Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Indium [^{111}In] Oxine Solution
Indium [^{111}In] Oxine 37MBq/ml Radiopharmaceutical Precursor

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Indium [^{111}In]Oxine complex	37 MBq/vial
(No carrier added)	(37 MBq/ml) at the activity reference date

^{111}In disintegrates by electron capture with a half-life of approximately 67 hours (2.8 days) and emits gamma radiation with principal energies of 172 keV (91%) and 246 keV (94%). By internal conversion, X radiations of 23 and 26 keV are also emitted.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Radiopharmaceutical Precursor.
Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Indium [^{111}In] oxine is used as an ingredient for the *in vitro* radiolabelling of separated blood cells which are subsequently administered intravenously for a variety of investigative purposes using appropriate imaging/counting procedures.

Investigative procedures using indium [^{111}In]-labelled blood cells include:

-*^{111}In-labelled leucocytes or granulocytes:* Investigation of sites of inflammatory processes and abscesses, complementary with other imaging investigations; for example, localisation of sites of focal infection such as abdominal abscess, confirmation of bone infection after prosthesis, investigation of pyrexia of unknown origin and evaluation of inflammatory conditions not associated with infection such as inflammatory bowel disease. In red marrow bearing regions of the skeleton, osteomyelitis may present as sites of reduced uptake of ^{111}In-labelled leucocytes. Diffuse or local pulmonary uptake of ^{111}In-labelled leucocytes should be interpreted with caution, as this can be due to physiological marginal location.

-*^{111}In-labelled platelets (thrombocytes)*: Determination of platelet survival and biodistribution, particularly spleen and liver uptake in cases of thrombocytopenia, arterial or vascular thrombosis, aneurysms and sites of inflammation in rejecting transplants, for example, renal and pancreatic.

- *^{111}In-labelled erythrocytes*: Investigation of sites of gastrointestinal haemorrhage.

4.2 Posology and method of administration

The vial contains a sterile isotonic solution for the *in vitro* radiolabelling of blood cells which are subsequently administered intravenously.

4.2.1 ^{111}In-labelled leucocytes or granulocytes:
The recommended activity for adults and the elderly is 7.4-30 MBq by intravenous administration.

Scintigraphic studies to detect focal accumulations of ^{111}In-labelled leucocytes can usefully be commenced 3-6 hours after administration. The relative accumulation in inflammatory lesions is, however, much more marked on scanning 24 hours post-injection.

4.2.2 ^{111}In-labelled platelets:
The recommended activity for adults and the elderly is 1.85-3.7 MBq for platelet survival studies and 3.7-18.5 MBq for platelet distribution studies. In both cases the labelled platelets are administered intravenously.

In platelet survival studies, the timing of sampling and the number of samples taken will depend on the purpose of the study and the anticipated mean survival. It is recommended that samples should be taken at least 20 minutes, 2, 3 and 4 hours after injection and thereafter daily up to 10 days.

Scintigraphic studies to detect deposition of labelled platelets may usefully be commenced 2-6 hours after administration. It is recommended that imaging should be performed serially up to 48 or 72 hours after injection.

4.2.3 ^{111}In-labelled erythrocytes:
The recommended activity for adults and the elderly is 3.7-18.5 MBq by intravenous administration.

4.2.4 Use in children:
The activity to be administered to children may be calculated approximately by correcting on a weight, body surface area or age basis the activity to adults. For the newborn and children under about one year of age, the target organ size in relation to the whole body must also be taken into consideration.

In very young children (up to 1 year) a minimum dose of 10% of the recommended adult dose is recommended to obtain images of sufficient quality. (See section 11).

4.3 Contraindications

None known.

4.4 Special warnings and precautions for use

The contents of the vial of Indium [^{111}In] Oxine Solution are intended only for use in the *in vitro* labelling of separated blood cells and are not to be administered directly to the patient.

Radiopharmaceutical agents should only be used by qualified personnel with the appropriate government authorisation for the use and manipulation of radionuclides. They may be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the local competent official organisations. Literature references to the clinical uses of indium-111 labelled blood cells refer mainly to the use of autologous blood cells; clearly there could be hazards associated with the administration of donor cells.

4.5 Interaction with other medicinal products and other forms of interaction

Corticosteroids and antibiotics have been reported to reduce the uptake of indium [^{111}In]-labelled leucocytes into abscess, but the evidence is far from clear. Antibiotics which are successful in treatment might be expected to impair leucocyte migration because of reduced chemotactic stimulus.

4.6 Pregnancy and lactation

No data are available on the use in human pregnancy of indium [^{111}In]-labelled blood cells prepared using indium [^{111}In] oxine. There is some evidence from animal studies of teratogenicity of indium.

When it is necessary to administer radioactive medicinal products to women 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 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 the mother and the foetus.

Administration of 30 MBq indium [^{111}In]-labelled leucocytes results in an absorbed dose to the uterus of 3.6 mGy; administration of 18.5 MBq indium [^{111}In]-labelled platelets results in an absorbed dose to the uterus of 1.8 mGy. Doses above 0.5 mGy should be regarded as a potential risk for the foetus.

Advice on avoidance of pregnancy until the calculated dose to the uterus is below 0.5 mGy should be given to women of child-bearing potential.

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 and the expressed feeds discarded. Breast feeding 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

None known.

4.8 Undesirable effects

A very few reports have been received of hypersensitivity, evidenced by skin reactions and generalised reactions, possibly anaphylactic in nature, following administration of blood cells labelled with indium-111. It should also be noted that materials used in cell separation may cause hypersensitivity reactions. It is essential that cells are washed free of sedimentation agents before they are re-injected into the patient.

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.

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

4.9 Overdose

In the event of administration of an overdose of indium [^{111}In]-labelled blood cells, very little supportive treatment can be undertaken since elimination of the radionuclide is entirely dependent on the normal physiological breakdown of the cells.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diagnostic pharmaceuticals, inflammation and infection detection, indium (^{111}In) oxinate labelled cells, ATC code: V09HB01

At the activities normally administered, indium-111 labelled blood cells do not exert pharmacological effects.

5.2 Pharmacokinetic properties

Indium forms a saturated (1:3) complex with 8-hydroxyquinoline (oxine). The complex is neutral and lipid-soluble, which enables it to penetrate the cell membrane. Within the cell, indium becomes firmly attached to cytoplasmic components: the liberated hydroxyquinoline is released by the cell.

It is thought likely that the mechanism of labelling cells with indium [^{111}In] oxine involves an exchange reaction between the hydroxyquinoline carrier and subcellular components which chelate indium more strongly than hydroxyquinoline. The low stability constant of the indium oxine complex, estimated at approximately 10^{10}, supports this theory.

Indium [^{111}In]-labelled blood cells upon re-injection follow the pathways of the non-labelled cells and thus allow visualisation of areas of accumulation.

After injection of labelled leucocytes into normal volunteers about 60% of the dose is taken up immediately by the liver, spleen, bone marrow and other tissues. There is only a very short transient hold up in the lungs. The remainder shows exponential clearance from the circulation with a half-life between 5 and 10 hours, resulting in a final uptake of about 20% in the liver, 25% in the spleen, 30% in the bone marrow and 25% in other organs.

Clearance from whole blood and biological distribution can vary considerably with the individual recipient, the condition of the injected cells and the labelling techniques used.

Indium [^{111}In]-labelled leucocytes will accumulate at sites of inflammatory processes and abscess.

Indium [^{111}In]-labelled erythrocytes (red cells) are robust and on re-injection behave as the unlabelled cells. They remain within the vascular system and only leave it if the red cells are destroyed or lost during bleeding. The indium-111 is bound strongly to the cells and has virtually no gastrointestinal secretion in the normal gut, thus allowing visualisation of the vascular system for up to 72 hours. The labelled red cells show the presence and/or site of occult gastrointestinal bleeding.

Following intravenous injection of indium [^{111}In]-labelled platelets in normal individuals some are rapidly taken up by the liver and spleen due to equilibration with the marginating cell pools in those organs. The residual cells remain in the circulation for a period determined by the remaining lifetime of the platelets.

Approximately 30% of the injected dose is immediately distributed in the spleen and about 10% in the liver. The remaining activity is cleared from the circulation with a half-life of about 4 days and is distributed in the spleen (5%), the liver (20%), the bone marrow (25%) and other tissues (10%).

Normally platelets survive in blood for about 9 days and are then destroyed on an age-dependent basis, mainly in the spleen and bone marrow. Short survival times are associated with a variety of disease states such as thrombocytopenia.

^{111}In-labelled platelets will also accumulate at sites of active thrombus formation and imminent transplant rejection.

Clearance of activity for both labelled leucocytes and platelets from liver and spleen is very slow. In addition, there is very low excretion of activity in either urine or faeces. Elimination from the body is probably mainly through decay to stable cadmium, but for the purposes of radiation dosimetry calculations, body clearance is assumed to be analogous to that of ionic indium (half-life 70 days).

5.3 Preclinical safety data

Indium [^{111}In]-labelled blood cells, prepared using indium [^{111}In] oxine have been found to be viable after labelling and to take part in normal cell traffic around the body. Some chromosomal aberrations have been reported in ^{111}In-labelled human lymphocytes, labelled using indium [^{111}In] oxine.

Following radiolabelling, 8-hydroxyquinoline is believed to be released from the labelled cells and this and any unreacted indium [^{111}In] oxine will be removed during cell processing prior to administration. Nevertheless, studies have been performed which demonstrate that no signs of toxicity that could be attributed to the administration were observed when indium [^{111}In] oxine (equivalent to 0.3 mg oxine/kg) was administered to rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

8-hydroxyquinoline (oxine)
HEPES buffer (N-2-hydroxyethyl piperazine-N-^{1} 2- ethane sulphonic acid)
Polysorbate 80
Sodium Chloride
Water for Injections

6.2 Incompatibilities

Indium [^{111}In] oxine is a non-specific blood cell labelling agent and in the presence of whole blood it will rapidly form indium-111 labelled transferrin. Care must therefore be taken in the preparation of separated blood cells to be labelled to ensure separation of unwanted blood cells and other blood proteins.

It is important that all glassware used for the preparation of reagents be thoroughly clean to ensure freedom from trace metal impurities.

6.3 Shelf Life

The shelf life for this product is not more than 11 days from the date of release.

The reference day is four days before expiry. Once opened the product should be used within 8 hours.

6.4 Special precautions for storage

The product should not be stored above 25°C.

Do not freeze.
Once opened the product should be stored at 2-8^{o}C.
Store in accordance with national regulations for radioactive materials.

6.5 Nature and contents of container

The product is supplied in a clear, colourless Type I Ph. Eur., borosilicate glass vial sealed with a PTFE-faced butyl rubber closure and aluminium overseal. Each vial is packed into a lead metal shielding container.

The product is available as a single 37 MBq pack size

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

Radiopharmaceuticals intended for administration to patients should be prepared by the user in a manner which satisfies both radiological safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken, complying with the requirements of Good Pharmaceutical Manufacturing Practice, in order to maintain sterility throughout the labelling procedures and to maintain the sterility of the Indium [^{111}In] Oxine Solution.

Since the product does not contain an antimicrobial preservative and is marketed for multidose use, all doses from a single vial should be taken within a single working day and the product stored a 2-8°C after removal of the first aliquot.

Because of the small mass of the chemical substances present, no special handling precautions are recommended other than those necessary because of the radioactive and pharmaceutical nature of the product.

The normal precautions for handling radioactive materials should be observed.

The administration of radiopharmaceuticals creates risks for other person from external radiation on contamination from spills of urine, vomiting, etc. Radiation protection precautions in accordance with national regulations must therefore be taken. Storage procedures and the disposal of waste should be in accordance with national guidelines.

After use, all materials associated with the preparation and administration of radiopharmaceuticals, including any unused product and its container, should be decontaminated or treated as radioactive waste and disposed of in accordance with the conditions specified by the local competent authority. Contaminated materials must be disposed of as radioactive waste via an authorised route.

For information concerning the procedures recommended for the separation of blood cells and their subsequent radiolabelling using Indium [^{111}In] oxine solution, users are referred to the pack leaflet supplied with the product.

7 MARKETING AUTHORISATION HOLDER

GE Healthcare Limited,
Amersham Place,
Little Chalfont,
Buckinghamshire, HP7 9NA,
United Kingdom**.**

8 MARKETING AUTHORISATION NUMBER

PA 0240/026/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 November 1999
Date of last renewal 26 November 2004

10 DATE OF REVISION OF THE TEXT

February 2009

11 DOSIMETRY

The tables below show the dosimetry as calculated according to the Publication 53 of the ICRP (International Commission on Radiological Protection, Radiation Dose to Patients from Radiopharmaceuticals, Pergamon Press 1987).

Indium-111 labelled leucocytes:

Organ	**Absorbed dose per unit activity administered (mGy/MBq)**				
	Adult	**15 year**	**10 year**	**5 year**	**1 year**
Adrenals	3.1E-01	4.0E-01	5.9E-01	8.2E-01	1.4E+00
Bladder wall	7.2E-02	1.0E-01	1.6E-01	2.4E-01	4.1E-01
Bone surfaces	3.5E-01	5.0E-01	8.0E-01	1.4E+00	2.9E+00
Breast	9.0E-02	9.0E-02	1.5E-01	2.3E-01	3.9E-01
GI tract					
Stomach wall	2.8E-01	3.3E-01	4.9E-01	6.8E-01	1.1E+00
Small intestine	1.6E-01	1.9E-01	2.9E-01	4.3E-01	7.1E-01
ULI wall	1.6E-01	1.9E-01	3.0E-01	4.7E-01	7.8E-01
LLI wall	1.3E-01	1.6E-01	2.4E-01	3.3E-01	5.4E-01
Heart	1.7E-01	2.1E-01	3.0E-01	4.3E-01	7.3E-01
Kidneys	3.3E-01	3.9E-01	6.0E-01	8.7E-01	1.4E+00
Liver	7.1E-01	8.8E-01	1.3E+00	1.8E+00	3.2E+00
Lungs	1.6E-01	2.1E-01	3.1E-01	4.6E-01	8.1E-01
Ovaries	1.2E-01	1.7E-01	2.4E-01	3.5E-01	5.6E-01
Pancreas	5.2E-01	6.1E-01	9.1E-01	1.3E+00	2.1E+00
Red marrow	6.9E-01	8.8E-01	1.3E+00	2.3E+00	4.5E+00
Spleen	5.5E+00	7.6E+00	1.1E+01	1.7E+01	3.0E+01
Testes	4.5E-02	6.4E-02	9.9E-02	1.5E-01	2.8E-01
Thyroid	6.1E-02	9.0E-02	1.3E-01	2.1E-01	3.8E-01
Uterus	1.2E-01	1.4E-01	2.1E-01	3.0E-01	5.0E-01
Other tissue	1.1E-01	1.4E-01	2.0E-01	3.0E-01	5.3E-01
Effective dose equivalent (mSv/MBq)	**5.9E-01**	**7.9E-01**	**1.2E+00**	**1.8E+00**	**3.2E+00**

Indium-111 labelled platelets:

Organ	**Absorbed dose per unit activity administered (mGy/MBq)**				
	Adult	**15 year**	**10 year**	**5 year**	**1 year**
Adrenals	3.7E-01	4.7E-01	7.2E-01	1.0E+00	1.8E+00
Bladder wall	6.6E-02	9.2E-02	1.4E-01	2.2E-01	3.9E-01
Bone surfaces	2.3E-01	3.2E-01	5.1E-01	8.7E-01	1.8E+00
Breast	1.0E-01	1.1E-01	1.8E-01	2.9E-01	4.9E-01
GI tract					
Stomach wall	3.5E-01	4.1E-01	6.0E-01	8.3E-01	1.4E+00
Small	1.4E-01	1.7E-01	2.7E-01	4.2E-01	7.4E-01
intestine	1.4E-01	1.8E-01	2.9E-01	4.7E-01	8.0E-01
ULI wall	9.7E-02	1.3E-01	2.0E-01	2.9E-01	5.0E-01
LLI wall	3.9E-01	4.8E-01	7.1E-01	1.0E+00	1.8E+00
Heart					
	4.1E-01	5.0E-01	7.6E-01	1.1E+00	1.8E+00
Kidneys	7.3E-01	9.1E-01	1.3E+00	1.9E+00	3.4E+00
Liver	2.8E-01	3.6E-01	5.5E-01	8.5E-01	1.5E+00
Lungs	9.8E-02	1.3E-01	2.0E-01	3.1E-01	5.3E-01
Ovaries	6.6E-01	7.5E-01	1.1E+00	1.6E+00	2.6E+00
Pancreas					
	3.6E-01	4.6E-01	6.8E-01	1.1E+00	2.1E+00
Red marrow	7.5E+00	1.0E+01	1.5E+01	2.3E+01	4.1E+01
Spleen	4.3E-02	6.0E-02	9.1E-02	1.4E-01	2.7E-01
Testes	8.1E-02	1.1E-01	1.8E-01	2.9E-01	5.4E-01
Thyroid	9.5E-02	1.2E-01	1.8E-01	2.8E-01	4.9E-01
Uterus					
	1.2E-01	1.4E-01	2.1E-01	3.1E-01	5.6E-01
Other tissue					
Effective dose equivalent (mSv/MBq)	**7.0E-01**	**9.3E-01**	**1.4E+00**	**2.1E+00**	**3.7E+00**

The effective dose resulting from an administered activity of 30 MBq indium-111 leucocytes is 10.8 mSv, (ICRP 80, 1998).
The effective dose resulting from an administered activity of 18.5MBq indium-111-labelled platelets is 7.72 mSv, (ICRP 80, 1998).
These effective dose equivalents are in the same range as that resulting from some commonly performed radiographic examinations.
Administration of 3 MBq indium-111 labelled leucocytes to very young children (up to 1 year) results in an absorbed dose to the spleen of 90 mGy and an effective dose equivalent of 9.6 mSv. Administration of 1.85 MBq indium-111 labelled platelets similarly results in an absorbed dose to the spleen of 76 mGy and an effective dose equivalent of 6.8 mSv.
Indium-114m may be present as a radionuclidic impurity in indium-111.This isotope has a longer half-life (49.5 days) than indium-111 (2.83 days) and will therefore make an increasing contribution to the radiation dose with time.Indium-111 labelled blood cells should not be administered later than 4 days from the-Indium (^{111}In) Oxine Solution reference date in order to ensure that the level of indium-114m present is less than 0.2%.

The effective dose equivalent for indium-114m labelled leucocytes and platelets are given by ICRP 53 as follows:

Effective Dose Equivalent (mSv/MBq)	**Adult**	**15 years**	**10 years**	**5 years**	**1 year**
^{114m}In-leucocytes:	6.9E+01	9.3E+01	1.5E+02	2.5E+02	4.9E+02
^{114m}In-platelets:	8.3E+01	1.2E+02	2.0E+02	3.2E+02	6.2E+02

No data are available in ICRP 53 on the radiation dosimetry of indium-111 labelled erythrocytes. However, based on the same methodology, the following effective dose equivalent has been calculated:

	Adult	**15 years**	**10 years**	**5 years**	**1 year**
Effective Dose Equivalent (mSv/MBq)	4.0E-01	4.0E-01	7.0E-01	1.1E+00	2.0E+00

The effective dose equivalent resulting from an administered activity of 18.5 MBq**-**indium-111 labelled erythrocytes is 7.4 mSv.