IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0401/003/001
Case No: 1010602

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

Amersham Health Srl

Via Crescentino, **13040 Saluggia (Vercelli)**, **Italy**

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

Macrotec

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 **23/11/2007** until **22/11/2012**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Macrotec
Powder for suspension for injection
Kit for radiopharmaceutical preparation

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human albumin macroaggregates (MAA) 2.0mg

Each vial contains 4.5 x 10^6 MAA particles. The size range is 10-90µm.

The product is prepared from batches of human albumin.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Kit for the preparation of Technetium (^{99m}Tc) Macrosalb Injection PhEur. The product comprises five vials each containing a sterile white to off-white solid deposit.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

This medical product is for diagnostic use only

After labelling with sodium pertechnetate (^{99m} TC) solution, the agent may be used for:

- Pulmonary perfusion scintigraphy.
- As secondary indication ^{99m} Tc-albumin macroaggregates may be used for venoscintigraphy.

4.2 Posology and method of administration

Adult doses

Recommended activities to be administered intravenously to an adult weighing 70 kg varies between 37 - 185 MBq (1-5 mCi). The number of particles per administered dose must be in a range of 60 x 10^3 - 700 x 10^3. The lung test may start immediately after injection.

Paediatric doses

The activity to be administered in children should be a fraction of the adult activity and should be calculated according to the following equation:

$$\text{Paediatric dose (MBq)} = \frac{\text{Adult dose (MBq) x child weight (kg)}}{70 \text{ kg}}$$

Although body weight is the more used factor on which to base the adjustment of the activity administered, in a limited number of cases the body
surface area may be considered to be more appropriate.

$$\text{Paediatric dose (MBq)} = \frac{\text{Adult dose (MBq) x child surface } (m^2)}{1.73}$$

4.3 Contraindications

There are no specific contraindications.

4.4 Special warnings and precautions for use

Radiopharmaceuticals should be used only by authorised persons. Their receipt, use, transfer and disposal are subject to national licensing regulations.
Radiopharmaceuticals should be prepared by the user in a manner which satisfies both radiological safety and pharmaceuticals requirements.
When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donatorion and pools of plasma for signs if virus/infections. Manufacturers of these proudcts also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to an unknown or emerging viruses or other types of infections.

There are no reports of virus infections with albumin manufactured to European Pharmacopoeia specifications by estabilised processes.

It is strongly recommended that every time you receive a dose of Macrotec the name and the batch number of the product are recorded in order to maintain a record of the batches used.

The possibility of hypersensitivity including serious, life-threatening, fatal anaphylactic/anaphylactoid reactions should always be considered. Advanced life support facilities should be readily available.

The syringe should be gently swirled immediately prior to injection to homogenise the injectate. Blood should never be drawn into the syringe because that induces the formation of small clots.
Special care should be exercised when administering ^{99m}Tc-MAA to patients with significant right to left cardiac shunt. In order to minimise the possibility of microembolism to the cerebral and renal circulations ^{99m}Tc-MAA should be given by slow intravenous injection and the number of particles reduced by up 50%. Such precautions are also advised in patients with respiratory failure complicating pulmonary hypertension.

4.5 Interaction with other medicinal products and other forms of interaction

Changes in the biological distribution of ^{99m}Tc-MAA are induced by different drugs.

- Pharmacologic interactions are caused by chemotherapeutic agents, heparin, bronchodilators.

- Toxicologic interactions are caused by heroin, nitrofurantoin, busulfan, cyclophosphamide, bleomycin, methotrexate, methysergide.

- Pharmaceutic interactions are caused by magnesium sulphate.

4.6 Pregnancy and lactation

Elective exposure to diagnostic radiation should be restricted in so far as possible to the first 10 days of the ovulation cycle.

When it is necessary to administer radioactive medicinal products to women of childbearing potential, information should always be sought about pregnancy. Any women 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 achieving the desired clinical information. Alternative techniques which do not involve ionising radiation should always be considered.

Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus. Only imperative investigations should therefore be carried out during pregnancy, when the likely benefit exceeds the risk incurred by the mother and the foetus.

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 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 12 hours and the expressed feeds discarded. Breast feeding can be restarted when the activity 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

None are to be expected after use of this product.

4.8 Undesirable effects

Single or repeated injections of ^{99m}Tc-albumin macroaggregates may be associated with hypersensitive-type reactions, with chest pain, rigor and collapse. Local allergic reactions have been seen at the injection site.

For each patient, exposure to ionising radiation must be justifiable 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 with 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 (EDE) is less than 20 mSv. Higher doses may be justified in some clinical circumstances.

4.9 Overdose

Overdose, as commonly intended (i.e., excessive quantity in weight) is not expected, but overdose may be understood as the administration of a very high number of particles. The number of MAA particles per adult patient must not exceed 1.5×10^6.

The dangers to be expected relating to the inadvertent administration of excess radioactivity may be reduced by promoting a diuresis and frequent voiding of urine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacodynamic properties
ATC code V09EB01

^{99m}Tc-MAA, when administered at the recommended doses, shows no pharmacodynamic effects detectable clinically or/and analytically.

5.2 Pharmacokinetic properties

Following injection into a superficial vein of the systemic venous circulation, the macroaggregates are carried at the speed of this circulation to the first capillary filter, i.e. the capillary tree of the pulmonary artery system.

The albumin macroaggregates particles do not penetrate the lung parenchyma (interstitial or alveolar) but remain in a temporary occlusive position in the lumen of the capillary. When pulmonary flow distribution is normal, the compound distributes over the entire pulmonary area following physiologic gradients; when district flow is altered the areas of reduced flow are reached by a proportionally smaller amount of particles. The technetium labelled macroaggregates remain in the lungs for variable periods of time, depending of the structure, size and number of particles.

The disappearance of activity from the particles in the lungs is governed by an exponential law: the larger aggregates have a longer biological half-life, whereas particles between 5 and 90 μm in diameter have a half-life ranging from 2 to 8 hours.

The decrease in pulmonary concentration is caused by the mechanical break-down of the particles occluding the capillaries, stemming from the systo-diastolic pressure pulsations within the capillary itself.

The products of macroaggregate break-down, once recirculated as albumin microcolloid, are quickly removed by the macrophages of the reticuloendothelial system, i.e. essentially the liver and the spleen.

The microcolloid is metabolized with introduction of the radioactive label (^{99m}Tc) into the systemic circulation from which it is removed and excreted in urine.

5.3 Preclinical safety data

Correlation exists between the size of the MAA and their toxic effects.

The pathophysiologic mechanism responsible for toxicity is shown to be the increase of the pulmonary blood pressure. With particles from 10 to 50 μm in a diameter the first pulmonary signs of toxicity in dogs (e.g. tachypnea) appear after injection of 20 to 25 mg per kg of body weight.

A sharp increase of the pulmonary blood pressure is noticed when 20 mg of less than 80 μm sized MAA are injected, while not significant pressure changes are recorded with 40 mg of less than 35 μm MAA particles.

With suspension of MAA up to 150 μm diameter, no blood pressure changes appear below 10 mg/kg, while larger diameter suspensions (up to 300 μm) typical blood pressure changes in pulmonary artery appear when the doses exceeds 5 mg/kg.

Doses of 20-50 mg/kg cause sudden death for respiratory failure. A safety factor of 100 is found after injection in dogs of 14,000 ^{99m}Tc-MAA (size: 30-50 μm).

The repeated-dose toxicity studies performed in dogs show no detectable variations in the general behaviour of the animals.

No evidence of pathological changes in the main organs has been detected.

There is no evidence in the literature of teratogenic, mutagenic or carcinogenic effect of the unlabelled product.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Stannous chloride
Human albumin
Sodium acetate
Water for injections

6.2 Incompatibilities

None known

6.3 Shelf Life

Unopened:
18 months

Reconstituted with Sodium Pertechnetate [^{99m}Tc] Solution Ph.Eur.:
6 hours after labelling

6.4 Special precautions for storage

Unopened vial

Store at 2-8°C

Reconstituted: store below 25°C. Do not freeze.

6.5 Nature and contents of container

10ml type I Ph.Eur., clear, colourless, borosilicate glass vial sealed with a grey, bromobutyl rubber closure and oversealed with an aluminium overseal with central aperture.

Pack sizes: Kit of 5 multidose vials

6.6 Special precautions for disposal and other handling

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

Method of preparation

- Place vial containing the MAA in a convenient lead shield
- Aseptically introduce in the vial 4-10 sodium-pertechnetate (Tc-99m) injection Ph.Eur with a radioactivity ranging from 1480 to 3700 MBq (40 to 100 mCi).
- Do not use a breather needle.
- Invert carefully a few times to suspend the dried albumin macroaggregates. Then allow to stand for about 5 min at room temperature.
- Shake before withdrawing a dose.
- In no case should the preparation be left in contact with air.

Quality Control

Both of the following methods can be used:

A – Non filterable radioactivity at 5 min after labelling:

Membrane filter ……3 µm diameter pore filter
Filtered volume …… 200 µL
Wash solution …… 20 ml saline solution

The radioactivity remaining in the membrane must be ≥ 90% of the total radioactivity

B – Radiochemical purity test at 5 min after labelling
Free ^{99m} Tc by chromatography on ITLC-SG:
Support ……. ITLC-SG
Eluent …….. Methanol : water 85:15 v/v
Time ……... 5-10 min
Free ^{99m} Tc …… ≤ 5.0%
Rf ……..…0.9±10%

7 MARKETING AUTHORISATION HOLDER

Amersham Health Srl
Via Crescentino
13040 Saluiggia (Vercelli)
Italy

8 MARKETING AUTHORISATION NUMBER

PA 401/3/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 23rd November 2007

10 DATE OF REVISION OF THE TEXT

11 DOSIMETRY

Technetium (^{99m}Tc) decays with the emission of gamma radiation with energy of
140 keV an a half life of 6 hours to technetium (^{99}Tc) which can be regarded as quasi stable.

For this product the effective dose equivalent resulting from an administered activity of 185 MBq is typically 2.2 mSv (per 70 Kg individual).

According to ICRP 80(1998) the radiation doses absorbed by the patient are the following:

Absorbed dose Per unit activity administered (mGy/MBq)					
Organ	**Adult**	**15 year**	**10 year**	**5 year**	**1 year**
*Adrenals	5.8E-03	8.7E-03	1.3E-02	1.9E-02	3.1E-02
*Bladder wall	1.0E-02	1.3E-02	1.9E-02	2.8E-02	5.1E-02
Bone surfaces	3.5E-03	4.4E-03	6.4E-03	9.7E-03	1.9E-02
Breast	5.6E-03	5.5E-03	1.0E-02	1.4E-02	2.2E-02
GI tract:					
Stomach wall	4.0E-03	5.2E-03	7.8E-03	1.2E-02	2.0E-02
Small intestine	2.1E-03	2.6E-03	4.3E-03	7.0E-03	1.3E-02
ULI wall	2.2E-03	2.9E-03	5.0E-03	8.4E-03	1.5E-02
LLI wall	1.6E-03	2.1E-03	3.5E-03	5.4E-03	1.0E-02
Kidneys	3.7E-03	4.8E-03	7.2E-03	1.1E-02	1.8E-02
*Liver	1.6E-02	2.1E-02	3.0E-02	4.3E-02	7.5E-02
Lungs	6.7E-02	9.9E-02	1.4E-01	2.1E-01	4.0E-01
Ovaries	1.8E-03	2.3E-03	3.7E-03	5.9E-03	1.1E-02
*Pancreas	5.8E-03	7.5E-03	1.1E-02	1.7E-02	2.9E-02
Red marrow	4.4E-03	6.2E-03	8.3E-03	1.1E-02	1.7E-02
*Spleen	4.4E-03	5.6E-03	8.3E-03	1.3E-02	2.2E-02
Testes	1.1E-03	1.4E-03	2.3E-03	3.7E-03	7.1E-03
Thyroid	2.0E-03	3.3E-03	5.5E-03	9.0E-03	1.6E-02
Uterus	2.4E-03	2.9E-03	4.6E-03	7.1E-03	1.3E-02
Other tissues	2.9E-03	3.6E-03	5.2E-03	7.8E-03	1.4E-02
Effective dose equivalent (mSv/MBq)	1.2E-02	1.8E-02	2.5E-02	3.8E-02	6.9E-02

For an administered activity of 185 MBq the typical radiation dose to the target organ, lungs, 12.2 mGy an the typical radiation dose to the critical organs adrenals, blader wall, liver, pancreas, spleen are 1.26 – 1.61 – 2.96 – 1.04 and 0.76 mGy, respectively.