



27. February 2020

## SUMMARY OF PRODUCT CHARACTERISTICS

for

### Indium (In-111) Oxinate, radiopharmaceutical precursor

#### 1. NAME OF THE MEDICINAL PRODUCT

Indium (In-111) Oxinate

#### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Indium (In-111) Oxinate            37 MBq (1 mCi)

Oxine                                    0.025 mg

<sup>111</sup>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.

Excipient with known effect:

Sodium

For a full list of excipients, see section 6.1.

#### 3. PHARMACEUTICAL FORM

Radiopharmaceutical precursor.

pH = 2.5-3.5.

#### 4. CLINICAL PARTICULARS

##### 4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Indium (<sup>111</sup>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 (<sup>111</sup>In)-labelled blood cells include:

- <sup>111</sup>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  $^{111}\text{In}$ -labelled leucocytes. Diffuse or local pulmonary uptake of  $^{111}\text{In}$ -labelled leucocytes should be interpreted with caution, as this can be due to physiological marginal location.

- $^{111}\text{In}$ -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.
- $^{111}\text{In}$ -labelled erythrocytes: Investigation of sites of gastro-intestinal 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.

### $^{111}\text{In}$ -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  $^{111}\text{In}$ -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.

### $^{111}\text{In}$ -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 at 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.

### $^{111}\text{In}$ -labelled erythrocytes

The recommended activity for adults and the elderly is 3.7-18.5 MBq by intravenous administration.

### Use in children

The dosage 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 one year) a minimum dose of 10% of the recommended adult dose is recommended to obtain images of sufficient quality. (see section 11)

### **Method of administration**

Intravenous use after in-vitro labelling of blood cells.

For instructions on preparation of the medicinal product, see section 12.

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

#### Potential for hypersensitivity or anaphylactic reactions

If hypersensitivity or anaphylactic reactions occur, the administration of the medicinal product must be discontinued immediately and intravenous treatment initiated, if necessary. To enable immediate action in emergencies, the necessary medicinal products and equipment such as endotracheal tube and ventilator must be immediately available.

The contents of the vial of Indium (<sup>111</sup>In) Oxine are intended only for use in the *in-vitro* labelling of separated blood cells, and are not to be administered directly to the patient.

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.

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.

#### Individual benefit/risk justification

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.

#### Paediatric population

For information on the use in the paediatric population, see section 4.2.

Careful consideration of the indication is required since the effective dose per MBq is higher than in adults (see section 11).

#### Specific warnings

This medicinal product contains less than 1 mmol sodium (23 mg) per milliliter solution for injection, i.e. it is essentially 'sodium-free'.

### **4.5 Interaction with other medicinal products and other forms of interaction**

No interaction studies have been performed.

Corticosteroids and antibiotics have been reported to reduce uptake of indium (<sup>111</sup>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**

#### Women of childbearing potential / Contraception in males and females

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.

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

#### Pregnancy

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

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 labelled leucocytes results in an absorbed dose to the uterus of 3.6 mGy; administration of 18.5 MBq indium-111 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.

#### Breastfeeding

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 of In-111 labeled blood cells is considered necessary, no interruption of breast feeding is recommended.

#### **4.7 Effects on ability to drive and use machines**

No studies on the effects on the ability to drive and use machines have been performed.

#### **4.8 Undesirable effects**

The frequencies of undesirable effects are defined as follows:

Very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ) and not known (cannot be estimated from the available data)

The following undesirable effects are recognised for indium-111 labelled blood cells (i.e, the suspension for re-injection of labelled blood cells):

<b>Immune system disorders</b> Frequency not known (cannot be estimated from the available data)	Anaphylactic reactions, hypersensitivity.
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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 (see also section 4.4).

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 10.8 mSv for labelled leucocytes [7.2 mSv for labelled thrombocytes] when the maximal recommended activity of 30 MBq for labelling of leucocytes is administered [18,5 MBq in case of thrombocytes] these adverse reactions are expected to occur with a low probability.

#### 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:

Lægemiddelstyrelsen

Axel Heides Gade 1

DK-2300 København S

Websted: [www.meldenbivirkning.dk](http://www.meldenbivirkning.dk)

## **4.9 Overdose**

In the event of the accidental administration of an overdose of indium-111 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**

ATC: V09HB01 – Diagnostic radiopharmaceuticals, inflammation and infection detection, Indium (<sup>111</sup>In) compounds.

At the activities normally administered, indium (<sup>111</sup>In) -labelled blood cells do not exert pharmacological effects.

### **5.2 Pharmacokinetic properties**

#### Distribution

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 (<sup>111</sup>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<sup>10</sup>, supports this theory.

#### Organ uptake

Indium (<sup>111</sup>In)-labelled blood cells upon re-injection follow the pathways of the non-labelled cells and thus allows 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 ( $^{111}\text{In}$ )-labelled leucocytes will accumulate at sites of inflammatory processes and abscess. Indium ( $^{111}\text{In}$ )-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 ( $^{111}\text{In}$ )-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 spleen and bone marrow. Short survival times are associated with a variety of disease states such as thrombocytopenia.  $^{111}\text{In}$ -labelled platelets will also accumulate at sites of active thrombus formation and imminent transplant rejection.

#### **Elimination**

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 ( $^{111}\text{In}$ )-labelled blood cells, prepared using indium ( $^{111}\text{In}$ ) 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  $^{111}\text{In}$ -labelled human lymphocytes, labelled using indium ( $^{111}\text{In}$ ) oxine.

Following radiolabelling, 8-hydroxyquinoline is believed to be released from the labelled cells and this and any unreacted indium ( $^{111}\text{In}$ ) 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 ( $^{111}\text{In}$ ) oxine (equivalent to 0.3 mg oxine/kg) was administered to rats.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Sodium acetate  
Sodium chloride  
Iron (III)  
Hydrochloric acid  
Water for injection.

Tris buffer:  
Trometamol  
Hydrochloric acid  
Water for injection  
pH = 7.9-8.1.

### **6.2 Incompatibilities**

Indium (<sup>111</sup>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. Therefore, care must 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 ion impurities.

### **6.3 Shelf life**

1 day after activity reference date and time. The expiry date is stated on the label of each vial and on the outer package.

Tris buffer expires 3 years after the date of manufacture.

### **6.4 Special precautions for storage**

Store below 25°C.

The product does not contain an antimicrobial preservative.

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

### **6.5 Nature and contents of container**

Indium (In-111) Oxinate: 10 ml glass vial (Type I, Ph.Eur.) closed with a bromobutyl rubber stopper sealed with a non-coloured, aluminium crimp cap, supplied in a lead shielding Tris buffer: 10 ml glass vial (Type I, Ph.Eur.) closed with a bromobutyl rubber stopper sealed with a yellow coloured, aluminium crimp cap.

### **6.6 Special precautions for disposal and other handling**

Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal is subject to the regulations and/or appropriate licences of the local competent official organisation.

Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

If at any time in the preparation of this product the integrity of the vials is compromised they should not be used.

Administration procedures should be carried out in a way to minimise the risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.

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.

Instructions for waste disposal:

Unused Indium ( $^{111}\text{In}$ ) oxinate should be allowed to decay until the activity has dropped to such a low level that, according to local regulations, it is no longer considered radioactive. Then it may be disposed of as harmless waste. Unused vials with Tris buffer may be disposed of as harmless waste.

Any unused product or waste material should be disposed of in accordance with local requirements.

**7. MARKETING AUTHORISATION HOLDER**

Curium Netherlands B.V.  
Westerduinweg 3  
1755 LE PETTEN  
Holland

**8. MARKETING AUTHORISATION NUMBER**

DK R 1180

**9. DATE OF FIRST AUTHORISATION**

31. January 1995

**10. DATE OF REVISION OF THE TEXT**

27. February 2020



## 11. DOSIMETRY

Data are taken from ICRP 53, International Commission on Radiological Protection, "Radiation dose to Patients from Radiopharmaceuticals", Pergamon Press, 1988, (Annals of ICRP, vol. 18 (1-4), 1987).

<sup>111</sup>In-labelled leucocytes:

Absorbed dose per unit activity administered (mGy/MBq).

<b>Organ</b>	<b>Adult</b>	<b>15 year</b>	<b>10 year</b>	<b>5 year</b>	<b>1 year</b>
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
<b>Effective dose Equivalent (Sv/MBq)</b>	<b>5.9E-01</b>	<b>7.9E-01</b>	<b>1.2E+00</b>	<b>1.8E+00</b>	<b>3.2E+00</b>

<sup>111</sup>In-labelled platelets:

Absorbed dose per unit activity administered (mGy/MBq).

<b>Organ</b>	<b>Adult</b>	<b>15 year</b>	<b>10 year</b>	<b>5 year</b>	<b>1 year</b>
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 intestine	1.4E-01	1.7E-01	2.7E-01	4.2E-01	7.4E-01
ULI wall	1.4E-01	1.8E-01	2.9E-01	4.7E-01	8.0E-01
LLI wall	9.7E-02	1.3E-01	2.0E-01	2.9E-01	5.0E-01
Heart	3.9E-01	4.8E-01	7.1E-01	1.0E+00	1.8E+00
Kidneys	4.1E-01	5.0E-01	7.6E-01	1.1E+00	1.8E+00
Liver	7.3E-01	9.1E-01	1.3E+00	1.9E+00	3.4E+00
Lungs	2.8E-01	3.6E-01	5.5E-01	8.5E-01	1.5E+00
Ovaries	9.8E-02	1.3E-01	2.0E-01	3.1E-01	5.3E-01
Pancreas	6.6E-01	7.5E-01	1.1E+00	1.6E+00	2.6E+00
Red marrow	3.6E-01	4.6E-01	6.8E-01	1.1E+00	2.1E+00
Spleen	7.5E+00	1.0E+01	1.5E+01	2.3E+01	4.1E+01
Testes	4.3E-02	6.0E-02	9.1E-02	1.4E-01	2.7E-01
Thyroid	8.1E-02	1.1E-01	1.8E-01	2.9E-01	5.4E-01
Uterus	9.5E-02	1.2E-01	1.8E-01	2.8E-01	4.9E-01
Other tissue	1.2E-01	1.4E-01	2.1E-01	3.1E-01	5.6E-01
<b>Effective dose</b>	<b>7.0E-01</b>	<b>9.3E-01</b>	<b>1.4E+00</b>	<b>2.1E+00</b>	<b>3.7E+00</b>
<b>Equivalent (mSv/MBq)</b>					

ICRP 80 provides 3.6E-01 mSv/MBq as effective dose for adults regarding Indium (<sup>111</sup>In) labeled leucocytes. The effective dose equivalent resulting from an administered activity of 30 MBq indium (<sup>111</sup>In)-labelled leucocytes is in that case 10.8 mSv. Furthermore, ICRP 80 provides 3.9E-01 mSv/MBq as effective dose for adults regarding Indium (<sup>111</sup>In) labeled platelets. The effective dose equivalent resulting from an administered activity of 18.5 MBq indium (<sup>111</sup>In)-labelled platelets is in that case 7.2 mSv. These effective dose equivalents are in the same range as that resulting from some commonly performed radiographic examinations.

Administration of 3 MBq <sup>111</sup>In-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 <sup>111</sup>In-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 (<sup>111</sup>In)-labelled blood cells

should not be administered later than 1 day from the indium ( $^{111}\text{In}$ )-oxine 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:

<b>Effective dose equivalent (mSv/MBq)</b>	<b>Adult</b>	<b>15 years</b>	<b>10 years</b>	<b>5 years</b>	<b>1 year</b>
$^{114\text{m}}\text{In}$ -leucocytes:	6.9E+01	9.3E+01	1.5E+02	2.5E+02	4.9E+02
$^{114\text{m}}\text{In}$ -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 ( $^{111}\text{In}$ )-labelled erythrocytes. However, based on the same methodology, the following effective dose equivalent has been calculated:

<b>Effective dose equivalent (mSv/MBq)</b>	<b>Adult</b>	<b>15 years</b>	<b>10 years</b>	<b>5 years</b>	<b>1 year</b>
	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 ( $^{111}\text{In}$ )-labelled erythrocytes is 7.4 mSv.

## 12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Instructions for blood cell labelling:

Leucocyte labelling:

1. In 50 ml syringe:
  - 4.5 ml ACD
  - 30 ml blood
  - 3 ml hydroxyethyl starch
2. Mix gently, leave to sediment standing on plunger for 45-60 minutes.
3. Transfer platelet rich plasma (PLRP) via butterfly system into sterile vial/tubes. Avoid contamination with erythrocytes.
4. Spin PLRP at 130-170 g for 5-10 minutes.
5. Remove all supernatant plasma and transfer to sterile vial/tubes.
6. Resuspend the cell pellet in 2 ml (PBS or saline).
7. Spin supernatant plasma at 1000 g for 10 minutes.
8. Transfer supernatant plasma to sterile vial.
9. Add 0.4 ml Tris buffer to 1 ml in oxinate. It is recommended to add the tris buffer just before the preparation is administered to the blood cells to prevent adsorption to the glass vial or syringe.
10. Incubate 4-37 MBq In oxinate for 15 minutes with the suspension.
11. Acidify plasma to pH 6.5 (0.8 ml ACD per 10 ml plasma).
12. Add 5 ml ACD plasma to the labelled cell suspension.
13. Spin at 170 g for 5 minutes, keep supernatant for measuring activity (=A).
14. Resuspend in 2-5 ml ACD plasma and measure activity (=B).
15. Calculate labelling percentage (=B/A+B).

Thrombocyte labelling:

A volume of 42.5 ml of blood is collected in 7.5 ml ACD and centrifuged for 15 minutes at 200 g.

The supernatant platelet rich plasma (PRP) is collected with a syringe and acidified with ACD, 0.1 ml per ml PRP. The PRP is centrifuged at 640 g.

After removal of the supernatant platelet poor plasma (PPP), the pellet is resuspended in 3 ml saline.

Add 0.4 ml Tris buffer to 1 ml in oxinate. It is recommended to add the tris buffer just before the preparation is administered to the blood cells to prevent adsorption to the glass vial or syringe.

Label the thrombocyte suspension with 4-37 MBq  $^{111}\text{In}$  oxinate.

Incubate at room temperature for 20 minutes.

After incubation is completed, PPP is added to a volume of 5 ml and the radioactivity is measured.

Free (unbound) Indium is removed (as supernatant) by centrifugation at 1000 g for 15 minutes.

Thrombocytes are resuspended in 3 ml PPP.

Additional PPP is added to a volume of 5 ml and radioactivity is measured again for the calculation of the labelling efficiency.

The suspension is now ready for injection.

Any unused product or waste material should be disposed of in accordance with local requirements.