure of the reaction vial complex or of its technetium labeled form is not known at this time.



Calcium Gluceptate

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† USP/USAN term for glucoheptonate

Stannous Gluceptate Injection for Cardiac Blood Pool Imaging

The contents of the kit may be reconstituted with sterile, non-pyrogenic preservative-free normal saline to form Stannous Gluceptate Injection for cardiac blood pool imaging and administered 10 to 30 minutes before injecting Sodium Pertechnetate Tc 99m Injection.

ACTION

Technetium Tc 99m Gluceptate Injection for Brain and Kidney Imaging

When injected intravenously, Technetium Tc 99m Gluceptate Injection is rapidly cleared from the blood. The blood clearance curve is tri-exponential with the two faster components accounting for more than 90 % of the injected dose. In patients with normal renal function, less than 15 % of the initial activity remains in the blood after one hour. About 40 % of the injected dose is excreted in the urine in one hour, while about 70 % is excreted in 24 hours. In patients with renal disease, the blood clearance and urine excretion of the radiopharmaceutical are delayed.

Up to 15 % of the injected dose is retained in the kidneys with the remainder being excreted in the urine. The renal retention is greater in the cortex than in the medulla. This may be due to the binding of the radiopharmaceutical to the proximal or distal convoluted tubules, which are primarily located in the renal cortex.

Technetium Tc 99m Gluceptate Injection tends to accumulate in intracranial lesions with excessive neo-vascularity or an altered blood-brain barrier. It does not accumulate in the choroid plexus or salivary glands.

Stannous Gluceptate Injection for Cardiac Blood Pool Imaging

When tin, as stannous gluceptate, is injected intravenously, it is taken up by red blood cells and by an unknown mechanism facilitates the labeling of these cells by technetium-99m when the latter is subsequently administered as Sodium Pertechnetate Tc 99m Injection.

Following *in vivo* red blood cell labeling in both normal volunteers and patients, approximately 89 % of the injected dose of Sodium Pertechnetate Tc 99m Injection remained in the intravascular compartment ten minutes post-injection. The blood clearance curve can be resolved into two exponential components; the first may have been due to the extra-vascular distribution and urinary excretion of ^{99m}Tc sodium pertechnetate, as well as accumulation of damaged red blood cells by the spleen.

About 6 % of the injected dose was excreted in the urine of normal volunteers in 3 hours, and about 28 % was excreted in 24 hours. In five patients with ischemic heart disease however, only about 3 % of the injected dose was excreted in 2 hours, and only about 13 % was excreted in 24 hours.

INDICATIONS AND USAGE

Technetium Tc 99m Gluceptate Injection may be used to perform kidney and brain imaging, and to assess renal and brain perfusion.

Stannous Gluceptate Injection may be used in conjunction with Sodium Pertechnetate Tc 99m Injection for cardiac blood pool imaging.

CONTRAINDICATIONS

Hypersensitivity to this agent.

WARNINGS

The contents of the kit before preparation are not radioactive. However, after the Sodium Pertechnetate Tc 99m Injection is added, adequate shielding of the final preparation must be maintained.

Radiopharmaceuticals should be used only by or under the control of physicians who are qualified by specific training in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to licence the use of radionuclides.

Since adequate reproduction studies have not been performed in animals to determine whether this drug affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus, this radiopharmaceutical preparation should not be administered to pregnant or nursing women unless it is considered that the benefits to be gained outweigh the potential hazards.

Where an assessment of the risk to benefit ratio suggests use of this product in lactating mothers, nursing should be stopped.

Adequate studies do not exist to support the use of this radiopharmaceutical in pediatric patients. As in pregnancy and lactating mothers, the risk to benefit ratio should be assessed before consideration is given to the use of this product in this age group.

Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of a woman of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses.

PRECAUTIONS

The Stannous Gluceptate Injection kit may be used to prepare Technetium Tc 99m Gluceptate Injection for brain and kidney imaging by addition of Sodium Pertechnetate Tc 99m Injection. However, the contents may also be reconstituted with sterile, non-pyrogenic, preservative-free normal saline to form Stannous Gluceptate Injection for cardiac blood pool imaging and administered intravenously 10 to 30 minutes before injecting Sodium Pertechnetate Tc 99m Injection.

The components of the kit are sterile and non-pyrogenic. It is essential that the user follows the directions carefully and adheres to strict aseptic procedures during preparation.

The ^{99m}Tc labeling reactions involved depend on maintaining the tin (stannous ion) in the reduced state. Hence, ^{99m}Tc sodium pertechnetate containing oxidants should no be employed.

As in the use of any other radioactive material, care should be taken to insure minimal radiation exposure to the patient, consistent with proper patient management, and to insure minimum radiation exposure to occupational workers.

Brain and Kidney Imaging

The patient should be encouraged to drink fluids before and after the examination. To minimize the radiation dose to the bladder, the patient should be encouraged to void when the imaging procedure is completed and as often thereafter as possible for the next 4 to 6 hours.

The image quality may be adversely affected by impaired renal function.

Literature reports indicate that the target to non-target ratio for intracranial lesions may take several hours to fully develop, and the possibility of missing certain lesions by restricting imaging to only the early period after injection should be borne in mind.

Blood Pool Imaging

Stannous Gluceptate Injection should be administered by direct venipuncture. Heparinized catheter systems must be avoided.

When the cardiac blood pool is imaged, the patient's cardiac condition should be stable. Imaging in conjunction with stress-exercise should be conducted under the supervision of an experienced cardiologist in an examination room equipped with an ECG recorder, a defibrillator and standard resuscitation equipment. Similarly, during the scanning procedure of patients with known or suspected myocardial infarction, the required clinical supervision and supportive therapy must be maintained.

Subsequent re-administration of Sodium Pertechnetate Tc 99m Injection within one week after a cardiac blood pool imaging procedure will re-label some of the red blood cells. Therefore, if an imaging procedure using Sodium Pertechnetate Tc 99m Injection is anticipated, this examination should be carried out prior to the use of Stannous Gluceptate Injection or not less than one week after the administration of the drug.

ADVERSE REACTIONS

Similarly to other imaging agents, rare reactions of nausea, vomiting, erythema, allergic dermatitis (allergic skin reaction), rash, pruritus (itching), flushing and dyspnea (difficulty breathing) have been reported following the administration of Technetium Tc 99m Gluceptate Injection from post-market experience. Rare cases of hypersensitivity have also occurred.

PHARMACOLOGY

Technetium Tc 99m Gluceptate Injection for Brain and Kidney Imaging

Intravenous administration of Technetium Tc 99m Gluceptate Injection to rats resulted in rapid clearance of the drug from the blood pool with less than 3 % of the injected dose remaining in the circulation at 1 hour post-injection. The kidney retention of the radiopharmaceutical was approximately 12 % of the dose, which decreased slowly to less than 8 % within 24 hours. A similar pattern was observed in rabbits except that the kidney retention was lower and the blood clearance was slower. About half of the injected dose was excreted in the urine within the first hour post-injection.

Stannous Gluceptate Injection for Cardiac Blood Pool Imaging

In a dose range study, rabbits were injected with doses of Stannous Gluceptate Injection containing between 2.6 and 31.6 µg of tin. The following table indicates the percentage of labeled red blood cells with the increasing dose of tin.

Tin (µg/kg body weight)	% Labeled RBC
2.6	86.3
5.3	93.6
10.5	95.5
15.8	95.3
31.6	96.2

Therefore, a dose of 16 µg of tin per kilogram of body weight is considered optimal for red blood cell labeling.

When *in vivo* red blood cell labeling is performed in rats, not less than 90 % of the injected dose of Sodium Pertechnetate Tc 99m Injection remains in the blood thirty minutes after injection. More than 98 % of the radioactivity in the blood is associated with the red blood cells and there is a minimal loss of the label over a 6-hour period.

TOXICOLOGY

A safety assessment in two rodent and one non-rodent species was made using Stannous Gluceptate Injection reconstituted with saline but without any ^{99m}Tc sodium pertechnetate.

The acute intravenous lethal dose$_{50}$ (LD_{50}) of Stannous Gluceptate Injection in Swiss Albino mice is 605 mg/kg body weight, and 440 mg/kg in BBL Sprague-Dawley rats. The signs of acute intoxication in mice were moderate respiratory depression and clonic-tonic convulsions shortly after drug administration. No signs of acute drug intoxication were observed in rats.

A slow intravenous injection of 56 mg Stannous Gluceptate Injection (6 mg stannous chloride dihydrate) per kg body weight in four beagle dogs produced no toxic or gross pathological changes. This dose represents a 200 fold excess over the human dose (0.28 mg/kg).

PHYSICAL CHARACTERISTICS

Technetium-99m decays by isomeric transition with a physical half-life of 6.02 hours.[1] The principal photon that is useful for detection and imaging studies is listed in Table 1.

Table 1

Principal Radiation Emission Data

Radiation	Mean % per Disintegration	Mean Energy (keV)
Gamma-2	89.07	140.5

The specific gamma ray constant for technetium-99m is 5.44 $\mu C \cdot kg^{-1} \cdot MBq^{-1} \cdot hr^{-1}$ (0.78 R/mCi-hr) at 1 cm. The half-value layer is 0.2 mm of Pb. To facilitate control of the radiation exposure from millicurie amounts of this radionuclide, the use of 2.5 mm thickness of Pb will attenuate the radiation emitted by a factor of about 1 000.

Table 2

Radiation Attenuation by Lead Shielding

Shield Thickness (Pb) mm	Coefficient of Attenuation
0.2	0.5
0.8	10^{-1}
1.6	10^{-2}
2.5	10^{-3}
3.3	10^{-4}
4.5	10^{-5}

To correct for physical decay of this radionuclide, the fractions that remain at selected intervals after the time of calibration are shown in Table 3.

Table 3

Physical Decay Chart of Technetium-99m
Half-Life: 6.02 Hours

Hours	Fraction Remaining	Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.000	5	0.562	10	0.316
1	0.891	6	0.501	11	0.282
2	0.794	7	0.447	12	0.251
3	0.708	8	0.398	18	0.126
4	0.631	9	0.355	24	0.063

*Calibration Time

RADIATION DOSIMETRY

Brain and Kidney Imaging

The estimated absorbed radiation doses[2,3] to various organs of an average adult patient (70 kg) from an intravenous injection of a maximum dose of 740 MBq (20 mCi) of Technetium Tc 99m Gluceptate Injection are shown in Table 4.

Table 4

Estimated Absorbed Radiation Doses

Tissue	mGy/MBq	rad/mCi
Adrenals	0.0046	0.017
Bladder wall	0.056	0.21
Bone surfaces	0.0026	0.0096
Breast	0.0014	0.0052
GI-tract		
Stomach wall	0.0027	0.010
Small intestine	0.0037	0.014
Large intestine wall (upper)	0.0033	0.012
Large intestine wall (lower)	0.0044	0.016
Kidneys	0.049	0.18
Liver	0.0027	0.010
Lungs	0.0017	0.0063
Ovaries	0.0046	0.017
Pancreas	0.0036	0.013
Red marrow	0.0039	0.014
Spleen	0.0039	0.014
Testes	0.0029	0.011
Thyroid	0.0011	0.0041
Uterus	0.0077	0.029
Other tissue	0.0023	0.0085
Effective dose equivalent (mSv/MBq)	0.0090	

Blood Pool Imaging

The estimated absorbed radiation doses[4] to various organs of an average patient (70 kg) from an intravenous injection of a maximum dose of 925 MBq (25 mCi) of Sodium Pertechnetate Tc 99m Injection thirty minutes after the intravenous administration of Stannous Gluceptate Injection are shown in Table 5.

Table 5

Estimated Absorbed Radiation Doses

Organ	rad/25 mCi (10^{-2} Gy/925 MBq)
Blood	1.375
Urinary bladder wall	2.750
Ovaries	0.525
Testes	0.375
Whole body	0.375

DOSAGE AND ADMINISTRATION

Brain and Kidney Imaging

The recommended dose range for intravenous administration of Technetium Tc 99m Gluceptate Injection in the average adult patient (70 kg) is:

Renal imaging studies: 370 to 555 MBq (10 to 15 mCi)
Brain imaging studies: 555 to 740 MBq (15 to 20 mCi)

Dynamic kidney or brain perfusion studies may be performed immediately after injection. Depending on the indication, these may be followed by delayed static imaging one-half to several hours after injection for renal studies, and one to several hours after injection for brain studies.

Cardiac Blood Pool Imaging

Stannous Gluceptate Complex should be reconstituted with 3.0 mL of sterile, pyrogen-free saline without preservative. A dose of 0.03 mL/kg (16 µg Sn/kg) of body weight (Table 6) is injected intravenously 10 to 30 minutes before intravenous administration of 555 to 925 MBq (15 to 25 mCi) of Sodium Pertechnetate Tc 99m Injection. Therefore, for a 100 kg patient, the entire 3.0 mL is used. For patients weighing less, the exact dose of Stannous Gluceptate Injection may be determined by using the body weight in **kilograms** as a percentage to calculate the volume required, e.g., for a 70 kg patient, 2.1 mL is required (70 % x 3.0 mL = 2.1 mL).

Table 6

Dose in mL of Stannous Gluceptate Injection by Body Weight

Body Weight (kg)	Body Weight (lb)	Dose (mL)	Body Weight (kg)	Body Weight (lb)	Dose (mL)
10	22	0.30	60	132	1.80
15	33	0.45	65	143	1.95
20	44	0.60	70	154	2.10
25	55	0.75	75	165	2.25
30	66	0.90	80	176	2.40
35	77	1.05	85	187	2.55
40	88	1.20	90	198	2.70
45	99	1.35	95	209	2.85
50	110	1.50	100	220	3.00
55	121	1.65			

The patient dose of Sodium Pertechnetate Tc 99m Injection should be measured by a suitable calibration system immediately prior to administration. Withdrawals for administration must be made aseptically.

DIRECTIONS FOR PREPARATION

Technetium Tc 99m Gluceptate Injection for Brain and Kidney Imaging

NOTE: Use aseptic procedures throughout and take precautions to minimize radiation exposure by use of suitable shielding.

Before reconstituting a vial, it should be inspected for cracks and/or a melted plug or any other indication that the integrity of the vacuum seal has been lost.

To prepare Technetium Tc 99m Gluceptate Injection:

1. Remove the protective disc from a reaction vial and swab the closure with an alcohol swab.

2. Place the vial in a suitable radiation shield. Obtain 2 to 10 mL of Sodium Pertechnetate Tc 99m Injection using a shielded syringe. The recommended maximum amount of technetium-99m to be added to a reaction vial is 11.1 GBq (300 mCi). ^{99m}Tc sodium pertechnetate containing an oxidizing agent is not suitable for use.

3. Add the Sodium Pertechnetate Tc 99m Injection to the reaction vial aseptically.

4. Agitate the shielded vial until the contents are completely dissolved. Using proper shielding, the vial should be visually inspected and not used if there is evidence of particulate or foreign matter. To ensure maximum tagging, allow the preparation to stand at room temperature (15 ºC to 30 ºC) for 15 minutes after mixing.

5. Assay the product in a suitable calibrator, record the radioassay information on the label with a radiation warning symbol, and apply it to the vial shield.

6. The radiochemical purity of the finished preparation should be checked prior to patient administration. The radiochemical purity should not be less than 90 %.

7. Withdrawals for administration must be made aseptically using a sterile syringe and needle. Since the vials contain nitrogen to prevent oxidation of the complex, the vials should not be vented. If repeated withdrawals are made, minimize the replacement of the contents with room air.

8. The finished preparation should be stored at 2 ºC to 8 ºC when not in use and discarded after 8 hours.

Stannous Gluceptate Injection for Blood Pool Imaging

NOTE: Use aseptic procedures throughout.

To prepare Stannous Gluceptate Injection:

1. Remove the protective disc from a reaction vial and swab the closure with an alcohol swab.

2. Add 3.0 mL of sterile, non-pyrogenic, preservative-free normal saline to the reaction vial aseptically.

3. Agitate the vial until the contents are completely dissolved. The vial should be visually inspected and not used if there is evidence of particulate or foreign matter.

4. Withdrawals for administration must be made aseptically using a sterile syringe and needle. Since the vials contain nitrogen to prevent oxidation of the complex, the vials should not be vented. If repeated withdrawals are made, minimize the replacement of the contents with room air.

5. The finished preparation should be stored at 2 ºC to 8 ºC when not in use and discarded after 8 hours.

The ^{99m}Tc pertechnetate eluate should be less than 2 hours old and should be obtained from a generator which has been eluted within the last 24 hours.

Radiochemical Purity

Chromatographic Methods

The following procedure describes a series of simple steps for running chromatograms. Steps 1 to 6 describe the method for determining free pertechnetate in a mixture of chelated and reduced technetium. The TLC procedure requires the following :

Solid phase : ITLC-SG
Solvent: Acetone (for determination of pertechnetate)

Step 1

Add 1 mL of the required solvent to an 18 mm x 150 mm test tube. Stopper and allow the atmosphere in the tube to equilibrate for 1 minute.

Step 2

Prepare one chromatography strip (1 x 10 cm) of silica gel impregnated glass fiber sheets (ITLC type SG). Apply one small drop (~ 20 000 cpm) of the radioactive gluceptate solution to the origin at 1.5 cm from one end and dry under a nitrogen jet.

Step 3

Develop the chromatogram by placing it, with the origin down, in the previously equilibrated test tube. Stopper the test tube. The test tube should be kept upright, ideally in a test tube rack. Development requires about 10 minutes for ITLC-SG strips.

Step 4

When the solvent front has climbed to the top of the strip, remove it with forceps and allow it to dry. The strips can be dried by placing them radioactive side up on a disposable non-porous pad at room temperature.

The bound and reduced technetium appear at the origin or Rf 0 and the free pertechnetate $^{99m}TcO_4^-$ migrates to the front at Rf 0.85 to 1.0.

Step 5

Cut the dried strip 2 cm from the solvent front end. The short piece is marked *Part II* and the long piece is marked *Part I* . Count the pieces in a suitable counter and determine the percentage of free perctechnetate according to the following formula:

$$\text{Percent } {}^{99m}TcO_4^- = \frac{\text{Counts in } \textit{Part II}}{\text{Counts } \textit{Part I} + \textit{Part II}} \times 100$$

Step 6

Store all waste radioactive strips for 48 hours before disposing of them as non-radioactive waste. Store used chromatographic solvents in a similar fashion.

HOW SUPPLIED

DRAXIMAGE® GLUCEPTATE

Kit for the Preparation of Technetium Tc 99m Gluceptate Injection or Stannous Gluceptate Injection

Product No. 500220

The kit consists of 5 vials of stannous gluceptate complex, each vial containing in lyophilized form under an atmosphere of nitrogen:

Calcium gluceptate	25 mg
Stannous chloride dihydrate	3 mg

The pH has been adjusted with sodium hydroxide and/or hydrochloric acid.

Labels with a radiation warning symbol and (directions) product monograph are supplied with each kit.

STORAGE

Store kit at or below room temperature. Do not use the kit beyond the expiry date stamped on the box.

REFERENCES

1. Martin, M.J., Ed. Nuclear Decay Data for Selected Radionuclides, ORNL Report No. 5114, page 24, March 1976.

2. Arnold, R. W., et al., Comparison of ^{99m}Tc Complexes for Renal Imaging J. Nucl. Med. 16: 357, 1975.

3. Radiation Internal Dose Information Center, Oak Ridge Associated Universities, Oak Ridge, TN, Jan. 5, 1977.

4. Calculated by Mr. Jack L. Coffey, Radiation Internal Dose Information Center, Oak Ridge Associated Universities, Oak Ridge, TN.

Revised: [to be completed] Version 4.0

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