SOREQ RADIOPHARMACEUTICALS
NUCLEAR RESEARCH CENTER (NRC)
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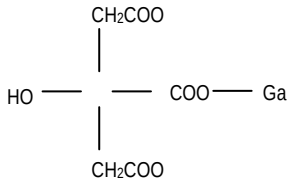
GALLIUM CITRATE Ga67 INJECTION

To Be Used In Diagnostic Institutes Only

פורמט עלון זה נבדק ותוכנו אושר על ידי משרד הבריאות

DESCRIPTION: Gallium Citrate Ga67 Injection is supplied in isotonic solution as a sterile, non-pyrogenic diagnostic radiopharmaceutical for intravenous administration. Each milliliter of the isotonic solution contains Gallium Citrate Ga67 1.5-2 mCi, at the time of calibration, Sodium Citrate 1.5-2 mg and Sodium Chloride 0.9% sol. The pH is adjusted to between 5-8 with hydrochloric acid and/or sodium hydroxide solution. Gallium Ga67, with a half-life of 78.3 hours, is cyclotron produced by the proton irradiation of enriched zinc oxide, is essentially carrier-free and contains negligible concentrations of other radioactive isotopes.

The radionuclidic composition at calibration time is not less than 99.89% Gallium Ga67, less than 0.01% Gallium Ga66 and less than 0.1% due to other radio contaminants, each expressed as a percentage of total activity. The radionuclidic composition at calibration time is not less than 99.89% Gallium Ga67, essentially zero (0.0002%) Gallium Ga66 and essentially zero of other radio contaminants each expressed as a percentage of total activity.
The chemical structure for Gallium Citrate is shown below:



Physical Characteristics

Gallium Ga67 decays to stable Zinc Zn67 by electron capture with a physical half-life of 78.3 hours.[1]

TABLE 1. Principal Radiation Emission Data

Radiation	Mean %/Disintegration	Mean Energy (keV)
Gamma-3	35.7	93.3
Gamma-4	19.7	184.6
Gamma-6	16.0	300.2

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

External Radiation

The specific gamma ray constant for Gallium Ga67 is 5.58 microcoulombs/Kg-hr-MBq (0.80R/hr-mCi) at 1cm. The first half value thickness of lead is 0.066cm. 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 0.41cm of Pb will decrease the external radiation exposure by a factor of 10.

TABLE 2. Radiation Attenuation by Lead Shielding

cm of Pb	Radiation Attenuation Factor	cm of Pb	Radiation Attenuation Factor
0.066	0.5	2.5	10^{-3}
0.41	10^{-1}	4.8	10^{-4}
1.2	10^{-2}		

To correct for physical decay of this radionuclide, the fractions that remain at selected time intervals after the time of calibration are shown in Table 3.

TABLE 3. Gallium Ga67 Decay Chart Half-life 78.3 Hours

Hours	Fraction Remaining	Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.00	42	0.69	84	0.48
6	0.95	48	0.65	90	0.45
12	0.90	54	0.62	96	0.43
18	0.85	60	0.59	108	0.38
24	0.81	66	0.56	120	0.35
30	0.77	72	0.53	132	0.31
36	0.73	78	0.50	144	0.28
				156	0.25
				168	0.23

* Calibration Time

CLINICAL PHARMACOLOGY:
Carrier-free Gallium Citrate Ga67 Injection has been found to concentrate in certain viable primary and metastatic tumors, as well as focal site of infection. The mechanism of concentration is unknown, but investigational studies have shown that Gallium Ga67 accumulates in lysosomes and is bound to a soluble intracellular protein.

It has been reported in the scientific literature that following intravenous injection, the highest tissue concentration of Gallium Ga67 - other than tumors and sites of infection - is in the renal cortex. After the first day, the maximum concentration shifts to bone and lymph nodes, and after the first week, to liver and spleen. Gallium is excreted relatively slowly from the body. The average whole body retention is 65% after 7 days, with 26% having been excreted in the urine and 9% in the stools.

INDICATIONS AND USAGES: Gallium Citrate Ga67 injection may be useful in demonstrating the presence of the following malignancies: Hodgkin's disease, lymphomas and bronchogenic carcinoma. Positive Ga67 uptake in the absence of prior symptoms warrants follow-up as an indication of a potential disease state.
Gallium Citrate Ga67 Injection may be useful as an aid in detecting some acute inflammatory lesions.

CONTRAINDICATIONS: None known.

PRECAUTIONS:

General
A thorough knowledge of the normal distribution of intravenously administered Gallium Citrate Ga67 Injection is essential in order to accurately interpret pathologic studies.
The finding in an abnormal gallium concentration usually implies the existence of underlying pathology, but further diagnostic studies should be done to distinguish benign from malignant lesions. Gallium Citrate Ga67 is intended for use as an adjunct in the diagnosis of certain neoplasms. Certain pathologic conditions may yield up to 40% false negative gallium studies. Therefore, a negative study cannot be definitively interpreted as ruling out the presence of disease.
Lymphocytic lymphoma frequently dose not accumulate Gallium Ga67 sufficiently for unequivocal imaging; and the use of gallium with this histological type of lymphoma is not recommended at this time.
Gallium Ga67 localization cannot differentiate between tumor and acute inflammation; and other diagnostic studies must be added to define the underlying pathology.
Gallium Citrate Ga67 Injection, as well as any other radioactive drugs, must be handled with care, and appropriate safety measures should be used to minimize external radiation exposure to clinical personnel. Care should also be taken to minimize radiation exposure to patients consistent with proper patient management.
Radiopharmaceuticals should be used only by physicians who are qualified by training and experience in the safe use and handling of radio nuclides and whose experience and training have been approved by the appropriate government agency authorized to appropriate government agency authorized to license the use of radio nuclides.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term animal studies have been performed to evaluate carcinogenic potential or whether Gallium Citrate Ga67 Injection affects fertility in males or females.

Pregnancy Category C

Animal reproductive studies have not been conducted with Gallium Citrate Ga67 Injection. It is also not known whether Gallium Citrate Ga67 Injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Gallium Citrate Ga67 Injection should be given to a pregnant woman only if clearly needed.

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

Nursing Mothers

Gallium Citrate Ga67 Injection is excreted in human milk during lactation; therefore, formula feedings should be substituted for breast-feeding.

Pediatric Use

Safety and effectiveness in children below the age 18 have not been established.

ADVERSE REACTIONS: Severe itching, erythema, and rash were observed in one patient of 300 studied.

The rare occurrence of hypersensitivity reactions or allergic reactions, skin rash, fast heartbeat and nausea has been reported in association with Gallium 67 use.

DIAGNOSTIC INTERFERENCE:

Due to other medications

Antineoplastics, which cause an elevation of serum iron, such as:

Cytarabine, Fluorouracil, Methotrexate or Iron:

Concurrent use may result in more unbound Ga67, thus increasing renal excretion and bone uptake of Ga67, possibly by elevating serum iron, which in turn may displace Ga67 from plasma protein-binding sites; tumor or abscess localization of Gallium Citrate Ga67 is decreased.

Calcium gluconate, parenteral

Soft tissue accumulation of Gallium Citrate Ga67 may occur as a result of extravasated calcium gluconate.

COPP chemotherapy

Thymic uptake of Gallium Citrate Ga67 may occur during or after cyclophosphamide – vincristine – procarbazine – prednisone [COPP] therapy.

Corticosteroids, glucocorticoid

Concurrent use may decrease Gallium Citrate Ga67 uptake by brain tumor or abscess because of reduced peritumor edema caused by the steroid.

Thymic uptake of Gallium Citrate Ga67 may concurrent use of prednisone.

Gallium nitrate

Gallium nitrate competes with Gallium Citrate Ga67 for plasma protein binding sites, resulting in reduced tumor or abscess uptake and increased skeletal uptake, increased renal excretion, and reduced liver uptake, increased renal excretion, and reduced liver uptake of Gallium Citrate Ga67.

Iron dextran

Abscess to muscle ratio may be increased when iron dextran is given 24 hours after the injection of Gallium Citrate Ga67, but may be decreased if given before or concurrently with it. This effect is probably due to a displacement of Ga67 from plasma protein binding sites by the iron, which results in increased elimination of the radiopharmaceutical.

Mechlorethamine or vincristine

Concurrent use may decrease whole body retention and increase bone deposition and urinary excretion of Gallium Citrate Ga67.

Due to other medications

Cardio toxicity, doxorubicin-induced

Doxorubicin-induced cardio toxicity may enhance myocardial uptake of Gallium Citrate Ga67.

Gynecomastia or hyperprolactinemia, diethylstilbestrol, imipramine, metoclopramide, oral contraceptive, phenothiazine, or reserpine induced

Possible localization of Gallium Citrate Ga67 in breast (females and males).

Lymphadenopathy, phenytoin induced

False positive images that resemble true lymphoma may occur since phenytoin has been associated with the development of local or generalized lymphadenopathy; condition should be differentiated from other types of lymph node pathology and the patient observed for an extended period of time.

Nephritis, drug induced

Interstitial nephritis induced by drugs (e.g., allopurinol, cephalosporins, furosemide, gold compounds, nonsteroidal anti-inflammatory drugs, pentamidine, Phenobarbital, rifampin, sulfonamides, thiazide diuretics) may result in kidney uptake of Gallium Citrate Ga67 that resembles the observed with other inflammatory kidney disease and possibly may be mistaken for glomerulonephritis, pyelonephritis, or the nephrotoxic syndrome.

Pseudomembranous colitis, antibiotic induced

Inflammation of the colon induced by antibiotics or other drugs may result in colonic uptake of Gallium Citrate Ga67 that resembles that observed with other inflammatory bowel diseases.

Pulmonary disease, amiodarone, bleomycin, busulfan, combination chemotherapeutic agent, or nitrofurantoin induced

Pulmonary interstitial pneumonitis and/or fibrosis induced by therapy with these medications may result in diffuse pulmonary localization of Gallium Citrate Ga67 that resembles that observed with other diffuse pulmonary diseases not related to drug therapy.

DOSAGE AND ADMINISTRATION: The recommended adult (70kg) dose of Gallium Citrate Ga67 Injection is 74-185 MBq (2-5mCi). Gallium Citrate Ga67 Injection is intended for intravenous administration only.

Approximately 10% of the administered dose is excreted in the feces during the first week after injection. Daily laxatives and/or enemas are recommended during the first week after injection until the final images are obtained in order to cleanse the bowel of radioactive material and minimize the possibility of false positive studies.

Studies indicate the optimal tumor to background concentration ratios are often obtained about 48 hours post-injection. However, considerable biological variability may occur in individuals, and acceptable image may be obtained as early as 6 hours and as late as 120 hours after injection.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Waterproof gloves should worn during the handling procedures.

With a shielded sterile syringe, aseptically withdraw the material for use.

The expiration date of the drug is ten days after the date of calibration.

Radiation Dosimetry

The estimated absorbed radiation doses[2] from an intravenous injection of 185Mbq (5mCi) of Gallium Citrate Ga67 are shown in Table 4.

Table 4. Dosimetry of Gallium Citrate Ga67 Injection for Maximum Dose of 185Mbq (5mCi)

	mGy/185MBq	Rads/5mCi
Whole Body	13.0	1.30
Skeleton	22.0	2.20
Liver	23.0	2.30
Bone Marrow	29.0	2.90
Spleen	26.5	2.65
Kidney	20.5	2.05
Ovaries	14.0	1.40
Testes	12.0	1.20
Gastrointestinal Tract		
Stomach	11.0	1.10
Small Intestine	18.0	1.80
Upper Large Intestine	28.0	2.80
Lower Large Intestine	45.0	4.50

[2]MIRD Dose Estimate Report No. 2, J. Nucl. Med. 14:755-6 (1973)

HOW SUPPLIED: Gallium Citrate Ga67 Injection is supplied sterile and non-pyrogenic for intravenous use. Each milliliter of the isotonic solution contains Gallium Citrate Ga67 1.5-2 mCi at the time of calibration.

Vials are available in the following quantities of radioactivity: From 2mCi to 20mCi Gallium Citrate Ga67.

Store at room temperature (15-30°C).

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

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