SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MON.MIBI.KIT
1 mg lyophilized powder for I.V. injection in a vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:
Tetrakis (2-metoxy isobutyl isonitrile)
Cupper (I) tetrafluoroborate 1.0 mg

Excipients:
Sodium citrate dihydrate 2.6 mg
Sodium hydroxide q.s (for pH adjustment)
Mannitol 20 mg

For a full list of excipients, see section 6.1

It does not contain bacteriostatic protector.
There is no radioactive substance in the formulation of MON.MIBI KIT before labelling with Technetium-99m sodium pertechnetate.

3. PHARMACEUTICAL FORM

Sterile, non-pyrogenic, lyophilized powder.
White powder in 10 ml glass vial.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

It can be used for the following indications after diluted with sodium pertechnetate (^{99m}Tc) solution for intravenous injection.

Cardiology:
- It is indicated for diagnosis and follow-up of ischemic heart disease/ infarctus with myocardial perfusion scintigraphy;
- It is indicated for evaluation of left ventricle functions and wall movements.
- It is not indicated for phasing of myocardial infarctus.

Oncology:
- Diagnosis and phasing of malign tumors with overall body scintigraphic imaging;
- Scintimammographic imaging as the second phase diagnosis agent when mammography results are insufficient or doubted for the patients with intense breast tissue and doubted breast cancer.

Endocrinology:
- Diagnosis and localization of parathyroid adenoma/ hyperplasia with parathyroid scintigraphy in hyperparathyroid cases.

4.2 Posology and method of administration

Posology / administration frequency and time
Cardiac imaging: Rest and stress images may be taken in the form of same day and different day protocols. The dose recommended for an adult having the weight of 70 kg at one time is 370- 1110 MBq (10-30 mCi).
Oncologic imaging: The recommended dose for application at one time is 740- 1110 MBq (20-30 mCi).
Endocrinological imaging: The recommended dose for intravenous application at one time is 185- 740 MBq (5-20 mCi) according to the imaging technique. In the double phase technique, the image must be taken 20 minutes after injection and at 2nd hours.

Method of administration :
MON.MIBI KIT is a sterile, non-pyrogenic lyophilized powder. It is not administered directly to the patient. It is administered to patients intravenously after in vitro radio labeling with ^{99m}Tc-sodium pertechnetate.

Additional information on special populations

Renal/hepatic impairment
There is not any special study conducted on patients with renal and hepatic failure for administration of ^{99m}Tc-MIBI.

Pediatric population
While it is applied on children, there is not any study conducted specifically for this group.
Therefore, it should be taken into consideration that the diagnostic benefit is higher than the risk that may arise from radiation in the decision for application on children.

Geriatric population
There is not any study conducted specifically for application on old patients. However, any case that requires specific care for this group has not been reported in the clinic researches and the studies that contain geriatrics.

4.3 Contraindications

There is no specific contraindication defined.
It is contraindicated for the patients that have hypersensitivity to radiopharmaceutical products.

4.4 Special warnings and precautions for use

RADIOPHARMACEUTICALS SHOULD BE ADMINISTERED ONLY BY NUCLEAR MEDICINE PHYSICIANS IN NUCLEAR MEDICINE CENTERS.

The content of MON.MIBI KIT is sterile and non-pyrogenic. The preparation process should be carried out definitely under aseptic conditions.

The sodium pertechnetate solution containing oxidant agent may cause adverse effect in the processes of preparing radiopharmaceuticals. **Therefore, it should be taken care not to ventilate into the vial during procedure.**

Analysis under stress must definitely be performed under surveillance of specialized physician and in the laboratory environment that has the equipments to be able to perform the emergency intervention together with the resuscitation equipments.
The cases that require interruption of the study during an analysis under stress application and the percentage of occurrence of these cases are as follows as mentioned in the clinic study reports.

Disorder	Percentage of occurrence
Weakness	35%
Shortness of breath	17%
Chest ache	16%
ST-suppression	7%
Arrhythmia	1%

This medical product contains sodium less than 1 mmol (23 mg) in each ml. Therefore, any caution related to sodium is not required.
Any caution related to mannitol due to the administration way is not required.

4.5. Interaction with other medicinal products and other forms of interaction

Any specific study has not been conducted concerning medicine- medicine interaction.
However, radiation may affect binding to proteins inside the cell on the patients under radiotherapy, and consequently, Tc-99m-sestamibi uptake in the myocardial cells may decrease.

Additional information on special populations

Renal/hepatic impairment

There is not any additional information about the patients with renal/ liver failure.

Paediatric population
Any interaction study specific to the children has not been reported.

Geriatric population
Any interaction study specific to the geriatric population has not been reported.

4.6 Pregnancy and lactation

General recommendation
Pregnancy category: C

Women with child bearing potential/ Contraception
Effects on reproduction system with ^{99m}Tc-sestamibi have not been studied on animals. Therefore, the effects on the fertility system are not known.

Pregnancy
There is not adequate data regarding use of ^{99m}Tc-sestamibi on pregnant women.
Studies conducted on animals are inadequate with respect to effects on pregnancy / and-or / embryonic / fetal development / and-or / birth / and-or / development after birth. (See part 5.3).
Potential risk posed to humans is unknown.
MON.MIBI KIT should not be used during pregnancy unless it is necessary (^{99m}Tc-MIBI should be applied if the expected benefit is higher than potential damage.)

Lactation
Although Tc-99m-MIBI is excreted in breast milk at very low quantity (0.0084% in the first 24 hours), free ^{99m}Tc-sodium pertechnetate is excreted at a higher rate. Therefore, babies must not be fed their mother's milk for a minimum 24 hours after the analysis.

Fertility
The effect of Tc-99m-MIBI on fertility is unknown. The ideal time for administration to women at the age of fertility is 10 days following the end of menstruation.

4.7 Effects on ability to drive and use machines
Administration of ^{99m}Tc -sestamibi has no adverse effect on driving and using machines.

4.8 Undesirable effects
Adverse effects are classified according to following frequency:
Wide spread (≥1/10); common (≥1/100 to ≤1/10); not common (≥1/1000 to ≤1/100); rare (≥1/10.000 to 1/1000); very rare (≤1/10.000); unknown .

Gastrointestinal effects
Uncommon:
Metallic taste, feeling of bitter in mouth

Rare:
Dry mouth

Skin and subcutaneous
Rare:
Irritation and itch on skin
Inflammation and edema at the point of injection

Other effects
Common:
Fever
The following serious hypersensitivity reactions have been reported very rarely following second injection of ^{99m}Tc-Sestamibi.

In a short time after injection;

Neurological system
Very rate:
Dizziness
Feeling of faint

Cardiovascular system
Very rare:
Arrhythmia

Gastrointestinal system
Very rare:
Stomach ache
Vomit

Within 2 hours after injection;

Cardiovascular system
Very rare:
Hypotension
Bradycardia

Gastrointestinal system
Very rare:
Vomiting

Other
Very rare:
Weakness
Shortness of breath

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose
No symptom related to overdose administration was reported. However, the bladder should be discharged by giving plenty of liquid and diuretics to patient when it is required to apply over radiation dose due to ^{99m}Tc-sestamibi administration.

5. PHARMACOLOGIC PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Diagnostic
ATC code : V09GA01

No pharmacodynamic effect associated with the injection of Technetium-99m-sestamibi is expected.

5.2 Pharmacokinetic properties

General properties
MON.MIBI KIT is manufactured in the form of lyophilized powder as sterile and non-pyrogenic.
The solution obtained after in vitro labeling with Technetium-99m has radioactive properties and it is used through intravenous injection.

Absorption:
Technetium-99m-MIBI is the ^{99m}Tc complex that accumulates in the live myocardial tissues and that has the lipophilic cationic (+1) structure in a similar structure to Thallium chloride (Tl-201). 9^{9m}Tc-sestamibi uptake in myocardial tissue occurs through passive diffusion without using Na^+-K^+-ATPaz pump. The passive uptake rate of the medicine is determined with permeability of membrane and surface area of the vascular bed. Therefore, myocardial uptake is based on the myocardial blood stream.

Distribution:

Approximately 8% of the injected dose remains in circulation within 5 minutes after injection. Percentage of 99m Tc-sestamibi that is bound to protein in plasma is less than 1%. Myocardial uptake associated with coroner stream is 1.2% of the dose injected during rest and 1.5% of the dose injected at the exercise conditions.
Although myocardial retention mechanism has not been revealed exactly, it is seen that the distribution of medicine in myocardia is in the form of analogue of Tl-201. 99m Tc-sestamibi accumulates in the live myocardial tissue and the areas where accumulation does not occur when injected in rest position are determined as the infarct areas. When injected under stress (with exercise or pharmacological vasodilatation), ^{99m}Tc-sestamibi accumulates in myocardial muscle in association with the myocardial blood flow rate and the areas with little accumulation are determined as the ischemic areas.

Elimination:
The rate of discharge from the blood of 99m Tc-sestamibi after intravenous injection is $t_{½}$ = 4.3 minutes in rest position, and $t_{½}$ = 1.6 minutes under exercise conditions. The following Table 1.3.1-2 shows the biological and effective discharge of ^{99m}Tc-MIBI from heart and liver. (Organ concentrations are shown as the percentage of dose injected; the data are given as the average of 5 persons in rest position and 5 persons under exercise conditions).

Table 1.3.1-2: Biological and effective discharge of 99m Tc-MIBI from heart and liver

	Rest				**Exercise**			
	Heart		Liver		Heart		Liver	
Time	Biological	Effective	Biological	Effective	Biological	Effective	Biological	Effective
5 minutes	1.2	1.2	19.6	19.4	1.5	1.5	5.9	5.8
30 minutes	1.2	1.0	12.2	11.5	1.4	1.3	4.5	4.2
1 hour	1.0	0.9	5.6	5.0	1.4	1.2	2.4	2.1
2 hours	1.0	0.8	2.2	1.7	1.2	1.0	0.9	0.7
4 hours	0.8	0.5	0.7	0.4	1.0	0.6	0.3	0.2

Biological half-time is approximately 6 hours for myocardia after injection under rest or exercise conditions and approximately 30 minutes for liver. Pulmonary activity measured immediately after injection of ^{99m}Tc-sestamibi is insignificant.

^{99m}Tc-sestamibi is discharged from the body without metabolizing. It is not re-circulated on contrary to Tl-201.

The most important discharge route of Technetium-99m-sestamibi is liver-gall system. The activity taken from the gall bag is seen in the intestines within 1 hour after injection. 27% of dose injected is discharged with urine and approximately 33% is discharged with feces within 48 hours. The effective half time for discharge from body (with biological half time and radionuclide degradation) is approximately 3 hours for heart and approximately 30 minutes for liver after injection under rest or exercise conditions.

5.3 Preclinical safety data

In the acute intravenous toxicity studies conducted on mice, rats and dogs, the lowest ^{99m}Tc-sestamibi dose that causes mortality in female mice (denominated as Cu $(MIBI)_4BF_4$) is 7 mg/kg. This value is equal to 500 times the maximum dose (70 kg adult dose: 0.014 mg/kg). MIBI labelled the dose of 0.42 mg/kg (30 times the maximum human dose) was applied to rats and 0.07 mg/ kg (5 times the maximum human dose) was applied to dogs and any effect associated with the therapy was not seen in both species during 28 days. Any study has not been conducted for reproduction system toxicity. Cu $(MIBI)_4BF_4$ has not demonstrated any genotoxic activity in Ames, CHO/HPRT and sister chromatid variation tests. In the in-vitro human lymphocyte analyses, an increase has not been observed in the chromosome abnormalities in the cytotoxic concentrations. Genotoxic activity has not been observed in the study conducted at the dose of 9 mg/ kg with in vivo mouse micronucleus test. Any study has not been conducted in relation to the carcinogenic potential activities.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate dihydrate
L-cysteine HCl.H_2O
Mannitol
Stannous (II) chlorine dihydrate
Sodium hydroxide
Hydrochloric acid

6.2 Incompatibilities

Oxidizing agents which may be in ^{99m}Tc sodium pertechnetate solutions have negative effect on labelling process.

6.3 Shelf life

Shelf life for MON.MIBI KIT is 24 months.
Shelf life after labelling with radionuclide: Shelf life for ^{99m}Tc-MIBI radiopharmaceutical product after the labeling time is 8 hours.

6.4 Special precautions for storage

MON.MIBI KIT should be stored at 2-8 ºC, in refrigerator its original package and protected from light.
The kit labelled with ^{99m}Tc (^{99m}Tc-MIBI radiopharmaceutical product) should be stored at room temperature below 25 ºC in the lead shield.

6.5 Nature and contents of container

Type I borosilicate glass vial with bromobutyl stopper and aluminum flip-off cap within cardboard box.
5 vials / box.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

After labelling with ^{99m}Tc, any unused product or waste material should be disposed of in accordance with local requirements.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting etc. Radiation protection precautions in accordance with national regulations must therefore be taken.

The solution that is prepared with MON.MIBI KIT should be checked visually before use. Only clear solutions not containing visible particles should be used.

See section 12 for detailed information about preparation of MON.MIBI KIT.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER(S)

226/52

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14.10.2010
Date of last renewal: -

10. DATE OF REVISION OF THE TEXT

-

11. DOSIMETRY

Radiation Dose Equivalents (mSv/MBq)

Organ	Newborn	Child				Adult
		Age 1	Age 5	Age 10	Age 15	
Gall bladder wall	0.24	0.11	0.047	0.030	0.021	0.018
Large intestine-colon wall	0.58	0.27	0.14	0.078	0.047	0.037
Small intestine	0.12	0.064	0.076	0.055	0.034	0.027
Small intestine- cecum wall	0.32	0.16	0.16	0.10	0.064	0.050
Heart	0.043	0.022	0.013	0.0084	0.0056	0.0044
Kidneys	0.17	0.071	0.044	0.030	0.022	0.018
Liver	0.045	0.023	0.015	0.010	0.0066	0.0051
Lung	0.028	0.013	0.0071	0.0047	0.0033	0.0024
Ovaries	0.083	0.046	0.038	0.026	0.018	0.014
Bone surface	0.052	0.026	0.015	0.010	0.0070	0.0058
Red bone marrow	0.034	0.016	0.011	0.0079	0.0054	0.0045
Spleen	0.057	0.026	0.016	0.011	0.0070	0.0052
Testicles	0.038	0.018	0.012	0.0076	0.0046	0.0035
Thyroid	0.082	0.056	0.030	0.014	0.0093	0.0061
Bladder wall	0.19	0.084	0.10	0.068	0.047	0.037
Effective dose equivalent	0.13	0.061	0.045	0.029	0.019	0.015

Ref: *Radiation Dose Estimates to Adults and Children from Various Radiopharmaceuticals Latest Revision Date: 4/30/96 Radiation Internal Dose Information Center. Oak Ridge Institute for Science and Education. Oak Ridge, TN 37831*

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Preparation of ^{99m}Tc-MIBI solution via labelling of MON.MIBI KIT with Tc-99m sodium pertechnetate solution should be performed as described below under aseptic conditions and behind an appropriate lead shield, in order to protect from radiation.

- Plastic sterile gloves should be used throughout procedure.
- Kit sample stored at 2 - 8°C is taken and allowed to come to room temperature.
- Remove the flip-off cap, wipe the rubber stopper with the sanitizing swab provided and place the vial into lead shield.
- Adhere the solution label within the cardboard box to the lead shield.
- Since the product vial is sealed under the nitrogen gas, stick a sterile needle to the vial cap in order to equilibrate pressure in the vial.

With the method of boiling in water bath:

- Sterile, non-pyrogenic sodium pertechnetate solution (2-5 ml) is injected into the vial with a lead shield sterile injector. Be careful not to have air bubbles in the solution. Injector is not removed directly from the flacon.
- Maximum ^{99m}Tc activity recommended for reconstitution of a vial content is 500 mCi.
- Before removing injector needle, in order to equilibrate pressure in the vial, air is withdrawn in a volume equal to the volume of solution added to the vial.
- Kit vial in the lead shield closed with a cap is shaked up and down strongly approx. for 1 minute, in order to ensure that the lyophilized powder is completely dissolved.
- Vial is removed from the lead shield and immersed in water bath in vertical position under an appropriate lead shield and boiled for 10 minutes. (The period of 10 minutes should be started as from the time when the water starts to re-boil after immersing the vial in the water bath). During this process, care should be taken that the vial remains suspended within the water bath, and the vial bottom does not contact directly to the surface of water bath and the boiling water does not contact the aluminum cap of the vial.
- After the end of this process, the flacon is removed from the water bath and placed inside the lead shield and kept for about 15 minutes to cool down.
- Check the solution visually behind a lead shield, if it contains any particulate matter and if the solution is clear. If the solution is blurred or discoloured, it should not be used.
- Write the preparation date and time, volume, activity of the solution, and name of the preparer on the solution label on the lead shield.
- The prepared 99m Tc-sestamibi radiopharmaceutical product must be stored at room temperature below 25 ºC inside the lead shield until the expiry date.
- 99m Tc-sestamibi must be used within 8 hours after it is prepared.
- Shelf life of ^{99m}Tc-MIBI solution is 8 hours. Until the expiration time it should be stored at room temperature below 25ºC. Dispose of the remaining part which is not used after 8 hours.
- Before using ^{99m}Tc-MIBI solution, take a measurement in the dose calibrator and determine the radioactivity amount.

Kit vial contains nitrogen to avoid oxidation. Care should be taken not to apply air inside the vial while drawing the patient administration doses.

Determination radiochemical purity:

Warning: The study should be carried out in consideration of the operating conditions for radiation safety!

Radiochemical impurity determination is performed 15 minutes after kit labelling procedure.

Constant phase: TLC plate saturated with aluminum oxide

Mobile phase: Ethanol

Process steps:

1. Reconstitution of MIBI KIT with 99m Tc-pertechnetate solution is performed as described under “Preparation and Use”.

2. TLC plates saturated with aluminum oxide are cut at the dimensions of 2.5 x 7.5 cm and dried for 1 hour at 100 ºC in oven. It is stored in desiccator until the time of use and must be removed immediately before use.
3. Ethanol at 3-4 mm level is placed in chromatography tank and the cover is closed and kept for about 10 minutes and the medium is saturated.
4. 1 drop of ethanol per 1.5 cm is applied from the lower edge of plate. Before the dropped point dries out, 1 drop of ^{99m}Tc-MIBI solution are applied on ethanol. The sample drops are waited to dry out for approximately 15 minutes.
5. The plate is placed on tank and it advances for 5 cm from the drop point. The plate is removed from the tank and it is waited to dry out in air.
6. The plate is cut into two separate parts from 2.5 cm distance from dropping point and activity of the each part is counted in a dose calibrator. After this procedure, percentage of the technetium MIBI complex is calculated from the equation given below:

$$\% \ ^{99m}\text{Tc-MIBI} = \frac{\text{Upper part activity } (\mu Ci)}{\text{Lower + Upper part activity } (\mu Ci)} \times 100$$

CONCLUSION: Activity of Technetium-MIBI complex (99m Tc-Sestamibi) must not be less than 90% of the total activity.

NOTE: If the process is performed with TLC scanner, solvent is developed for 10 cm on the plate. The distribution of activity is determined with TLC scanner. From the Rf values of peaks found and the rate of peak areas, the percentage of 99m Tc-MIBI is calculated.

Pertechnetate impurity: Rf < 0.5

99m Tc-MIBI complex: Rf = 0.8- 0.9

CAUTION: In order to describe 99mTc-sestamibi solution after labeling MON.MIBI KIT with ^{99m}Tc-sestamibi, please stick specially designed paper label onto the lead shield following the completion of process or stick them on the vial before the labeling process.

Each box contains swab for disinfection of vial rubber stoppers. When you are preparing the vial for usage, please use this swabs which contain 70% isopropyl alcohol. Do not use any additional antiseptic other than the one swab contains.