SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Hepatate
Kit for the preparation of Technetium $^{99m}$Tc Colloidal Tin Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Stannous fluoride USP 0.125mg/vial

3 PHARMACEUTICAL FORM

Radiopharmaceutical kit. Powder for solution for injection.

4 CLINICAL PARTICULARS

4.1 Diagnostic indications

After reconstitution with Sodium Pertechnetate $^{99m}$Tc Injection solution.

- Reticuloendothelial imaging of liver and spleen

4.2 Posology and method of administration

The solution is administered intravenously. In adults, the dose is 37 to 185MBq for static imaging, other doses may be justifiable. Imaging may commence 10 minutes after injection. For dynamic imaging the dose in adults is 80 to 185MBq, other doses may be justifiable. Imaging may commence immediately after i.v. administration. The dose to be administered in a child should be a fraction of the adult dose calculated from the body weight according to the following table:
Table: Dose calculation for use of Technetium $^{99m}$Tc Hepatate Injection in Children. Fraction of adults dose:

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Kg</th>
<th>Dose</th>
<th>Kg</th>
<th>Dose</th>
<th>Kg</th>
<th>Dose</th>
<th>Kg</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Kg</td>
<td>0.1</td>
<td>22 Kg</td>
<td>0.50</td>
<td>42 Kg</td>
<td>0.78</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4 Kg</td>
<td>0.14</td>
<td>24 Kg</td>
<td>0.53</td>
<td>44 Kg</td>
<td>0.80</td>
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<td></td>
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</tr>
<tr>
<td>6 Kg</td>
<td>0.19</td>
<td>26 Kg</td>
<td>0.56</td>
<td>46 Kg</td>
<td>0.82</td>
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<td></td>
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</tr>
<tr>
<td>8 Kg</td>
<td>0.23</td>
<td>28 Kg</td>
<td>0.58</td>
<td>48 Kg</td>
<td>0.85</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 Kg</td>
<td>0.27</td>
<td>30 Kg</td>
<td>0.62</td>
<td>50 Kg</td>
<td>0.88</td>
<td></td>
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</tr>
<tr>
<td>12 Kg</td>
<td>0.32</td>
<td>32 Kg</td>
<td>0.65</td>
<td>52-54 Kg</td>
<td>0.90</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>14 Kg</td>
<td>0.36</td>
<td>34 Kg</td>
<td>0.68</td>
<td>56-58 Kg</td>
<td>0.92</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 Kg</td>
<td>0.40</td>
<td>36 Kg</td>
<td>0.71</td>
<td>60-62 Kg</td>
<td>0.96</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 Kg</td>
<td>0.44</td>
<td>38 Kg</td>
<td>0.73</td>
<td>64-66 Kg</td>
<td>0.98</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 Kg</td>
<td>0.46</td>
<td>40 Kg</td>
<td>0.76</td>
<td>68 Kg</td>
<td>0.99</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

(Paediatric Task Group, EANM)

In very young children (up to 1 year) a minimum dose of 15MBq is necessary to obtain images of sufficient quality.

4.3 **Contraindications**

There are no specific contraindications.

4.4 **Special warnings and precautions for use**

This radiopharmaceutical may be used and administered only by authorized persons.

Radiopharmaceuticals intended for administration to patients should be prepared by the user in a manner which satisfies both radiological safety and pharmaceutical quality requirements.

4.5 **Interactions with other medicinal products and other forms of interaction**

Drugs known to be associated with short-term or long-term hepatotoxicity, such as cancer chemotherapy, contraceptives, tetracyclines and drugs which may affect hepatic blood flow, such as certain anaesthetics, may be expected to affect the biodistribution patterns of radiolabelled colloids.

4.6 **Pregnancy and lactation**

When it is necessary to administer radioactive medicinal products to a woman of childbearing potential, information should always 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 the radiation exposure should be the minimum consistent with achieving the desired clinical information. Alternative techniques which do not involve ionising radiation should be considered.

Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus. Only imperative investigations should be carried out during pregnancy, when the likely benefit exceeds the risk incurred by mother and 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 the breast feeding should be interrupted for 12 hours and the expressed feeds discarded. Breast feeding can be restarted when the level in milk will not result in a radiation dose to the child greater than 1mSv.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive or to operate machines are to be expected after use of this product.

4.8 Undesirable effects

Adverse reactions have occasionally been reported following the intravenous injection of colloids for liver and spleen imaging. The reactions generally involve vaso-motor problems with malaise, bradycardia and lowered blood pressure. Angio-oedema, often facial, may occur, as may central chest or back pain with shortness of breath, occasionally complicated by true bronchospasm. Cutaneous reactions are relatively rare. The majority of reactions have been relatively mild but supportive treatment and/or an antihistamine may be required.

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 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 (EDE) is less than 20 mSv. Higher doses may be justified in some clinical circumstances.

4.9 Overdose

No specific therapy is possible in the event of the administration of an overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code V09D B04

At doses used for diagnostic procedures, technetium $^{99m}$ Tc colloidal tin does not appear to exert any pharmacodynamic effects.
5.2  **Pharmacokinetic properties**

The process of ingestion of foreign materials including particulate matter by the cells of the reticuloendothelial system is well documented.

The site of phagocytosis depends on a number of factors including the size of the particles - large particles are trapped in the lungs, smaller particles are taken up in the liver and spleen.

Upon intravenous injection, technetium \(^{99m}\) Tc colloidal tin is rapidly cleared from the blood by the reticuloendothelial system with a nominal clearance half-life of approximately 1½ minutes.

Uptake of the radioactive colloid by the components of the reticuloendothelial system is dependent upon relative blood flow rates and the functional capacity of phagocytic cells. In an average patient, 80 to 90% of the injected colloid particles are phagocytosed by the Kupffer cells of the liver, 5 to 10% are taken up by the spleen and by the bone marrow.

If hepatic function is impaired, particles will be phagocytosed in the lung and bone marrow more than in the liver. Increased uptake in the spleen indicates diffuse liver disease.

5.3  **Preclinical safety data**

A single dose toxicity study of the intravenous administration of a stannous fluoride based agent in rats showed no adverse reactions, changes in body weight or mortalities at a dose equivalent to at least 400 times the maximum human dose.

In rabbits a similar study showed no significant toxicity at 168 times the maximum human dose on a mg/kg basis.

Fourteen day subacute (IV) studies in mice and dogs produced no significant signs of toxicity at levels of 3108 and 490 times the maximum human dose.

5.4  **Radiation dosimetry**

Absorbed radiation dose estimates following intravenous injection of technetium \(^{99m}\) Tc as colloid are given from ICRP Publication 53. These provide values for three liver conditions:

1. Normal
2. Early to intermediate diffuse parenchymal disease
3. Intermediate to advanced diffuse parenchymal disease

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

<table>
<thead>
<tr>
<th>Absorbed dose per unit activity administered (mGy/MBq)</th>
<th>Adult</th>
<th>15 year</th>
<th>10 year</th>
<th>5 year</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenals Bladder wall Bone surfaces Breast GI-tract Stomach wall Small intestine ULI wall LLI wall Kidneys</td>
<td>1.0E-02</td>
<td>1.5E-02</td>
<td>2.1E-02</td>
<td>2.8E-02</td>
<td>4.2E-02</td>
</tr>
<tr>
<td></td>
<td>1.1E-03</td>
<td>1.6E-03</td>
<td>2.8E-03</td>
<td>5.7E-03</td>
<td>9.5E-03</td>
</tr>
<tr>
<td></td>
<td>6.4E-03</td>
<td>8.4E-03</td>
<td>1.3E-02</td>
<td>2.2E-02</td>
<td>4.6E-02</td>
</tr>
<tr>
<td></td>
<td>2.7E-03</td>
<td>2.7E-03</td>
<td>4.6E-03</td>
<td>7.3E-03</td>
<td>1.3E-02</td>
</tr>
<tr>
<td></td>
<td>6.2E-03</td>
<td>8.3E-03</td>
<td>1.3E-02</td>
<td>2.1E-02</td>
<td>3.5E-02</td>
</tr>
<tr>
<td></td>
<td>4.3E-03</td>
<td>5.1E-03</td>
<td>9.0E-03</td>
<td>1.4E-02</td>
<td>2.5E-02</td>
</tr>
<tr>
<td></td>
<td>5.6E-03</td>
<td>6.9E-03</td>
<td>1.2E-02</td>
<td>2.1E-02</td>
<td>3.4E-02</td>
</tr>
<tr>
<td></td>
<td>1.8E-03</td>
<td>2.2E-03</td>
<td>3.8E-03</td>
<td>6.1E-03</td>
<td>1.1E-02</td>
</tr>
<tr>
<td>Liver</td>
<td>9.7E-03</td>
<td>1.1E-02</td>
<td>1.7E-02</td>
<td>2.4E-02</td>
<td>3.5E-02</td>
</tr>
<tr>
<td></td>
<td>7.4E-02</td>
<td>9.2E-02</td>
<td>1.4E-01</td>
<td>1.9E-01</td>
<td>3.4E-01</td>
</tr>
<tr>
<td>Lungs</td>
<td>5.5E-03</td>
<td>7.5E-03</td>
<td>1.0E-02</td>
<td>1.5E-02</td>
<td>2.5E-02</td>
</tr>
<tr>
<td>Ovaries</td>
<td>2.2E-03</td>
<td>2.9E-03</td>
<td>4.9E-03</td>
<td>7.9E-03</td>
<td>1.4E-02</td>
</tr>
<tr>
<td>Pancreas Red marrow</td>
<td>1.2E-02</td>
<td>1.7E-02</td>
<td>2.5E-02</td>
<td>3.7E-02</td>
<td>5.9E-02</td>
</tr>
<tr>
<td>Spleen</td>
<td>1.1E-02</td>
<td>1.5E-02</td>
<td>2.3E-02</td>
<td>3.8E-02</td>
<td>7.2E-02</td>
</tr>
<tr>
<td></td>
<td>7.7E-02</td>
<td>1.1E-01</td>
<td>1.6E-01</td>
<td>2.5E-01</td>
<td>4.5E-01</td>
</tr>
<tr>
<td>Testes</td>
<td>6.2E-04</td>
<td>7.6E-04</td>
<td>1.3E-03</td>
<td>2.2E-03</td>
<td>4.5E-03</td>
</tr>
<tr>
<td>Thyroid</td>
<td>7.9E-04</td>
<td>1.2E-03</td>
<td>2.0E-03</td>
<td>3.5E-03</td>
<td>6.5E-03</td>
</tr>
<tr>
<td>Uterus Other tissue Effective dose equivalent (mSv/MBq)</td>
<td>1.9E-03</td>
<td>2.5E-03</td>
<td>4.4E-03</td>
<td>7.4E-03</td>
<td>1.3E-02</td>
</tr>
<tr>
<td></td>
<td>2.8E-03</td>
<td>3.4E-03</td>
<td>4.9E-03</td>
<td>7.3E-03</td>
<td>1.3E-02</td>
</tr>
<tr>
<td></td>
<td>1.4E-02</td>
<td>1.8E-02</td>
<td>2.8E-02</td>
<td>4.1E-02</td>
<td>7.3E-02</td>
</tr>
</tbody>
</table>

In normal liver function, the effective dose equivalent resulting from an administered activity of 185MBq technetium [\(^{99m}\text{Tc}\)] colloidal tin is 2.6mSv.
In early to intermediate diffuse parenchymal disease, the effective dose equivalent resulting from an administered activity of 185MBq technetium [99mTc] colloidal tin is 2.6mSv.
In intermediate to advanced diffuse parenchymal disease, the effective dose equivalent resulting from an administered activity of 185MBq technetium $^{99m}$Tc colloidal tin is 3.1mSv.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium fluoride Poloxamer 188 Nitrogen Gas

6.2 Incompatibilities

The technetium-99m labelling reaction involved in preparing technetium $^{99m}$Tc colloidal tin depends on the maintenance of some tin in the divalent state. This is why the presence of oxidizing agents in the $^{99m}$Tc-pertechnetate solution may adversely affect the quality of the prepared agent.

Also the presence of water soluble complexants in certain syringes has been found to impair scan quality by the formation of a kidney localising technetium $^{99m}$Tc complex.

The presence of aluminium ion in technetium generator eluates may induce flocculation of colloid with subsequent uptake in lungs.
6.3 Shelf life

The shelf life for this kit is 78 weeks from the day of manufacture. The labelled product must be injected within 6 hours of reconstitution.

6.4 Special precautions for storage

Store the product at not above 25°C before and after reconstitution. Do not freeze.

Storage should be in accordance with national regulations for radioactive material.

6.5 Nature and contents of container

The product is supplied in a clear Type I Ph.Eur.glass vial sealed with a chlorobutyl rubber closure and metal overseal.

6.6 Instruction for use, handling and disposal

Method of preparation of the final dosage form for injection

Use aseptic technique throughout.

(1) Place one of the vials in a suitable shielding container and swab the rubber closure with the sanitizing swab provided.

(2) Using a 10 ml syringe inject between 3 and 9 ml of the eluate from a technetium-99m sterile generator into the shielded vial (see notes 1 and 2), withdraw an equal volume of gas from the space above the solution to normalise the pressure in the vial.

(3) Invert the vial several times to ensure complete dissolution of the powder.

(4) Assay the total activity, complete the label provided and attach to the vial.

(5) Incubate the injection for 20 minutes at room temperature.

(6) The preparation may be stored at any temperature in the range 2-25°C but should be administered within 6 hours after reconstitution. Notes:

(1) Up to 3.7 GBq (100 mCi) technetium-99m may be added to the vial.

(2) If the radioactive concentration of technetium-99m in the generator eluate is higher than needed for the patient doses, a small volume of eluate containing sufficient technetium99m activity should be diluted with saline for injection to a final volume between 3 and 9ml before being used in step 2.

(3) Certain syringes have been found to contain water soluble components which can complex with reduced technetium-99m. This can impair scan quality. The effect can be eliminated by use of an all plastic syringe for handling eluate and saline prior to reconstitution of the agent.

(4) The use of a technetium-99m pertechnetate solution complying with the specifications prescribed by and BP/Ph. Eur. monographs on Sodium Pertechnetate (99mTc) Injection will yield a preparation of an appropriate quality.
Radiochemical purity measurement

Chromatography on Gelman silica gel Instant Thin Layer Chromatography (ITLC) sheets may be used to assess the radiochemical purity of the injection. Development with 0.9% w/v sodium chloride solution will carry free pertechnetate and any soluble technetium-99m labelled species to the solvent front leaving the colloid at the origin. Use fresh saline on each occasion.

A radiochemical purity of at least 95% may be expected.

Waste must be disposed of according to national regulations for radioactive material.