MIBI RPHPHARMA

PLEASE READ CAREFULLY BEFORE USING THE PRODUCT.

DRUG FOR DIAGNOSTIC USE IN NUCLEAR MEDICINE.
This product is only for use in specialized clinics and hospitals.

PHARMACEUTICAL FORM AND PRESENTATION
Kit containing 5 vials of lyophilized, sterile and pyrogen-free reagents, sealed under nitrogen atmosphere.

COMPOSITION
Each vial contains:

COMPOSITION	AMOUNT
tetrafluoroborate cuprous tetramibi	1.0 mg
sodium citrate	5.0 mg
stannous chloride dihydrate	0.13 mg
cysteine hydrochloride monohydrate	1.11 mg
mannitol	20.0 mg
water for injection	1.1 mL

Table 1 – Composition of the MIBI kit vials

1. INDICATIONS
MIBI-Tc-99m is only recommended for diagnostic purposes and is a myocardial infusion agent useful in the evaluation of coronary artery diseases. Its uses include differentiating between normal and abnormal myocardium, locating abnormalities in patients with suspected myocardial infarction and assessing ischemic coronary diseases. In the case of ischemic cardiac disease, an assessment is made using rest and physical or pharmacological stress techniques. It can also be used in parathyroid scintigraphy and breast scintigraphy, as well as to determine the extent of tumor viability.

INTRAVENOUS ADMINISTRATION. ADULT AND PEDIATRIC USE.

2. EFFICACY
MIBI-Tc-99m use on myocardial imaging was demonstrated by several clinical researches (Wackers *et al.*, 1989). The benefits of Tc-99m-MIBI were shown in healthy patients and in ischemic heart disease patients, in comparison to Tallium-201, and validated to SPECT use (Wackers *et al.*, 1989; Verzijlbergen *et al.*, 1996; Zolle, 2007). Another diagnostic use of Tc-99m-MIBI is from breast cancer and parathyroid cancer diagnosis (Caveny *et al.*, 2012; Fukumoto, 2004; Prats *et al.*, 1999).

3. PHARMACOLOGICAL CHARACTERISTICS
MIBI contains the active ingredient cuprous terambi tetrafluoroborate. MIBI-Tc-99m is a cationic technetium-99m complex (99m Tc) that accumulated in viable myocardial tissue in proportion to the area of the coronary blood flow.
MIBI-Tc-99m from the blood stream is quickly distributed into the tissues. Five minutes after injection only 8% of the injected dose is still in circulation. Blood flow-dependent myocardial uptake is equal to 1.5% of the injected stress dose and 1.2% of the resting dose. Pulmonary activity is negligible, even immediately after injection. The major route of elimination for MIBI marked with technetium-99m (99m Tc) is through the hepatobiliary system. Activity in the gallbladder and intestine appears within one hour of injection. Twenty-seven percent (27%) of the injected dose is eliminated in the urine and approximately thirty percent (30%) through the feces within 48 hours. The agent is excreted with no evidence of metabolism.

4. CONTRAINDICATIONS
There are no reported contraindications.

5. WARNINGS AND PRECAUTIONS
During pregnancy or breastfeeding, this radiopharmaceutical should only be used in cases of extreme necessity, when the risk of exposure of the fetus or newborn to radiation is justified by the importance of diagnosis.
The administration of a radiopharmaceutical during pregnancy can cause mutagenic changes in the fetus.
During lactation, technetium-99m (99m Tc) is excreted in breast milk. Breastfeeding should be suspended for at least 12 hours after injection and the milk produced during this period discarded. Avoid close contact between mother and baby for the 12 hours following administration of the radiopharmaceutical.

6. DRUG INTERACTIONS
Medical products that affect myocardial function and/or blood flow can cause a false negative diagnosis in coronary artery disease results. As such, other medication taken simultaneously should be taken into account when interpreting the results of scintigraphic tests. In addition, drugs containing calcium antagonists, beta blockers, nitrates, sodium bicarbonate, dexamethasone, digitalis, doxorubicin, lidocaine, procainamide or vasopressin can also result in lower quality images or even false positives and/or negatives.

7. STORAGE PRECAUTIONS
This drug is valid for 12 months from the date of manufacture. Transport at room temperature and store in a cool dark place at temperatures between 2 and 8° C.
When added to the vial of MIBI without the presence of air, the sterile pyrogen-free solution of sodium pertechnetate (Na 99mTcO$_4$) produces rapid labeling that remains stable in vitro for 12 hours.
After complexation with technetium-99m (99m Tc) store in the dark between 2° and 30° C.

Lot number, manufacture and expiration dates: see packaging.
Do not take medicine that has expired.
All medicines should be kept out of reach of children.
Before administering to the patient, take note of the appearance of the product, which should be clear and colorless.

8. DOSAGE AND USE INSTRUCTIONS
Route of administration: intravenous.
Average recommended activity for an adult weighing 70 kg:
For myocardial scintigraphy: 370 to 1110 MBq (10 to 30 mCi).
The recommended dosage to diagnose ischemic heart disease is one stress and one resting dose in order to differentiate perfusion of the radiopharmaceutical in the heart muscle.
To diagnose reduced coronary perfusion and myocardial infarction: 185 – 740 MBq (5-20 mCi)
To assess overall ventricular function: 740 – 925 MBq (20-25 mCi)
For breast scintigraphy: 740 – 1110 MBq (20 – 30mCi)
For parathyroid image: 555 – 740 MBq (15 – 20 mCi)

8.1. INSTRUCTIONS FOR PREPARATION AND STORAGE AFTER COMPLEXATION
- Use aseptic procedures and take precautions to prevent exposure to radiation.
- Remove the lyophilized reagent from refrigeration and wait until it reaches room temperature.
- Remove the plastic cap and aseptically sterilize the upper section using 70% ethyl alcohol.
- Correctly and carefully place the inside the lead shield.
- Use freshly eluted sodium pertechnetate solution (99mTcO$_4^-$) within one hour of elution.
- Do not allow air to enter the vial and remove air bubbles from the syringe before adding the sodium pertechnetate solution.
- Add 3 to 6 mL of a sterile, pryogen-free and oxidant-free solution of Na - 99mTcO$_4$, with maximum activity of 22.200 MBq (600 mCi), recently eluted from a generator (less than 1 hour), with an inter-elution period no greater than 24 hours.
- Without removing the needle, aspirate an equal volume of air to maintain atmospheric pressure within the bottle.
- Use a lead cap for shielding purposes.
- Swirl the vial gently for 20 seconds until the lyophilisate has completely dissolved. The solution should be clear and free of particles.
- Remove the vial from the lead shield and place it upright in a water bath of boiling water for 10 minutes.
- Next, remove the vial from the water bath and transfer it back to the lead shield.
- Allow to cool at room temperature for 10 minutes.
- Carry out quality control.
- Following quality control procedures, extract doses in accordance with the patient's body weight, taking care to avoid the entry of air when handling the flask. Use sterile, disposable syringes.
- Whenever the solution and vial permit it, products intended for intravenous injection should be visually inspected to ensure there is no particulate matter present.

8.2. QUALITY CONTROL - RADIOCHEMICAL
Use Whatman plate (1) and a silica gel plate (2) 6.5 cm long and 1 cm wide, as shown in figure 1. Once the cooling time has elapsed, add a drop of the material to each of the plates.
Place the Whatman plate (1) in a chromatography tank containing methanol PA, and the silica gel plate (2) in a chromatography tank containing 0.9% NaCl. Wait until the solvents migrate to the top lines of the plates, which can happen at different times.
Remove the plates from the chromatography tanks. Cut both the plates 1.5 cm from the application point.
Calculate labeling efficiency using the formula below. Analyze the results of labeling efficiency in accordance with table 2.

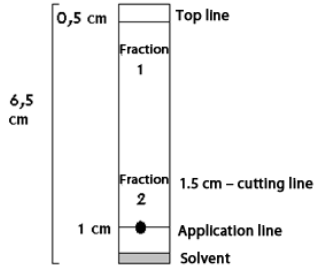

Figure 1 – Cutting chromatography plates

PLATE 1: % 99mTcO$_2$.

$$\frac{\text{activity fraction 2}}{\text{activity fraction 1} + 2} \times 100 = \%\ 99\text{mTcO2}$$

PLATE 2: % $99mTcO_4^-$:

$$\frac{\text{activity fraction 1}}{\text{activity fraction 1} + 2} \times 100 = \%\ 99\text{mTcO4} -$$

100 – (impurity plate 1 + impurity plate 2) = ≥ 90%

Labeling efficiency/radiochemical purity should be ≥ 90%.

CHROMATOGRAPHY ANALYSIS OF MIBI-Tc-99m			
Chromatography System		**(99m Tc) Species**	
Stationary Phase	**Mobile Phase**	**Origin**	**Front**
PLATE 1	Methanol PA	$99mTcO_2$	MIBI (99mTc) and $99mTcO_4^-$
PLATE 2	NaCl 0.9%	MIBI (99m Tc) and $99mTcO_2$	$99mTcO_4^-$

Table 2 – Chromatography systems for radiochemical control of MIBI-Tc-99m.

8.3. QUALITY CONTROL - pH

Apply a sample of the radiopharmaceutical on the pH indicator strip, ensuring the entire strip is wet.
Wait 30 seconds and compare the color of the strip against the parameters in this box.
The pH range for the radiopharmaceutical MIBI-Tc-99m should be between 5.0 and 6.0.

8.4. PRECAUTIONS ON ADMINISTRATION

This drug becomes radioactive after adding sodium pertechnetate solution. The use of lead shielding, suitable gloves and goggles should be mandatory.
The sets of reagents are sterile and pyrogen-free. In order to preserve the sterility of the product, it should be handled in accordance with the Good Practices on Handling Sterile Products (intravenous products).
Precautions should be taken when using ionizing radiation. As such, radioactive waste (used materials, recipients and other waste) should be correctly disposed of in compliance with radiation protection guidelines.

DOSES ADMINISTERED TO CHILDREN AND THE ELDERLY SHOULD BE CALCULATED ACCORDING TO THE BODY SURFACE AREA

8.5. TOXICITY TESTS

Toxicity is not an issue when considering the design and development of radiopharmaceuticals due to the small amount used, which does not produce a pharmacological response.

8.6. PHYSICAL CHARACTERISTICS OF METASTABLE TECHNETIUM-99m

Tecnetium-99m (99m Tc) has the ideal physical properties for studying scintilographic images.
(99m Tc) decreases into technetium-99 through isomeric transition and has a physical half-life of 6.02 hours.

RADIATION	AVERAGE/DECAY (5)	AVERAGE ENERGY (keV)
Gama -2	89.07	140.5

Table 3 – data on the main radiation emitted

8.7. DOSAGE

Doses for organs and tissues of an average weight patient (70 Kg) for 1110 MBq (30 mCi) of MIBI-Tc-99m injected intravenously are shown in table 4.

ESTIMATED RADIATION DOSE ABSORBED								
Organ	**REST (intervals)**				**STRESS (intervals)**			
	2 Hours		**4.8 Hours**		**2 Hours**		**4.8 Hours**	
	Rads /30 mCi	**mGy/ 110 MBq**	**Rads /30 mCi**	**mGy/ 110 MBq**	**Rads /30 mCi**	**mGy/ 110 MBq**	**Rads /30 mCi**	**mGy/ 110 MBq**
Breasts	0.2	2	0.2	1.9	0.2	2	0.2	1.8
Gallbladder	2	20	2	20	2.8	28.9	2.8	27.8
Small Intestine	3	30	3	30	2.4	24.4	2.4	24.4
Upper wall of the large intestine	5.4	55.5	5.4	55.5	4.5	44.4	4.5	44.4
Lower wall of the large intestine	3.9	40	4.2	41.1	3.3	32.2	3.3	32.2
Stomach walls	0.6	6.1	0.6	5.8	0.5	5.3	0.5	5.2
Heart wall	0.5	5.1	0.5	4.9	0.5	5.6	0.5	5.3
Kidneys	2	20	2	20	1.7	16.7	1.7	16.7
Liver	0.6	5.8	0.6	5.7	0.4	4.2	0.4	4.1
Lungs	0.3	2.8	0.3	2.7	0.3	2.6	0.2	2.4
Bone surface	0.7	6.8	0.7	6.4	0.6	6.2	0.6	6
Thyroid	0.7	7	0.7	6.8	0.3	2.7	0.2	2.4
Ovaries	1.5	15.5	1.6	15.5	1.2	12.2	1.3	13.3
Testicles	0.3	3.4	0.4	3.9	0.3	3.1	0.3	3.4
Bone marrow	0.5	5.1	0.5	5	0.5	4.6	0.5	4.4
Bladder walls	2	20	4.2	41.1	1.5	15.5	3	30
Entire body	0.5	4.8	0.5	4.8	0.4	4.2	0.4	4.2

Table 4 – Estimated radiation dose received

8.8. EXTERNAL RADIATION

The constant dose for technetium-99m (99m Tc) is 0.78 R/mCi*h at 1 cm. The first half-value layer is 0.017 cm of lead (Pb). Attenuation resulting from various thicknesses of lead is described in table 6.

SHIELD THICKNESS (Pb) cm	COEFFICIENT OF ATTENUATION
0.017	0.5
0.08	0.1
0.15	0.01
0.25	0.001
0.33	0.0001

Table 5 – Radiation attenuation by lead shielding.

Table 6 shows the correction for the physical decline of technetium-99m, after calibration time.

HOUR	REMAINING FRACTION	HOUR	REMAINING FRACTION
0*	1	7	0.447
1	0.891	8	0.398
2	0.794	9	0.355
3	0.708	10	0.316
4	0.631	11	0.282
5	0.562	12	0.251
6	0.501		

Table 6 – Physical decline; half-life of technetium-99m (99m Tc): 6.02 hours.

9. SIDE EFFECTS

Side effects may occur after the radiopharmaceutical is administered. These reactions are considered unusual or rare. Immediately after administration, a small percentage of patients may experience a bitter, metallic taste in their mouths and a slight headache.

Table 7 lists some possible side effects:

	Unusual	Rare
Chest pain	x	
Angina	x	
Abnormal ECG	x	
Arrhythmia		x
Headache	x	
Seizures immediately after administration		x
Nausea	x	
Abdominal pain		x
Skin allergy and mucosal reaction with rash		x
Itching and redness	x	
Metallic taste in the mouth	x	

Table 7 – Frequency of side effects

10. OVERDOSE

In case of a radiation overdose with MIBI-Tc-99m the patient's absorbed dose should be lowered as much as possible by ingesting more liquids to eliminate the radionuclide from the body through an increase of urination.

In case of poisoning call 0800 722 6001 for instructions of how to proceed.

RESPONSIBLE PHARMACIST
Manoela Michelon Grazziotin
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