**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1 NAME OF THE MEDICINAL PRODUCT

Gallium (Ga67) Citrate injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition per ml at activity reference date and time.

$^{67}$Ga as gallium citrate 37 MBq

The qualitative composition is in conformity with the monograph 555 of the European Pharmacopoeia. Gallium [$^{67}$Ga] is a radionuclide (Atomic number 31; atomic weight 67) and has a physical half-life of 3.3 days (78.3 hours). It decays to stable zinc by electron capture emitting gamma energies of 93 keV (38%), 185 keV (21%) and 300 keV (16.8%). A small but clinically insignificant amount of $^{66}$Ga is present as a natural contaminant (*see section 11, Dosimetry*).

*Excipient: Contains 9mg/ml benzyl alcohol*
For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless solution.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Non-specific tumour imaging and/or localising agent
Gallium may be used in conjunction with other imaging modalities in the diagnosis, staging and subsequent management of malignant lymphomas such as Hodgkin and non-Hodgkin lymphoma. It may also be of subsequent use in establishing response to chemotherapy. $^{67}$Ga imaging can be helpful in the diagnosis of bronchial neoplasm by establishing the extent of mediastinal spread. It has also been used to ascertain the degree of dissemination of other malignant primaries with varying reliability.

Localisation of inflammatory lesions
Gallium may be used in establishing a diagnosis in specific inflammatory disorders, particularly those affecting the lung such as sarcoidosis and opportunistic infections due to Pneumocystis carinii. In sarcoidosis and interstitial lung disease uptake is influenced by disease activity. Gallium [$^{67}$Ga] may be useful in characterising and/or localising extrapulmonary inflammatory lesions e.g. tuberculous lymphadenopathy or in the investigation of fever of unknown origin. It provides only non-specific evidence of inflammatory sites within the body and other imaging techniques or biopsy procedures are needed to supplement the information obtained.

## 4.2 Posology and method of administration

Adults/Elderly: Recommended activity range 74-185 MBq. Activities of 37 MBq may be adequate for the sequential follow up of disease activity in patients with interstitial lung disease. Higher activities in SPECT may be required for tumour imaging (up to 260 MBq). This is most commonly encountered when staging mediastinal Iymphomas.

Children: Limited experience is recorded for children. Where alternative non-ionising diagnostic methods are unavailable gallium [$^{67}$Ga] citrate may be used but the activities should be scaled down according to body-weight 1.85 MBq/kg is recommended.

Gallium [$^{67}$Ga] citrate may only be administered by intravenous injection. Imaging may be undertaken 24 and 92 hours after administration although preferably on the 2$^{nd}$ or 3$^{rd}$ day for tumours. When investigating inflammatory lesions early scintigraphy, possibly as little as 4 hours after administration, may also be of value.

## 4.3 Contraindications

This product contains 9 mg/ml benzyl alcohol. This product must not be given to premature babies or neonates.

## 4.4 Special warnings and precautions for use

This product contains 9 mg/ml benzyl alcohol. Benzyl alcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.

This radiopharmaceutical may be received, used and administered only by authorised persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the local competent official organisations.

Care must be exercised in interpreting images of the lung fields at 24-48 hours when non-specific uptake of gallium [$^{67}$Ga] may occur. Such findings may not indicate interstitial lung disease. The appearance of gallium [$^{67}$Ga] conjugates in the intestines, resulting from its accumulation in the liver and subsequent biliary excretion, can reduce its diagnostic usefulness in detecting intra-abdominal lesions. In such cases the administration of a laxative in advance of imaging may be helpful. The administration of laxatives in insulin dependent diabetics should be undertaken with due caution.

Gallium [$^{67}$Ga] is a bone-seeking radionuclide. Therefore, particular care should be exercised in young children where irradiation of the end-plates in growing bone and haemopoietic tissues may require special consideration (*see section 11, Dosimetry*).

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

The biodistribution of gallium [$^{67}$Ga] may be affected by a wide range of pharmacological substances including cytotoxic agents, immunosuppressants (including steroids), radiocontrast agents, phenothiazines, tricyclic antidepressants, metoclopramide, reserpine, methyl dopa, oral contraceptives and stilboestrol.

For example:
Pretreatment with some cytotoxic agents may lead to an increased uptake of radiogallium in the bony skeleton, accompanied by a reduced accumulation in the liver, in soft tissues and also in tumour.

Non-specific, non-pathological $^{67}$Ga lung uptake has been described in patients who have received contrast media for contrast-enhanced radiolymphangiography.

Significant uptake of gallium in the thymus gland may be observed in children who have undergone chemotherapy and radiotherapy. This is non-pathological and is as a consequence of secondary hyperplasia.

Drugs causing increases in plasma prolactin levels may be lead to increased gallium [$^{67}$Ga] uptake in the mammary tissues.

Alteration in gallium $^{67}$Ga radiokinetics and tissue binding may occur after iron therapy. Therefore, the possibility of false positive results should always be borne in mind.

## 4.6 Fertility, pregnancy and lactation

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.

All radionuclide procedures carried out on pregnant women involve radiation doses to the foetus. Radiogallium is not suitable for use during any stage of pregnancy although its administration may be justifiable in exceptional circumstances e.g. curable neoplastic disease requiring routine chemo- or radiotherapy with undisputed teratogenic potential. In such cases special consideration of dosimetry will be necessary. In particular, the potential risks to be incurred by both the mother and foetus will need to be carefully debated. An absorbed dose of greater than 0.5 mGy is normally considered hazardous to the developing foetus. Higher dosages may occasionally be justifiable later in pregnancy. However, it should be noted that when administering an activity of 185 MBq, the adsorbed dose to the uterus in a pregnant adult female will be in the order of 15 mGy. Gallium [$^{67}$Ga] should only be administered to lactating females after breast-feeding has been discontinued.

## 4.7 Effects on ability to drive and use machines

Administration of diagnostic activities of gallium [$^{67}$Ga] citrate involves amounts which are unlikely to result in effects on the ability to drive or to use machines.

## 4.8 Undesirable effects

Intravenous administration of Gallium [67Ga] citrate has been reported to provoke adverse reactions of an anaphylactoid nature with an estimated incidence of 1 to 5 per 100,000 administrations.

The following table lists the symptoms, which may occur after the use of Gallium, [67Ga] citrate, according to system organ classes and frequency.

| System Organ Class (MedDRA) | Very rare (< 1:10,000) |
|---|---|
| Immune System Disorders | Anaphylactoid reaction |
| Vascular Disorders | Flushing |
| Skin and Subcutaneous Disorders | Erythema, Urticaria, Pruritus |
| General Disorders and Administration Site Conditions | Feeling hot |

For each patient, exposure to ionising radiation must be justified 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 or therapeutic result.

Exposure to ionising radiation is linked with cancer induction and the 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 (effective dose/ EDE) is less than 20 mSv. Higher doses may be justified in some clinical circumstances.

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 HPRA Pharmacovigilance; Earlsfort Terrace; IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

### 4.9 Overdose

Gallium [$^{67}$Ga] citrate should only be administered intravenously by qualified personnel in authorised settings. Therefore, the possibility of a pharmacological overdose is remote.

In the unlikely event of inadvertent excess of activity being administered, the overall radiation to critical organs may be reduced by the intravenous administration of appropriate chelating agents (as for other heavy metals). In addition, increased fluids by mouth and the intensive use of laxatives may be indicated when it is necessary to promote excretion of the radiolabel.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other radiopharmaceuticals for inflammation and infection detection.
ATC Code V09H X01.
The accumulation of gallium in tumour tissue and in sites of inflammation is thought to be due to its behavioural similarity to iron. Incorporation of gallium in transferrin, ferritin and lactoferrin has been demonstrated *in-vivo* and, with respect to transferrin, also *in-vitro*.

In the chemical dosages administered in man for imaging procedures ($<10^{-7}$ mg/kg) it is not envisaged that gallium [$^{67}$Ga] would have clinically important pharmacodynamic effects. High doses of gallium are known to interact with body tissues and the effects of its decay product zinc (> 2 gm) are described in man as toxic.

### 5.2 Pharmacokinetic properties

During the first 24 hours after administration 15 to 25% of the administered dose is excreted via the kidneys. The remaining activity is slowly excreted via the intestinal tract (t½ of 25 days). By day 7 post injection, the body usually retains about 65% of the administered dose. The skeleton is the major site for gallium retention (25% of administered dose). Other organs that visibly retain activity are liver, spleen, kidneys, lachrymal and salivary glands, nasopharynx and the breast (especially when lactating).

### 5.3 Preclinical safety data

Single-dose intravenous toxicity of gallium [$^{67}$Ga] citrate is species dependent being significantly more toxic in dogs than rats. Gallium possesses cumulative toxic effects. Total doses of 6.5 to 20 mg/kg administered over periods of several weeks can be lethal. These doses are about 1000 times

more than the maximal human dose of gallium $^{67}$Ga administered for diagnostic purposes (i.e. <1 microgram/70 kg).
No data are available about possible mutagenic or carcinogenic effects of gallium. Gallium is known to be teratogenic when administered in high dosages but insufficient data are available in order to estimate the risk.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium chloride
Benzyl alcohol
Sodium citrate dihydrate
Water for injections
Sodium hydroxide
Hydrochloric acid.

### 6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products

### 6.3 Shelf life

Gallium (Ga67) Citrate Injection expires 16 days after production. The expiry date is provided on the outer packaging and on each vial.

After opening of the vial chemical and physical in-use stability has been demonstrated for 8 hours below 30° C. From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

### 6.4 Special precautions for storage

Do not store above 25°C.
Store after first use below 30 °C.
If multi-dose use is intended, each aliquot should be removed under aseptic conditions, and within 8 hours (please refer to section 6.3).

Storage should take place in accordance with national regulations for radioactive materials.

### 6.5 Nature and contents of container

10 ml glass vial (Type 1 Ph.Eur) closed with a fluoropolymer coated bromobutyl rubber stopper sealed with an aluminium crimp cap.

Gallium (Ga67) Citrate Injection is supplied in the following activity amounts at activity reference date and time:
82 MBq in 2.2 ml
123 MBq in 3.3 ml
205 MBq in 5.5 ml
370 MBq in 10.0 ml

### 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

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting, etc. Therefore, radiation protection precautions in accordance with national regulations must be taken.

## 7 MARKETING AUTHORISATION HOLDER

Curium Netherlands B.V.
Westerduinweg 3
1755 LE Petten
The Netherlands

## 8 MARKETING AUTHORISATION NUMBER

PA0690/003/001

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 March 2000 / Date of last renewal: 31 March 2010

## 10 DATE OF REVISION OF THE TEXT

April 2024

## 11 DOSIMETRY

For this product the effective dose equivalent resulting from an administered activity of 185 MBq is typically 22 mSv assuming a weight of 70 kg. The absorbed doses to bone surfaces would be in the order of 109 mGy with a 10-fold reduction of the activities required in children of 1 year in order to achieve similar absorbed doses.
The contribution of the contaminant $^{66}$Ga to the delivered radiation dose is less than 0.5% at the time of delivery of the product, and diminishes rapidly afterwards due to the short physical half-life of this isotope (9 hours). $^{66}$Ga is a positron and gamma emitter.
Below are the dosimetry tables (ICRP53) stating the absorbed doses to the seven standard organs and five additional organs according dose retention (marked with *).

| Absorbed dose per unit activity administered (mGy/MBq) | | | | | |
|---|---|---|---|---|---|
| **Organ** | **Adult** | **15 year** | **10 year** | **5 year** | **1 year** |
| Bone surfaces | 0.59 | 0.87 | 1.4 | 2.4 | 5.6 |
| Breast | 0.06 | 0.06 | 0.09 | 0.15 | 0.29 |
| Lungs | 0.06 | 0.08 | 0.12 | 0.19 | 0.36 |
| Gonads | | | | | |
| Ovaries | 0.08 | 0.1 | 0.16 | 0.24 | 0.44 |
| Testes | 0.05 | 0.07 | 0.11 | 0.17 | 0.33 |
| Red marrow | 0.19 | 0.25 | 0.4 | 0.74 | 1.5 |
| Thyroid | 0.06 | 0.08 | 0.13 | 0.2 | 0.37 |

| Absorbed dose per unit activity administered (mGy/MBq) | | | | | |
|---|---|---|---|---|---|
| **Organ** | **Adult** | **15 year** | **10 year** | **5 year** | **1 year** |
| *Adrenals | 0.14 | 0.18 | 0.26 | 0.36 | 0.57 |
| *Spleen | 0.15 | 0.2 | 0.31 | 0.48 | 0.87 |
| *ULI wall | 0.12 | 0.15 | 0.25 | 0.41 | 0.75 |
| *LLI wall | 0.2 | 0.27 | 0.45 | 0.72 | 1.4 |
| *Liver | 0.12 | 0.16 | 0.23 | 0.33 | 0.61 |
| **Effective dose equivalent (mSv/MBq)** | **0.12** | **0.16** | **0.25** | **0.4** | **0.79** |

## 12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

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