SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Gallium (^{67}Ga) Citrate Injection 37 MBq/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains 37 MBq gallium-67 citrate at activity reference time and date (ART).
Gallium (^{67}Ga) is a radionuclide with a physical half-life of 3.3 days (78.3 hours). It decays to stable zinc (^{67}Zn) 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 gallium-66 (^{66}Ga) is present as a natural contaminant (see section 11).

Excipient with known effect: benzyl alcohol (9 mg/mL).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless solution, with a pH between 5.0 and 8.0.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.
Gallium (^{67}Ga) citrate scintigraphy must only be used when positron emission tomography (PET) with (^{18}F) fludeoxyglucose ([^{18}F] FDG PET) is not available (see section 4.2).

Gallium (^{67}Ga) Citrate Injection is indicated in conjunction with other imaging modalities for:

- Non-specific tumour imaging and/or tumour localisation in adults and children over 1 month age:
  - Diagnosis, staging and subsequent management of malignant lymphomas such as Hodgkin and non-Hodgkin lymphomas. Gallium (^{67}Ga) citrate may also be of subsequent use in establishing response to chemotherapy.
  - Diagnosis of bronchial neoplasm by establishing the extent of mediastinal spread.
  - Ascertainment of the degree of dissemination of other malignant primaries with varying reliability.

- Localisation of inflammatory lesions in adults only for:
  - Diagnosis of specific inflammatory disorders, particularly those affecting the lung such as sarcoidosis and opportunistic infections due to *Pneumocystis carinii* (see section 4.4).
  - Characterisation and/or localisation of extrapulmonary inflammatory lesions e.g. tuberculous lymphadenopathy or investigation of fever of unknown origin. Gallium (^{67}Ga) citrate 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

Posology
Adults
The recommended activity range for a patient weighing 70 kg is 75-185 MBq. Activities of 40 MBq may be adequate for the sequential follow up of disease activity in patients with interstitial lung disease.
Higher activities (up to 260 MBq) may be required for tumour imaging techniques, such as SPECT. This is most commonly encountered when staging mediastinal lymphomas.
The injection of activities greater than local DRLs (Diagnostic Reference Levels) should be justified.

Elderly
No dose adjustment is required in elderly patients ≥ 65 years old.

Renal/ hepatic impairment:
Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients (see section 4.4).

Paediatric population:
Limited experience is recorded for children.
The use in children and adolescents has to be considered carefully, based upon clinical needs and assessing the benefit-risk ratio in this patient group (see section 4.4).
If alternative non-ionising diagnostic methods or [^{18}F]FDG PET are unavailable, gallium (^{67}Ga) citrate scintigraphy can be used in cases of proven malignancy only.
The activities to be administered to children and adolescents may be calculated according to the European Association of Nuclear Medicine dosage card (EANM 2016), by using the following formula:

Activity administered [MBq] = Baseline Activity of 5.6 x Multiple

A minimum activity of 10 MBq is recommended in order to obtain images of sufficient quality.

The resulting activities to be administered may be found in the table 1 below:

Table 1

Body weight (kg)	Activity (MBq)	Body weight (kg)	Activity (MBq)	Body weight (kg)	Activity (MBq)
3	**10**	22	**30**	42	**51**
4	**10**	24	**32**	44	**54**
6	**10**	26	**34**	46	**56**
8	**12**	28	**36**	48	**58**
10	**15**	30	**38**	50	**60**
12	**18**	32	**41**	52-54	**63**
14	**20**	34	**43**	56-58	**67**
16	**22**	36	**45**	60-62	**71**
18	**25**	38	**47**	64-66	**75**
20	**27**	40	**50**	68	**78**

Method of administration
Multidose vial.
Gallium (Ga ^{67}) Citrate Injection must only be administered by intravenous injection.
For patient preparation, see section 4.4.

Image acquisition
Imaging -can be undertaken 24 and 92 hours after administration, although for tumours it should preferably be performed on the 2nd or 3rd day. When investigating inflammatory lesions, early scintigraphy, possibly within 4 hours from administration, may also be of value.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy (see section 4.6)
- Breastfeeding (see section 4.6)
- In patients under 18 years old except if they have been diagnosed with cancer (see section 4.2)
- Premature baby and newborn (up to 4 weeks old) due to the presence of benzyl alcohol (see section 4.4).

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.

Individual benefit/risk justification
For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required diagnostic information.

Renal/hepatic impairment
Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible.

Paediatric population
For information on the use in the paediatric population, see subsection “Specific warnings”, sections 4.2 and 4.3.
Gallium (^{67}Ga) is a bone-seeking radionuclide. Therefore, particular care should be exercised in young children where irradiation of the endplates in growing bone and haemopoietic tissues may require special consideration. Careful consideration of the indication is required since the effective dose per MBq is higher than in adults (see section 11).

Patient preparation
The patient should be well hydrated before the start of the examination and urged to void as often as possible during the first hours after the examination in order to reduce bladder radiation exposure.

Interpretation of images
Caution is required when 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.

Significant uptake of gallium (^{67}Ga) 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.

In sarcoidosis and interstitial lung disease, uptake is influenced by disease activity.

After the procedure
Close contact with infants and pregnant women should be restricted for 3 days after administration.

Specific warnings
Sodium
This medicinal product contains less than 1 mmol (23 mg) of sodium per dose, i.e. essentially sodium-free.

Benzyl alcohol
This medicinal product contains 9 mg/ml benzyl alcohol.
Benzyl alcohol may cause allergic reactions.
Intravenous administration of benzyl alcohol to neonates has been associated with serious adverse events, including breathing problems ("gasping syndrome") and death. The minimum amount of benzyl alcohol at which toxicity may occur is not known.

Environmental hazard
Precautions with respect to environmental hazard see section 6.6.

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, methyldopa, oral contraceptives and stilboestrol.

For example:
- Pretreatment with some **cytotoxic agents** may lead to an increased uptake of gallium (^{67}Ga) in the bony skeleton, accompanied by a reduced accumulation in the liver, in soft tissues and also in tumour.
- **Immunosuppressants** (such as steroids) may interfere with gallium (^{67}Ga) when looking for inflammatory foci.
- Non-specific, non-pathological gallium (^{67}Ga) lung uptake has been described in patients who have received **contrast media** for contrast-enhanced radiolymphangiography. Gadolinium used for magnetic resonance imaging contrast enhancement has been observed to decrease gallium (^{67}Ga) tumour uptake when given within 24 hours of injection.
- **Drugs causing increases in plasma prolactin levels** (like phenothiazines, tricyclic antidepressants, metoclopramide, reserpine, methyldopa, oestrogens, stilboestrol…) may 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 kept in mind.

4.6 Fertility, pregnancy and lactation

Woman of childbearing potential
When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.), alternative techniques not using ionising radiation (if there are any) should be offered to the patient.

Pregnancy
The use of gallium (^{67}Ga) is contraindicated in pregnant women due to its long half-life and increased risk of birth defects after exposure to gallium (^{67}Ga) (see section 4.3). An absorbed dose of greater than 0.5 mGy is considered hazardous to the developing foetus. 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.

Breast-feeding
Gallium (^{67}Ga) citrate is excreted into breast milk. Before administering radiopharmaceuticals to a mother who is breast-feeding, consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breast-feeding and to what is the most appropriate choice of radiopharmaceuticals, bearing in mind the secretion of activity in breast milk and the long half-life of gallium (^{67}Ga). If the administration is considered necessary, breast-feeding should be permanently stopped, and the expressed feeds discarded (see section 4.3).

Close contact with the infants should be restricted for 3 days after administration.

Fertility
The effect of gallium (^{67}Ga) citrate administration on fertility is not known.

4.7 Effects on ability to drive and use machines

Gallium (^{67}Ga)Citrate Injection has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Intravenous administration of Gallium (^{67}Ga) Citrate Injection has been reported to provoke adverse reactions of an anaphylactic nature. The symptoms are generally mild and mainly being characterised as a warm sensation, generalised flushing, erythema, pruritus and/or urticaria.

Tabulated list of adverse reactions
The following table lists the symptoms, which may occur after the use of Gallium (^{67}Ga) Citrate Injection, according to the MedDRA system organ classes. The frequencies are defined as follows: very common (≥ 1/10); common (from ≥ 1/100 to <1/10); uncommon (from ≥ 1/1,000 to <1/100); rare (from ≥ 1/10,000 to <1/1,000); very rare (<1/10,000); frequency not known (cannot be estimated from the available data).

System Organ Class (SOCs)	Adverse reactions	Frequency
Immune system disorders	Hypersensitivity, including anaphylaxis (e.g: flushing, erythema, urticaria, pruritus, feeling hot)	Not known

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 26 mSv when the maximal recommended activity of 260 MBq is administered, 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 requested to report any suspected adverse reactions via
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

In the event of administration of radiation overdose with Gallium (^{67}Ga) Citrate Injection, the overall radiation to critical organs can be limited by the intravenous administration of appropriate chelating agents (as for other heavy metals). In addition, oral administration of large amounts of fluids and the intensive use of laxatives may be indicated when it is necessary to promote excretion of the radionuclide.
It might be helpful to estimate the effective dose that was applied.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other diagnostic radiopharmaceuticals for inflammation and infection detection. ATC code V09HX01.

Mechanism of action
The accumulation of gallium (^{67}Ga) in tumour tissue and in sites of inflammation is thought to be due to its behavioural similarity to iron. Incorporation of gallium (^{67}Ga) in transferrin, ferritin and lactoferrin has been demonstrated *in-vivo* and, with respect to transferrin, also *in-vitro*.

Pharmacodynamic effects
At the chemical concentrations used for diagnostic examinations (< 10^{-7}mg/kg), gallium does not appear to have any pharmacodynamic activity. High doses of gallium are known to interact with body tissues and the effects of its decay product zinc (> 2 g) are described in man as toxic.

5.2 Pharmacokinetic properties

Distribution and organ uptake
By day 7 post injection, the body usually retains about 65% of the administered dose. The skeleton is the major site for gallium (^{67}Ga) retention (25% of administered dose). Other organs that visibly retain activity are liver, spleen, kidneys, lacrimal and salivary glands, nasopharynx and the breast (especially when lactating).

Elimination
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 = 25 days).

Half-life
The physical half-life of gallium (^{67}Ga) is 3.3 days.

5.3 Preclinical safety data

Single-dose intravenous toxicity of gallium 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) citrate administered for diagnostic purposes (i.e. < 1 microgram/70 kg). This medicinal product is not intended for regular or continuous administration.
Mutagenicity studies and long-term carcinogenicity studies have not been carried out. Gallium is known to be teratogenic when administered at high doses but insufficient data are available in order to estimate the risk.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate dihydrate
Benzyl alcohol
Sodium chloride
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

16 days after production date. Activity reference date and time, and expiry date and time, are stated on the outer packaging and on each vial.
After first withdrawal: chemical and physical in-use stability has been demonstrated for 8 hours when stored below 30°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.
If multi-dose use is intended, each aliquot should be removed under aseptic conditions. For storage conditions after first withdrawal of the medicinal product, see section 6.3.
Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

6.5 Nature and contents of container

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

Gallium (^{67}Ga) Citrate Injection is supplied in the following activity amounts at activity reference date and time (ART):
82 MBq in 2.2 ml
123 MBq in 3.3 ml
205 MBq in 5.5 ml
370 MBq in 10.0 ml
Not all pack sizes may be marketed.

The pack contains 1 multi-dose vial. Each vial is packaged in a lead shield container of an appropriate thickness.

6.6 Special precautions for disposal and other handling

General warning
Radiopharmaceuticals should 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 licenses of the 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.

For instructions on the handling of the medicinal product before administration see section 12.

If at any time in the preparation of this product the integrity of the vial is compromised, it should not be used.

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

Any unused medicinal 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
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

March 2026

11 DOSIMETRY

The dosimetry data listed below are from the ICRP (International Commission for Radiological Protection) publication 128 and are calculated according to the following assumptions:

- The biokinetic model given in MIRD (Medical Internal Radiation Dosimetry) Dose Estimate Report No. 2 (1973), which is based on human data, is adopted without any change. In children, the bone uptake is predominantly in the metaphyseal growth zones.
- The activity excreted via faeces (0.09) is assumed to have entered the bowel in the small intestine. The mean residence times in the gut are those of the standard gastrointestinal tract model (ICRP publication 53).

Absorbed doses for gallium (^{67}Ga) citrate

	Absorbed dose per unit of activity administered (mGy/MBq)				
Organ	Adult	15 years	10 years	5 years	1 year
Adrenals	0.13	0.18	0.26	0.36	0.57
Bone surfaces	0.63	0.81	1.3	2.2	5.2
Brain	0.057	0.072	0.12	0.19	0.34
Breast	0.047	0.061	0.093	0.15	0.29
Gallbladder wall	0.082	0.11	0.17	0.25	0.38
Gastrointestinal tract					
Stomach wall	0.069	0.090	0.14	0.21	0.39
Small intestine wall	0.059	0.074	0.11	0.16	0.28
Colon wall	0.16	0.20	0.33	0.54	1.0
Upper large intestine wall	0.12	0.15	0.25	0.41	0.75
Lower large intestine wall	0.21	0.26	0.44	0.71	1.4
Heart wall	0.069	0.089	0.14	0.21	0.38
Kidneys	0.12	0.14	0.020	0.29	0.51
Liver	0.12	0.15	0.23	0.33	0.61
Lungs	0.063	0.083	0.13	0.19	0.36
Muscles	0.060	0.076	0.12	0.18	0.35
Oesophagus	0.061	0.079	0.12	0.19	0.35

Ovaries	0.082	0.11	0.16	0.24	0.45
Pancreas	0.081	0.10	0.16	0.24	0.43
Red marrow	0.21	0.23	0.38	0.71	1.5
Skin	0.045	0.057	0.092	0.15	0.29
Spleen	0.14	0.20	0.31	0.48	0.86
Testes	0.056	0.072	0.11	0.18	0.33
Thymus	0.061	0.079	0.12	0.19	0.35
Thyroid	0.062	0.080	0.13	0.20	0.38
Urinary bladder wall	0.081	0.11	0.15	0.20	0.37
Uterus	0.076	0.097	0.15	0.23	0.42
Remaining organs	0.061	0.078	0.12	0.19	0.35
Effective dose (mSv/MBq)	**0.10**	**0.13**	**0.20**	**0.33**	**0.64**

The effective dose resulting from the administration of a maximal recommended activity of 260 MBq for an adult weighting 70 kg is about 26 mSv. For an administered activity of 260 MBq, the typical radiation dose to the target organ (bone surfaces) is 164 mGy and the typical radiation dose to the critical organs (red marrow, lower large intestine wall) are 55 mGy.

The contribution of the contaminant (^{66}Ga) to the delivered radiation dose is not more than 0.2% at the time of delivery of the product and diminishes rapidly afterwards due to the short physical half-life of this isotope (9.4 hours). Gallium (^{66}Ga) is a positron and gamma emitter.

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

This is a ready-to-use medicinal product for intravenous injection.

Withdrawals should be performed under aseptic conditions. The vials must never be opened. After disinfecting the stopper, the solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle or using an authorised automated application system.

If the integrity of this vial is compromised, the product must not be used.