IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1052/001/001
Case No: 2041882

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Bristol-Myers Squibb Pharma

Chaussee de la Hulpe 185, **B-1170 Brussels**, **Belgium**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Cardiolite kit for radiopharmaceutical preparation

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **22/10/2007**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cardiolite kit for radiopharmaceutical preparation

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:

Active ingredients

Tetrakis (2-methoxy isobutyl isonitrile) copper (I) tetrafluoroborate	1	mg
Stannous Chloride Dihydrate	75	micrograms
Cysteine Hydrochloride Monohydrate	1	mg

For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation of Technetium Tc-99m Sestamibi.

Powder for solution for injection.

Sterile non-pyrogenic lyophilized white powder for reconstitution with oxidant-free Sodium Pertechnetate Tc-99m Injection Ph. Eur.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For intravenous injection after reconstitution with Sodium pertechnetate [^{99m} Tc] solution and may be used for:

Adjunct for diagnosis of ischaemic heart disease.

Adjunct for diagnosis and localisation of myocardial infarction.

Assessment of global ventricular function (first pass technique for determination of ejection fraction and/or regional wall motion).

Aid in the diagnosis of malignancy in patients who are suspected of cancer in the breast combined with inconclusive mammography, or palpable tumour and negative or inconclusive mammography.

Diagnostic aid in the investigation of patients with recurrent or persistent hyperparathyroidism.

4.2 Posology and method of administration

The vial is reconstituted with a maximum of 11.1 GBq (300 mCi) of oxidant-free Sodium Pertechnetate Tc-99m Injection Ph. Eur. in 1-3 ml.
Not less than 3 ml will be used for the highest activity of 11.1 GBq.
Radiochemical purity should be checked prior to patient administration (see section 12).
The suggested dose range for intravenous administration to a patient of average weight (70 kg) is:

Diagnosis of reduced coronary perfusion and myocardial infarction:
185 - 740 MBq

Assessment of global ventricular function:
740 - 925 MBq
Injected as a bolus

For diagnosis of ischaemic heart disease two injections (stress and rest) are required in order to differentiate transiently from persistently reduced myocardial uptake. Not more than a total of 925 MBq should be administered by these two injections which should be done at least six hours apart but may be performed in either order. After the stress injection, exercise should be encouraged for an additional one minute (if possible).

For diagnosis of myocardial infarction one injection at rest may be sufficient.

For breast imaging: 740 - 925 MBq
Injected as a bolus.

For parathyroid imaging: 185 - 740 MBq
Injected as a bolus

(The dose used should in every case be as low as reasonably practical).

Cardiac Imaging: If possible, patients should fast for **at least** four hours prior to the study. It is recommended that patients eat a light fatty meal or drink a glass or two of milk after each injection, prior to imaging. This will promote rapid hepatobiliary clearance of Technetium Tc-99m Sestamibi resulting in less liver activity in the image.

The heart to background ratio will increase with time but the ideal imaging time, reflecting the best compromise between heart count rate and contrast, is approximately 1-2 hours after rest injection and stress injection. There is no evidence for significant changes in myocardial tracer concentration or redistribution, therefore imaging for up to 6 hours post injection is possible.

Either planar or tomographic imaging can be performed for diagnosis of ischaemic heart disease and myocardial infarction. Both may be performed ECG gated.

For planar imaging: the standard three view (anterior, LAO 45º, LAO 70º or LL) planar projections should be used (e.g. 5-10 minutes each).

For tomographic imaging: each projection should be acquired for approximately 20-40 seconds depending on injected dose.

For assessment of **global ventricular function** the same standard techniques and projections can be used, as established for Tc-99m first pass ejection studies; data should be acquired in list or fast frame mode in a computer using a high count rate scintillation camera. Gated Blood Pool Imaging protocols may be used for assessment of regional wall motion; however, they must only be evaluated visually.

Breast imaging: is optimally initiated 5 to 10 minutes post injection with the patient in the prone position with breast freely pendant. A 10 minute lateral image of the breast suspected of containing cancer should be obtained with the camera face as close to the breast as practical.

The patient should then be repositioned so that the contralateral breast is pendant and a lateral image of it should be obtained. An anterior supine image may then be obtained with the patient's arms behind her head.

Parathyroid imaging: depends on whether subtraction technique or wash-out technique is used.

For the subtraction technique, either sodium iodide (I-123) or Tc-99m pertechnetate can be used. When I-123 is used, 11 to 22 MBq of oral sodium iodide (I-123) are administered. Four hours after the administration of I-123, I-123 neck and thorax images are obtained. After I-123 acquisition 185 to 370 MBq of Tc-99m Sestamibi are injected and images acquired 10 minutes post injection. When pertechnetate is used, 37 to 148 MBq of sodium pertechnetate are injected and neck and thorax images are acquired 30 minutes later. After image acquisition, 185-370 MBq of Tc-99m Sestamibi are injected and images acquired 10 minutes post injection.

If double-phase technique is used, 370 to 740 MBq of Tc-99m Sestamibi are injected and the first neck and thorax image obtained 10 minutes later. After a wash-out period of 1 to 2 hours, neck and thorax imaging is again performed.

Safety and efficacy in children below the age of 18 have not been established.

4.3 Contraindications

There are no known contraindications.

4.4 Special warnings and precautions for use

For each patient, exposure to ionising radiation must be justified on the basis of likely benefit. The activity administered must be such that the resulting radiation dose is as low as reasonably achievable bearing in mind the need to obtain the intended diagnostic or therapeutic result.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects.

For diagnostic nuclear medicine investigations the current evidence suggests that these adverse effects will occur with low frequency because of the low radiation doses incurred.
For most diagnostic investigations using a nuclear medicine procedure the radiation dose delivered (effective dose/ EDE) is less than 20 mSv. Higher doses may be justified in some clinical circumstances.

Contents of the vial are intended only for use in the preparation of Technetium Tc-99m Sestamibi and are not to be administered directly to the patient without first undergoing the preparative procedure.

This radiopharmaceutical may be received, used and administered only by authorised persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the local competent official organisation.

Radiopharmaceuticals should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken, complying with the requirements of Good Manufacturing Practice for pharmaceuticals.

Radiopharmaceutical agents should be used only by qualified personnel with the appropriate government authorisation for use and manipulation of radionuclides.

No data concerning the diagnostic efficacy in suspected recurrence or metastatic disease are available.

PROPER HYDRATION AND FREQUENT URINATION ARE NECESSARY TO REDUCE BLADDER IRRADIATION

IN CASE OF KIDNEY FAILURE, EXPOSURE TO IONISING RADIATION CAN BE INCREASED. THIS MUST BE TAKEN INTO ACCOUNT WHEN CALCULATING THE ACTIVITY TO BE ADMINISTERED

4.5 Interaction with other medicinal products and other forms of interaction

No drug interactions have been described to date.

4.6 Pregnancy and lactation

When it is necessary to administer radioactive products to women of childbearing potential, information should be sought about pregnancy.
Any woman who has missed a period should be assumed to be pregnant until proven otherwise.
Where uncertainty exists it is important that radiation exposure should be the minimum consistent with obtaining the desired clinical information. Alternative techniques which do not involve ionising radiation should be considered.

The anticipated dose to the uterus from a 740 MBq rest injection would be 5.8 mGy.
A radiation dose above 0.5 mGy (approximately equivalent to that exposure from annual background radiation) could potentially result in risk to the foetus.
It is therefore contraindicated in women known to be pregnant.

Before administering a radioactive medicinal product to a mother who is breast feeding consideration should be given as to whether the investigation could be reasonably delayed until after the mother has ceased breast feeding and as to whether the most appropriate choice of radiopharmaceutical has been made, bearing in mind the secretion of activity in breast milk.

If the administration is considered necessary, breast feeding should be interrupted for 24 hours and the expressed feeds discarded.
It is usual to advise that breastfeeding can be restarted when the level in the milk will not result in a radiation dose to the child greater than 1 mSv.

4.7 Effects on ability to drive and use machines

Effects on the ability to drive and use machines have not been described.

4.8 Undesirable effects

Immediately after injection of Technetium Tc-99m Sestamibi, a small percentage of patients experienced a metallic or bitter taste, transient headache, flushing and a non-itching rash.
A few cases of oedema, injection site inflammation, dyspepsia, nausea, vomiting, pruritus, urticaria, dry mouth, fever, dizziness, fatigue, dyspnoea and hypotension have been attributed to administration of the agent.
There have also been very rare reports (<0.001%) of signs and symptoms consistent with seizure after administration; a casual relationship to Cardiolite has not been established.

4.9 Overdose

In the event of administration of a radiation overdose with Technetium Tc-99m Sestamibi the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by frequent micturation and defaecation.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacodynamic effects are not expected after administration of Cardiolite.

Pharmacotherapeutic group: diagnostic radiopharmaceuticals V09G A01.

Further Clinical Information

Complementary information in the case of diagnosis of malignancy in patients who are suspected of cancer in the breast combined with inconclusive mammography or palpable tumour and negative or inconclusive mammography.

The overall clinical trial population consisted of 673 patients with palpable (286 subjects) or mammographically-detected, non palpable (387 subjects) abnormalities. The median age of the subjects was 52 years. When institutional read scintigraphy is compared to true disease state using core laboratory histopathology, the diagnostic statistics are good in the combined trial population. In this population, the prevalence of malignancy was 40% in the imaged subjects. Using whole breast analysis, the sensitivity of scintigraphy was 85.4%, the specificity was 78.8%, and the positive and negative predictive values were 72.7% and 89.1% respectively.

5.2 Pharmacokinetic properties

After reconstitution with Sodium Pertechnetate Tc-99m Injection, Ph. Eur. solution, the following complex forms (Technetium Tc-99m Sestamibi):

Tc-99m $(MIBI)_6^+$ Where : MIBI = 2-methoxyisobutylisonitrile

Like Thallous Chloride T1 201, this cationic complex accumulates in the viable myocardial tissue proportional to the circulation. Scintigraphic pictures which were obtained after i.v. injection of Technetium Tc-99m Sestamibi to animals and man are comparable with those obtained with Thallous Chloride T1 201. This correlation applies to normal as well as infarcted and ischaemic cardiac tissue.

Technetium Tc-99m Sestamibi from the blood is rapidly distributed into the tissue: 5 minutes after injection only about 8% of the injected dose is still in circulation.

Animal experiments have shown that uptake is not dependent on the functional capability of the sodium-potassium pump.

Elimination
The major metabolic pathway for clearance of Technetium Tc-99m Sestamibi is the hepatobiliary system. Activity from the gallbladder appears in the intestine within one hour of injection. About twenty-seven percent of the injected dose is cleared through renal elimination after 24 hours and approximately thirty-three percent of the injected dose is cleared through the faeces in 48 hours. At five minutes post injection about 8% of the injected dose remains in circulation.

Half-Life
The biological myocardial T½ is approximately seven (7) hours at rest and stress. The effective T½ (which includes biological and physical half-lives) is approximately three (3) hours.

Myocardial uptake
Myocardial uptake which is coronary flow dependent is 1.5% of the injected dose at stress and 1.2% of the injected dose at rest.

5.3 Preclinical safety data

In acute intravenous toxicity studies in mice, rats and dogs, the lowest dose of the reconstituted Cardiolite kit that resulted in any deaths was 7 mg/kg (expressed as Cu $(MIBI)_4$ BF_4 content) in female rats.

This corresponds to 500 times the maximal human dose (MHD) of 0.014 mg/kg for adults (70 kg).
Neither rats nor dogs exhibited treatment related effects at reconstituted Cardiolite kit doses of 0.42 mg/kg (30 times MHD) and 0.07 mg/kg (5 times MHD) respectively for 28 days.
Studies on reproductive toxicity have not been conducted. Cu $(MIBI)_4$ BF_4 showed no genotoxic activity in the Ames, CHO/HPRT and sister chromatid exchange tests.

At cytotoxic concentrations, an increase in chromosome aberration was observed in the in vitro human lymphocyte assay.
No genotoxic activity was observed in the in vivo mouse micronucleus test at 9 mg/kg.
Studies to assess the carcinogenic potential of Cardiolite have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Citrate
Mannitol

6.2 Incompatibilities

The Technetium labelling reactions involved depend on maintaining the stannous level in the reduced state. Hence, Sodium Pertechnetate Tc-99m Injection Ph.Eur., containing oxidants should not be employed.

6.3 Shelf Life

Finished product: 24 months
After reconstitution the product should be used within 10 hours

6.4 Special precautions for storage

Before and after preparation, the drug should not be stored above $25^{O}C$ and should be protected from light. The contents of the vial are not radioactive. However, after labelling with Sodium Pertechnetate Tc-99m Injection Ph.Eur. the contents are radioactive and the currently valid protection and safety regulations must be complied with.

6.5 Nature and contents of container

5 ml glass vials, type I borosilicate glass (Ph. Eur.) sealed with a halobutyl stopper and crimped with an aluminium seal. The product is available in packs of 2 and 5 vials.

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

See section 12

7 MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma Belgium Sprl
Chaussée de la Hulpe 185
B-1170 Brussels
Belgium

8 MARKETING AUTHORISATION NUMBER

PA1052/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First date of authorisation: 26 August 1991
Last date of renewal: 26 August 2006

10 DATE OF REVISION OF THE TEXT

January 2007

11 DOSIMETRY

The projected radiation doses to organs and tissues of an average (70kg) patient after intravenous injection of Technetium Tc-99m Sestamibi are given below:

Data adopted from ICRP-publication nr. 62 (Volume 22. nr. 3. 1993): “Radiological Protection in Biomedical Research.”

Absorbed dose per unit administered activity (mGy/MBq) for adults

Organ	At rest	Stress
Pancreas	7.7E-03	6.9E-03
Uterus	7.8E-03	7.2E-03
Adrenals	7.5E-03	6.6E-03
Bladder wall	1.1E-02	9.8E-03
Breast	3.8E-03	3.4E-03
Bone surface	8.2E-03	7.8E-03
Gall bladder wall	3.9E-02	3.3E-02
Heart	6.3E-03	7.2E-03
Brain	5.2E-03	4.4E-03
Skin	3.1E-03	2.9E-03
Liver	1.1E-02	9.2E-03
Lungs	4.6E-03	4.4E-03
GI-tract		
Stomach	6.5E-03	5.9E-03
Small intestine	1.5E-02	1.2E-02
Upper large intestine	2.7E-02	2.2E-02
Lower large intestine	1.9E-02	1.6E-02
Spleen	6.5E-02	5.8E-03
Kidneys	3.6E-02	2.6E-02
Ovaries	9.1E-03	8.1E-03
Red marrow	5.5E-03	5.0E-03
Thyroid	5.3E-03	4.4E-03
Oesophagus	4.1E-03	4.0E-03
Salivary glands	1.4E-02	9.2E-03
Muscle	2.9E-03	3.2E-03
Testes	3.8E-03	3.7E-03
Thymus	4.1E-03	4.0E-03
Other organs	3.1E-03	3.3E-03
ED (mSv/MBq)	8.5E-03	7.5E-03

The effective dose resulting from an administered amount of 925 MBq in the adult is 7.9 mSv at rest and 6.9 mSv at stress.

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

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

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 preparation contains no bacteriostatic preservative.

Technetium Tc-99m Sestamibi is to be used within ten (10) hours of reconstitution.

Reconstitute with oxidant-free Sodium Pertechnetate Tc-99m Injection, Ph.Eur. The resulting solution is clear and colourless.

As with any pharmaceutical product, if at any time in the preparation of this product the integrity of this vial is compromised it should not be used.

Instructions for Preparation of Technetium Tc-99m Sestamibi

A. Boiling Procedure

Preparation of Technetium Tc-99m Sestamibi from the Cardiolite Kit is to be done according to the following aseptic procedure:

1. Waterproof gloves should be worn during the preparation procedure. Remove the plastic disc from the Cardiolite Kit vial and swab the top of the vial closure with alcohol to disinfect the surface.

2. Place the vial in a suitable radiation shield appropriately labelled with date, time of preparation, volume and activity.

3. With a sterile shielded syringe, aseptically obtain additive-free, sterile, nonpyrogenic Sodium Pertechnetate Tc-99m solution (max 11.1 GBq – 300 mCi) in approximately 1 to 3 ml. Not less than 3 ml will be used for the highest activity of 11.1 GBq.

4. Aseptically add the Sodium Pertechnetate Tc-99m solution to the vial in the lead shield. Without withdrawing the needle, remove an equal volume of headspace to maintain atmospheric pressure within the vial.

5. Shake vigorously, about 5 to 10 quick upward-downward motions.

6. Remove the vial from the lead shield and place **upright** in a boiling water bath, such that the vial is suspended above the bottom of the bath, and boil for 10 minutes. The bath must be shielded. Timing for the 10 minutes commences as soon as the water **begins to boil** again.

Note: The vial **must** remain upright during the boiling step. Use a water bath where the stopper will be above the level of the water.

7. Remove the shielded vial from the water bath and allow to cool for fifteen minutes.

8. Inspect visually for the absence of particulate matter and discoloration prior to administration.

9. Aseptically withdraw material using a sterile shielded syringe. Use within ten (10) hours of preparation.

10. Radiochemical purity should be checked prior to patient administration according to the Radio TLC Method as detailed in the Package Insert.

Note: The potential for cracking and significant contamination exists whenever vials containing radioactive material are heated.

B. Thermal Cycler Procedure

Preparation of Technetium Tc-99m Sestamibi from the Cardiolite Kit is to be done according to the following aseptic procedure:

1. Waterproof gloves should be worn during the preparation procedure. Remove the plastic disc from the Cardiolite Kit vial and swab the top of the vial closure with alcohol to disinfect the surface.

2. Place the vial in a suitable radiation shield appropriately labelled with date, time of preparation, volume and activity.

3. With a sterile shielded syringe, aseptically obtain additive-free, sterile, non-pyrogenic Sodium Pertechnetate Tc-99m solution (max 11.1 GBq – 300 mCi) in approximately 1 to 3 ml. Not less than 3ml will be used for the highest activity of 11.1 GBq.

4. Aseptically add the Sodium Pertechnetate Tc-99m solution to the vial in the lead shield. Without withdrawing the needle, remove an equal volume of headspace to maintain atmospheric pressure within the vial.

5. Shake vigorously, about 5 to 10 quick upward-downward motions.

6. Place shield in the sample block. While slightly pressing downwards, give the shield a quarter turn to make certain there is a firm fit between the shield and the sample block.

7. Press the proceed button to initiate the program (the thermal cycle automatically heats and cools the vial and contents). Please see the Recon-o-stat Instruction Manual for further details.

8. Inspect visually for the absence of particulate matter and discoloration prior to administration.

9. Aseptically withdraw material using a sterile shielded syringe. Use within ten (10) hours of preparation.

10. Radiochemical purity should be checked prior to patient administration according to the Radio TLC Method as detailed below.

Radio - TLC Method for the Quantification of Technetium Tc-99m Sestamibi

1. Materials

1.1 Baker-Flex-Aluminium Oxide plate, #1 B-F, pre-cut to 2.5 cm x 7.5 cm.

1.2 Ethanol >95%.

1.3 Capintec, or equivalent instrument for measuring radioactivity in the 0.74 - 11.12 GBq (20-300 mCi) range.

1.4 1 ml syringe with a 22-26 gauge needle.

1.5 Small developing tank with cover, (100 ml beaker covered with Parafilm® is sufficient).

2. Procedure

2.1 Pour enough ethanol into the developing tank (beaker) to have a depth of 3-4 mm of solvent. Cover the tank (beaker) with Parafilm® and allow it to equilibrate for approximately 10 minutes.

2.2 Apply 1 drop of ethanol, using a 1 ml syringe with a 22-26 gauge needle on to the Aluminium Oxide TLC plate, 1.5 cm from the bottom. **Do not allow the spot to dry.**

2.3 Apply 1 drop of the kit solution on top of the ethanol spot. Dry the spot. **Do not heat!**

2.4 Develop the plate a distance of 5.0 cm from the spot.

2.5 Cut the strip 4.0cm from the bottom, the measure each piece in your dose calibrator.

2.6 Calculate the % Radiochemical purity as:
% Tc-99m Sestamibi = (Activity top portion)/(Activity both pieces) x 100.

2.7 % Tc-99m Sestamibi should be ≥ 94%, otherwise the preparation should be discarded.

Note: Do not use material if the radiochemical purity is less than 94%.

After reconstitution the container and any unused contents should be disposed of in accordance with local requirements for radioactive materials.