PRODUCT MONOGRAPH

INDIUM (111IN) OXINE SOLUTION

Radiodiagnostic Agent

(For Radiolabelling Autologous Leukocytes)

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NAME OF DRUG

INDIUM In-111 OXINE SOLUTION

THERAPEUTIC OR PHARMACOLOGICAL CLASSIFICATION

Radiodiagnostic Agent
(For Radiolabelling Autologous Leukocytes)

DESCRIPTION

Indium In-111 oxine is a diagnostic radiopharmaceutical intended for radiolabelling autologous leukocytes. It is supplied as a sterile, non-pyrogenic, isotonic aqueous solution with a pH range of 6.5 to 7.5. Each milliliter of the solution contains 37 megabecquerels (1 mCi) of indium In-111 [no carrier added, greater than 1.85 GBq/μg indium (greater than 50 mCi/μg indium)] at calibration time, 50 μg oxine (8-hydroxyquinoline), 100 μg polysorbate 80, and 6 mg of HEPES (N-2-hydroxyethylpiperazine-N'-2-ethane sulfonic acid) buffer in 0.75% sodium chloride solution. The drug contains no bacteriostatic agent. The radionuclidic impurity limit for In-114m is not greater than 37 kBq (1 μCi) of In-114m per 37 MBq (1mCi) of indium In-111 at calibration time. The radionuclidic composition at expiration time is not less than 99.75% of indium In-111 and not more than 0.25% of indium In-114m/114.

The precise structure of the indium In-111 oxine complex is unknown at this time. The empirical formula is $(C_9H_6NO)_3$ In-111.

PHYSICAL CHARACTERISTICS

Indium In-111 decays by electron capture with a physical half-life of 67.2 hours (2.8 days). The energies of the photons that are useful for detection and imaging studies are listed in Table 1.

Table 1. Principal Radiation Emission Data [1]

Radiation	Mean %/ Disintegration	Mean Energy (keV)
Gamma 2	90.2	171.3
Gamma 3	94	245.4

[1]Kocher, David C., Radioactive Decay Data Tables, DOE/TIC-11026, 115 (1981).

EXTERNAL RADIATION

The exposure rate constant for 37 MBq, 1 mCi indium In-111 is 8.3 x 10^{-4} C/kg/hr (3.21R/hr) at 1 cm. The first half value thickness of lead (Pb) for indium In-111 is 0.023 cm. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from the interposition of various thicknesses of Pb is shown in Table 2. For example, the use of 0.834 cm of lead will decrease the external radiation exposure by a factor of about 1,000.

Table 2. Radiation Attenuation by Lead Shielding [2]

Shield Thickness (Pb) cm	Coefficient of Attenuation
0.023	0.5
0.203	10^{-1}
0.513	10^{-2}
0.834	10^{-3}
1.12	10^{-4}

[2]Data supplied by Oak Ridge Associated Universities, Radiopharmaceutical Internal Dose Information Center, 1984.

These estimates of attenuation do not take into consideration the presence of longer-lived contaminants with higher energy photons, namely indium In-114m/114.

To allow correction for physical decay of indium In-111, the fractions that remain at selected intervals before and after the time of calibration are shown in Table 3.

Table 3. Physical Decay Chart for Indium In-111, Half-Life 67.2 hours

Day	Fraction Remaining	Day	Fraction Remaining
-2	1.641	2	0.610
-1	1.281	3	0.476
0*	1.000	4	0.372
1	0.781	5	0.290

*Calibration Time

CLINICAL PHARMACOLOGY

Indium forms a saturated (1:3) complex with oxine. The complex is a neutral and lipid-soluble, which enables it to penetrate the cell membrane. Within the cell, indium becomes firmly attached to cytoplasmic components; the liberated oxine is released by the cell. It is thought likely that the mechanism of labelling cells with indium In-111 oxine involves an exchange reaction between the oxine carrier and subcellular components which chelate indium more strongly than oxine. The low stability constant of the oxine complex, estimated at approximately 10, supports this theory.

Following the recommended leukocyte cell labelling procedure, approximately 77% of the added In-111 oxine is incorporated in the resulting cell pellet (which represents approximately 3-4 x 10^8 WBC).

Cell clumping can occur and was found in about one fifth of the leukocyte preparations examined. The presence of red blood cells or plasma will lead to reduced leukocyte labelling efficiency. Transferrin in plasma competes for indium In-111 oxine.

After injection of labelled leukocytes into normal volunteers, about 30% of the dose is taken up by spleen and 30% by liver, reaching a plateau at 2-48 hours after injection. No significant clearance of radioactivity is observed at 72 hours in these two organs. Pulmonary uptake is 4-7.5% at 10 minutes but is lost rapidly; pulmonary radioactivity is usually visible in scans only up to about 4 hours after injection.

The human biodistribution studies in three normal subjects injected with indium In-111 oxine labelled leukocytes indicate a biexponential disappearance of indium In-111 from the blood when monitored for up to 72 hours. Between 9.5 to 24.4% of the injected dose remains in whole blood and clears with a biological half-time of 2.8 to 5.5 hours. The remainder (13-18%) clears from the blood with a biological half-time of 64 to 116 hours.

Elimination from the body of injected indium In-111 oxine is probably mainly through decay to stable cadmium since only a negligible amount (less than 1%) of the dose is excreted in feces and urine in 24 hours.

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

Clearance from liver and spleen, for the purpose of calculating the radiation dose, is assumed to be equal to the physical half-life of indium In-111 (67.2 hours).

TOXICOLOGY

Male and female rats were given 1.0 ml of indium In-111 solution by the intravenous route; controls were given 0.9% saline solution. This is equivalent to the direct injection of approximately 460 ml of the preparation into a 70 kg human. Since the cell labelling process takes place in vitro, the indium In-111 oxine is not intended to be administered directly to the patient. Also, more than 99% of the indium In-111 oxine solution is eliminated in the cell labelling washing procedure.

Results of the above studies showed that neither test nor control animals showed any signs of reaction to the injected material, either immediately or during the subsequent seven day observation period. Body weight gains for test and control animals showed no significant differences. At necropsy, macroscopic examinations of liver, spleen, kidneys, heart, lungs, and G.I. tract revealed no abnormalities; there were no significant differences in the weights of the organs.

An experiment in dogs demonstrated acute toxic reactions to intravenously administered 2% oxine solution at approximately 20 mg/kg. Abnormal liver function, ECG and neurotoxic symptoms occurred in dogs administered 10 mg/kg or more, and increased toxicity occurred with more concentrated solutions. The safety factor for the toxicity of oxine administered as In-111 white blood cells is thus in the order of 10,000.

INDICATIONS AND USAGE

Indium In-111 oxine is indicated for radiolabelling autologous leukocytes.

Indium In-111 oxine labelled leukocytes may be used as an adjunct in the detection of inflammatory processes to which leukocytes migrate, such as those associated with abscesses or other infection, following reinjection and detection by appropriate imaging procedures. The

degree of accuracy may vary with labelling techniques and with the size, location and nature of the inflammatory process.

Indium In- 111 oxine labelled leukocyte imaging is not the preferred technique for the initial evaluation of patients with a high clinical probability of an abscess in a known location. Ultrasound or computed tomography may provide a better anatomical delineation of the infectious process and information may be obtained more quickly than with labelled leukocytes. If localization by these techniques is successful, labelled leukocytes should not be used as a confirmatory procedure. If localization or diagnosis by these methods fails or is ambiguous, indium In-111 oxine labelled leukocyte imaging may be appropriate.

CONTRAINDICATIONS

None known.

WARNINGS

Radiopharmaceuticals should be used only by or under the control of physicians who are qualified by specific training in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.

The content of the vial of indium In-111 oxine solution is intended only for use in the preparation of indium In-111 oxine labelled autologous leukocytes, and is not to be administered directly. Autologous leukocyte labelling is not recommended in leukopenic patients because of the small number of available leukocytes.

Due to radiation exposure, indium In-111 oxine labelled leukocytes could cause fetal harm when administered to pregnant women. If this radiopharmaceutical is used during pregnancy, the patient should be informed of the potential hazard to the fetus.

Where an assessment of the risk/benefits ratio suggests use of this product in lactating mothers, nursing should be stopped.

Adequate studies do not exist to support use in children. As in pregnancy and lactating mothers, the benefits to risk ratio should be assessed before consideration is given to the use of this product in this age group.

Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of a woman of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses.

Adequate reproduction studies have not been performed in animals to determine whether this drug affects fertility in males and females.

Indium In-111 oxine labelled leukocytes have been shown to be teratogenic in hamsters given 10 times the human dose.

Although earlier studies suggested that oxine might have carcinogenic potential, recent studies have found no evidence of carcinogenicity in either rats or mice given oxine in feed at concentrations of 1,500 or 3,000 ppm for 103 weeks.

It has been reported [ten Berge, R.J.M., Natarajan, A.T., Hardeman, M.R., et al, Labeling with Indium In-111 has detrimental effects on human lymphocytes, Journal of Nuclear Medicine, 24, 615-620 (1983)] that human lymphocytes labelled with recommended concentrations of indium In-111 oxine showed chromosome aberrations consisting of gaps, breaks and exchanges that appear to be radiation induced. At 555 kBq/10^7 (15 μCi/10^7) lymphocytes, 93% of the cells were

reported to be abnormal. The oncogenic potential of such lymphocytes has not been studied. It has been reported that the radiation dose to 10^8 leukocytes is $9x10^4$ mGy (0.9×10^4 rads) from 18.5 MBq (500μCi) [Goodwin, David, A., Cell labeling with oxine chelates of radioactive metal ions: Techniques and clinical implications, Journal of Nuclear Medicine, 19, 557-559 (1978)]

PRECAUTIONS

Clumping of cells may produce focal accumulations of radioactivity in lungs which do not wash out in 24 hours and thus may lead to false positive results. This phenomenon can be detected by imaging the chest immediately after injection.

The normally high uptake of indium In-111 oxine labelled leukocytes by spleen and liver may mask inflammatory lesions in these organs. Labelled leukocytes have been observed to accumulate in the colon and accessory spleens of patients with or without disease.

Chemotaxis of granulocytes deteriorates during storage, and loss of chemotaxis may cause false negative scans. The spontaneous release of indium In-111 has been reported to range from about 3% at one hour to 24% at 24 hours [ten Berge, R.J.M., Natarajan, A.T., Hardeman, M.R., et al, Labelling with indium In-111 has detrimental effects on human lymphocytes, Journal of Nuclear Medicine, 24, 615-620 (1983)]. The maximum amount of time recommended between drawing the blood and reinjection should not exceed 5 hours. It is recommended that the labelled cells be used within one hour of preparation, if possible, and in no case after three hours after preparation.

Plasma and red cell contamination impairs labelling efficiency of leukocytes. Hemolyzed blood in labelled leukocytes may produce heart pool activity and should be avoided.

Cell aggregates of various degrees have been reported. Cell labelling techniques and standing of cell preparation may be contributing factors.

In order to minimize patient radiation doses, the minimum amount of indium In-111 oxine necessary for the study should be used to label cells as soon as possible after receipt of the indium In-111 oxine.

Do not use after the expiration time and date (5 days after calibration time) stated on the label.

The contents of the vial are radioactive. Adequate shielding of the preparation must be maintained at all times.

ADVERSE REACTIONS

Sensitivity reactions (urticaria) have been reported. The presence of fever may mask pyrogenic reactions from indium In-111 oxine labelled leukocytes. The possibility of delayed adverse reactions has not been studied.

DOSAGE AND ADMINISTRATION

The recommended adult (70 kg) dose of indium In-111 oxine labelled autologous leukocytes is 7.4 to 18.5 megabecquerels (200-500 microcuries). Indium In-111 oxine solution is intended for the radiolabelling of autologous leukocytes. The indium In-111 oxine labelled autologous leukocytes are administered intravenously.

Imaging is recommended at approximately 24 hours post injection. Typically, anterior and posterior views of the chest, abdomen and pelvis should be obtained with other views as required.

Aseptic procedures and a shielded syringe should be employed in the withdrawal of indium In-111 oxine from the vial. Similar procedures should be employed during the labelling procedure and the administration of the labelled leukocytes to the patient. The user should wear waterproof

gloves during the entire procedure. The patient's dose should be measured by a suitable radioactivity calibration system immediately before administration. At this time, the leukocyte preparation should be checked for gross clumping and red blood cell contamination.

RADIATION DOSIMETRY

The estimated absorbed radiation doses to an adult patient weighing 70 kg from an intravenous dose of 18.5 megabecquerels (500 microcuries) of indium In-111 oxine labelled leukocytes including contributions from indium In-114m/114 as a radionuclidic impurity are shown in Table 4.

The Health Products and Food Branch has suggested that conventional radionuclide dosimetry cannot account for the high localized doses that result from the intracellular release of Auger electrons, and that actual risks could be higher than indicated by the conventional estimates. Further uncertainty in the dose estimates may arise from redistribution and re-utilization of indium In-111 released in vivo from labelled cells.

The dose of radiation absorbed by the organs will vary with the distribution of the blood cells in the organs, which in turn will depend on the predominance of the cell types labelled and their condition.

Table 4. Radiation Dose Estimates in a 70 kg Human for 18.5 MBq (500 μCi) at Expiry of Indium In-111 (99.75%) Oxine labelled leukocytes with Indium In-114m/114 (0.25%)

Organ	mGy/18.5 MBq In-111	Rads/500 μCi In-111
Spleen	130	13
Liver	19	1.9
Red Marrow	13	1.3
Skeleton	3.64	0.364
Testes	0.1	0.01
Ovaries	1.9	0.19
Total Body	3.1	0.31

Organ	mGy/46.25 kBq In-114m/114	Rads/1.25 μCi In-114m/114
Spleen	70	7
Liver	7.1	0.71
Red Marrow	6.9	0.69
Skeleton	0.85	0.085
Testes	0.04	0.004
Ovaries	0.06	0.006
Total Body	0.6	0.06

Organ	Total Dose in mGy	Total Dose in Rads
Spleen	200	20
Liver	26.6	2.66
Red Marrow	19.9	1.99
Skeleton	4.5	0.45
Testes	0.14	0.014
Ovaries	2.0	0.2
Total Body	3.7	0.37

Assumptions: 30% to spleen, 30% to liver, 34% to red marrow, 6% to remainder of body, with no excretion.

LABELLING PROCEDURES

Sterile technique must be used throughout. It is important that all equipment used for the preparation of reagents be thoroughly cleaned to assure the absence of trace metal impurities. The user should wear waterproof gloves during the handling and the administration procedure.

1. The following equipment is recommended:

   One (1) 60 cc or two (2) 30cc sterile disposable plastic syringes with a 19 or 20 gauge needle (**NOTE**: **Do not use a smaller gauge needle**).

   Ring stand and clamp(s).

   Three (3) 50 ml sterile conical plastic centrifuge tubes with screw caps. Label each set with patient ID and "WBC", "LPP" and "Wash" respectively (**NOTE: Three centrifuge tubes per patient).**

   Clinical Centrifuge with horizontal, 4 place rotor or equivalent.

   Three (3) disposable 5 or 10 ml syringes and 19 gauge needles.

   Syringe shield to dispense indium In-111 oxine.

   A dose calibrator.

   Butterfly catheter infusion set.

   Test tube rack.

   Lab timer.

   10 ml syringe with a 19 gauge or 20 gauge needle.

   19 gauge needle with filter (optional).

2. The following procedure should result in the preparation of 3-4 x 10^8 WBC's for labelling which is the recommended number of cells.

3. Withdraw from the patient 30-50 ml blood (preferably fifty (50) ml) using aseptic venipuncture technique using the 60 cc syringe fitted with a 19 gauge or 20 gauge needle and containing approximately 1000 -1500 units herapin in 1-2 ml. Blood withdrawal should be smooth and slow so as not to produce bubbles or foaming.

4. Remove and dispose of the needle and replace with a syringe cap. Gently mix the contents of the syringe and label with the patient's ID, date and time.
5. Upon receipt of the full syringe for processing, the contents should again be gently mixed.
6. Clamp the syringe barrel to the ring stand in an upright (needle side up) position and tilt the syringe 10-20 degrees from its position perpendicular to the bench.
7. Allow the red cells to sediment 30-60 minutes, depending upon when the supernatant [leukocyte rich plasma (LRP)] looks clear of red blood cells.
8. Replace the syringe cap with an infusion set.
9. Collect the plasma (LRP) in the centrifuge tube marked "WBC" by expressing the LRP through the catheter tubing making sure not to get any red cells into the WBC tube.
10. Immediately centrifuge the capped WBC tube at 400-450 g for 5 minutes.
11. Transfer the supernatant to the leukocyte poor plasma ("LPP") tube leaving behind 0.5-1.0 ml supernatant to cover the white cell button. **(NOTE: The button often contains a small number of red cells and may appear red.)**
12. Wash the white cell button with 4-6 ml Sodium Chloride (0.9%) Injection. Resuspend the button by gentle swirling.
13. Centrifuge the capped "WBC" tube at 400-450 g for 5 minutes, (alternatively, 150 g for 8 minutes) and discard all but 0.5 ml - 1.0 ml of the supernate to cover the cells.
14. Add 5.0 ml Sodium Chloride (0.9%) Injection. Resuspend the cells by gentle swirling.
15. With the shielded syringe, draw up approximately 22.2 MBq (600μCi) indium In-111 oxine. Check the amount of radioactivity in a dose calibrator set for indium In-111 and record for labelling efficiency calculations.

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration.

16. In several additions, add the indium In-111 oxine to the "WBC" tube, gently swirling after each addition.
17. Set the lab timer for 15 minutes and allow the capped "WBC" tube to incubate. Swirl the cell preparation several times during the incubation.
18. With a sterile plastic syringe, add half of the saved LPP (or about 8 ml) from the LPP tube. Cap and gently swirl the contents of "WBC" tube to resuspend the cells.
19. Centrifuge the "WBC" tube at 450g for 5 minutes (or 150 g for 8 minutes). Decant supernatant into the "Wash" tube leaving behind about 0.5 ml of the supernate to cover the cells.
20. Assay the activity in the "WBC" tube and in the "Wash" tube in a dose calibrator and record.
21. With a sterile plastic syringe add the remaining "LPP" to the cell button and gently resuspend by swirling. With a sterile syringe fitted with a 19 gauge needle, resuspend the cells by drawing the cells up into the syringe and expressing the suspension against the tube gently once or twice. Alternatively, draw up the cells into a syringe fitted with the filtered 19 gauge needle, and replace the needle with an unfiltered 19 or 20 gauge needle.
22. Reserve in the "WBC" tube a minimum amount of white cell suspension for a WBC count. A microscopic examination should also be completed to observe for clumping. Draw up the patient's dose [7.4 to 18.5 MBq (200-500μCi)] and check the syringe in the dose calibrator. Record the measurement.
23. It is recommended that the preparation be used within one hour of labelling (See Precautions).

QUALITY CONTROL

It is generally advantageous to record any observations on cell abnormalities (e.g., cell clumping). A trypan blue exclusion test may also be performed.

HOW SUPPLIED

Indium In-111 oxine solution is supplied in a vial as a single use only product containing 37 MBq (1.0 mCi) in 1.0 ml aqueous solution at the calibration date stated on the label. Vials are packaged in individual lead shields.

SPECIAL HANDLING AND STORAGE

The contents of the vial are radioactive and adequate shielding and handling precautions must be maintained.

Indium In-111 oxine solution should be stored at room temperature (15-25°C).

Indium In-111 oxine labelled autologous leukocytes should preferably be reinjected within one hour of labelling. The labelled cells may be stored at room temperature (15-25°C) for up to three hours following completion of the cell labelling procedure (step 21 above). Reinjection of indium In-111 oxine labelled autologous leukocytes more than 5 hours after initial blood drawing is not recommended.

Sterile technique must be used throughout the collection, labelling and re-injection procedures.