SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gallium (^{67}Ga) citrate injection, CIS bio international
Reference : GA-67-MM-1

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Gallium (^{67}Ga) citrate: 74 MBq/ml at calibration date

For a full list of excipients, see section 6.1.

Gallium (^{67}Ga) (Atomic number 31 ; atomic weight 67) has a physical half-life of 3.26 days (78.29 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 %). Not more than 0.2 % of the total radioactivity is due to gallium (^{66}Ga).

3. PHARMACEUTICAL FORM

Solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.
Scintigraphy with gallium (^{67}Ga) citrate is used only in cases where access to (^{18}F) FDG PET is impossible

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. Gallium (^{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 localizing 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 lymphomas.

Children : Limited experience is recorded for children. Where alternative non-ionising diagnostic methods are unavailable and access to (^{18}F) FDG PET is not possible 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 2nd or 3rd 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

Pregnancy
Breastfeeding
Children or adolescent under 18 years, except in case of diagnosed cancer
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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. Particular care should therefore be exercised in young children where irradiation of the end-plates in growing bone and haemopoietic tissues may require special consideration (see 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 :

a. 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.

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

c. 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.

d. Drugs causing increases in plasma prolactin levels may lead to increased gallium (^{67}Ga) uptake in the mammary tissues.

e. Alteration in gallium (^{67}Ga) radiokinetics and tissue binding may occur after iron therapy.

The possibility of false positive results should therefore always be born in mind.

4.6 Pregnancy and lactation

Women of childbearing potential : When it is necessary to administer radioactive medicinal products to women of childbearing potential, 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. Alternative techniques which do not involve ionising radiation should be considered.

Pregnancy : Gallium-67 citrate is contra-indicated in pregnant women (see section 4.3

All radionuclide procedures carried out on pregnant women involve radiation doses to the fetus.

Lactation : Before administering a radioactive medicinal product to a mother who is breast-feeding, consideration should be given as to whether the investigation could reasonably be delayed until the mother has ceased breast-feeding or to ensure, if not, that the most appropriate choice of method of investigation implementing a radiopharmaceutical has been made, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, breast-feeding should be interrupted.

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

Intravenous administration of gallium (^{67}Ga) citrate has been reported to provoke adverse reactions of an anaphylactoid nature (estimated incidence of 1 to 5 per 100,000 administrations). The symptoms are generally mild being characterised as a warm sensation, generalised flushing, cutaneous erythema, pruritis and/or urticaria.

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 or therapeutic result.

Exposure to ionising radiation is linked with cancer induction and a 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/E) is less than 20 mSv. Higher doses may be justified in some clinical circumstances.

4.9 Overdose

Gallium (^{67}Ga) citrate should only be administered intravenously by qualified personnel in authorised settings. The possibility of a pharmacological overdose is therefore 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: radiopharmaceutical preparation for diagnostic use.
ATC code: V09HX01

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 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 g) 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 ($t_{1/2}$ 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 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 (^{67}Ga) administered for diagnostic purposes (i.e. < 1 µg/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 citrate dihydrate
Sodium chloride
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

14 days from the date of manufacture.
24 hours after first withdrawal.

The expiry date is indicated on the outer packaging and on each vial.

6.4 Special precautions for storage

Do not store above 25°C Store in the original packaging.
After the first withdrawal, store in a refrigerator (2°C – 8°C).

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

6.5 Nature and contents of container

15 ml, colourless, European Pharmacopoeia type I, drawn glass vials, closed with chlorobutyl rubber stoppers coated with teflon and aluminium capsules.

6.6 Special precautions for disposal and other handling

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

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

7. MARKETING AUTHORISATION HOLDER

Country specific

8. MARKETING AUTHORISATION NUMBER(S)

Country specific

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Country specific

10. DATE OF REVISION OF THE TEXT

07/2012

11. DOSIMETRY

For this product the effective dose resulting from an administered activity of 180 MBq is typically 18 mSv assuming a weight of 70 kg. The absorbed doses to bone surfaces would be in the order of 113 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.

According to ICRP 80 (International Commission of Radiological Protection) the radiation doses absorbed by the patients are the following :

Organ	**Absorbed dose per unit activity administered (mGy/MBq)**				
	Adult	**15 years**	**10 years**	**5 years**	**1 year**
Adrenals	0,13	0,18	0,26	0,36	0,57
Bladder	0,081	0,11	0,15	0,20	0,37
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
Gall bladder	0,082	0,11	0,17	0,25	0,38
Stomach	0,069	0,090	0,14	0,21	0,39
Small Intestine	0,059	0,074	0,11	0,16	0,28
Colon	0,16	0,20	0,33	0,54	1,0
ULI	0,12	0,15	0,25	0,41	0,75
LLI	0,21	0,26	0,44	0,71	1,4
Heart	0,069	0,089	0,14	0,21	0,38
Kidneys	0,12	0,14	0,20	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
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**

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Usual precautions regarding sterility and radioprotection should be respected.

Before use, packaging, pH, radioactivity and gamma spectrum will be checked.

Gallium (^{67}Ga) citrate injection is a sterile solution with a pH ranging between 5 and 8, a radiochemical purity at least equal to 95 % and a radioactive concentration of 74 MBq/ml at the reference date stated on the label (calibration date).

The vial should never be opened and must be kept inside its lead shielding.

The product should be aseptically withdrawn through the stopper using sterilized single use needle and syringe after desinfection of the stopper.

When necessary, gallium (^{67}Ga) citrate injection can be diluted up to ten-fold with 0.9 % sodium chloride injection.

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