Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Metastron 37 MBq/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Strontium-89 chloride: 37 MBq/ml

A solution of the active ingredient strontium-89 chloride (150MBq) in 4ml water.

Strontium-89 is a pure beta emitter with an energy of 1.492MeV and a half-life of 50.5 days.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless solution

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Metastron is indicated as an adjunct to and as an alternative to external beam radiotherapy for the palliation of pain from bone metastases secondary to prostatic carcinoma at the stage of hormone therapy failure.

4.2 Posology and method of administration

Posology

Adults

Metastron is an aqueous solution for intravenous injection and should be used without dilution. The recommended dose is 150 MBq (4 mCi) per injection, based on the average patient weight of 70 kg.

Alternatively, in particularly heavy or light framed patients a dose of 2 MBq (55 microCi)/kg 'fat-free' body weight may be used. This dosage is suitable for the elderly. Repeat administrations should not be performed within 3 months of the previous Metastron injection. Further administrations are not indicated in patients who have not responded to a previous administration of Metastron.

Calcium-like flushing sensation can occur with rapid administration of the product. Flushing sensation should not occur if the compound is infused slowly.

Elderly Population

No dose adjustment is recommended based on age.

Renal impairment

Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients.

Paediatric population

The product is not for administration to children.

Method of administration
Metastron is for single use only. (For repeat use after several weeks see section 4.4).
The instructions for preparation of radiopharmaceuticals are given in section 12.
For patient preparation, see section 4.4.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Metastron should not be used as a primary treatment for cord compression secondary to spinal metastases where more rapid treatment may be necessary.

Use of the product in patients with evidence of seriously compromised bone marrow, particularly low neutrophil and platelet counts, is not recommended unless the potential benefit of the treatment is considered to outweigh the risk.

4.4 Special warnings and precautions for use

Bone marrow depression may increase due to administration of Metastron. Administer with caution to patients suspected of bone marrow depression as evidenced by low platelet counts and white blood cell counts or a gradual decrease in these blood cell counts prior to administration. The use of Metastron is contraindicated in patients with seriously compromised bone marrow function (see section 4.3).

Individual benefit/risk justification:
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 therapeutic result.

Renal impairment:
Careful consideration of the benefit risk ratio in patients with renal impairment is required since an increased radiation exposure is possible.

Paediatric population:
For information on the use in paediatric population, see section 4.2.

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 radiation. Special precautions, such as urinary catheterisation, should be taken following administration of Metastron to patients who are significantly incontinent to minimise risks of radioactive contamination. International guidelines for disposal of radioactive waste must be followed.

Specific warnings:
Use of the product in patients with evidence of seriously compromised bone marrow, particularly low neutrophil and platelet counts, is not recommended unless the potential benefit of the treatment is considered to outweigh the risk. The following values can be considered in general: Leukocytes >3000/µl, platelets >100,000/µl and haemoglobin (Hb) >90 g/l.

It is recommended that the haematology of patients should be monitored. In considering repeat administration of Metastron the patient's haematological response to his initial dose, current platelet levels and any other evidence of marrow depletion should all be carefully considered.

A cytotoxic agent may be administered to a patient who has previously received Metastron provided that haematological parameters are stable and within the normal range. An interval of 12 weeks is recommended between administrations of the two therapies.

Therapy with Metastron is inappropriate for patients with a life expectancy less than 4 weeks. Considering the latency in the onset of the palliative effect, is more beneficial in patients with a relatively long life expectancy.

It should be taken into account in patient management that the expected time of onset of pain relief is 10 to 20 days following Metastron administration. It is not recommended that Metastron is administered to patients with very short life expectancies. Retention of 89Sr in metastatic bone lesions is probably 90 days or more and thus significantly prolonged compared with retention in normal bone tissue.

Care should be exercised in the pre-treatment assessment of the haematological status of patients who, for the same cause, have previously received extensive bone radiation and/or another injectable bone-seeking isotope.

It is important that information concerning this treatment and the associated safety precautions are given to the patient, relatives and hospital staff. Users should refer to the accompanying Patient Information.

A calcium-like flushing sensation has been observed in patients following a rapid (less than 30 second injection) administration. See section 4.2.

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

For precautions with respect to environmental hazard see section 6.6.

4.5 Interaction with other medicinal products and other forms of interactions

Calcium therapy should be discontinued at least two weeks before Metastron administration.

4.6 Fertility, pregnancy and lactation

Not relevant due to indication.

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

The frequencies of undesirable effects are defined as follows:

Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data)

System Organ Class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Very common	Bone marrow depression, including serious thrombocytopenia, serious leukopenia, reduced haemoglobin or low red blood cell count (see section 4.4).
Vascular disorders	Common	Flushing
General disorders and administration site conditions	Very common	Pain exacerbated (transient)

Adverse effects may include an exacerbation of pain within the first few days of administration. In clinical trials this effect was temporary and controlled with analgesics. Some degree of haematological toxicity, including thrombocytopenia and leucopenia, is to be expected following administration of Metastron. Typically, platelets will be depressed by about 30% (95% confidence limits 10-55%) compared to pre-administration levels. Because of the natural progress of their disease, more severe depression of platelet levels may be observed in some patients.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects.

The radiation dose resulting from therapeutic exposure may result in higher incidence of cancer and mutations.

In all cases it is necessary to ensure that the risks of the radiation are less than from the disease itself. The effective dose is 465 mSv when the maximal recommended activity of 150 MBq is administered.

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

Not applicable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Therapeutic radiopharmaceuticals, pain palliation (bone seeking agents) strontium (^{89}Sr) chloride
ATC code: V10BX01

The chemical properties of strontium enable it to imitate calcium *in vivo*, rapidly localising in proliferating bone. Strontium-89 is a beta emitter (100%), with a physical half-life of 50.5 days. The range of β-particles in tissue is 0.8 cm.

5.2 Pharmacokinetic properties

Distribution
The extent of uptake and retention of strontium-89 will depend on the metastatic involvement of the skeleton.

Organ uptake
The longer retention of strontium-89 in metastatic lesions enables the isotope to deliver a larger radiation dose to metastases whilst delivering a relatively small dose to bone marrow.

Elimination
Strontium which is not localised in the skeleton is excreted mainly via the urine with a small amount via the faeces.

Half-life
Strontium is retained in lesions with a long biological half-life compared to the physical half-life of strontium-89, whilst strontium taken up into normal bone exhibits a half-life of about 14 days.

Renal/hepatic impairment
The pharmacokinetics in patients with renal or hepatic impairment has not been characterised.

5.3 Preclinical safety data

The chemical toxicity of non-radioactive strontium chloride is well-documented and of little consequence, particularly in terms of the risk/benefit to the patient for whom this product is intended.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Strontium 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

The shelf life of the product is 28 days post the radioactivity reference date.

6.4 Special precautions for storage

Store below 25°C. Do not refrigerate or freeze.
Storage of radiopharmaceuticals should be in accordance with national regulations on radioactive materials.

6.5 Nature and contents of container

The product is supplied in a neutral glass vial as an aqueous solution. The vial is sealed with a PTFE coated rubber closure and metal overseal and is individually packed. Each vial is packed within a radiation shielding container of lead metal.

Pack size: A single 150 MBq vial.

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 licences 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.

If at any time in the preparation of this product the integrity of the container 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 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

GE Healthcare B.V.
De Rondom 8
5612 AP Eindhoven
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA22734/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 August 1991
Date of last renewal: 20 August 2006

10 DATE OF REVISION OF THE TEXT

May 2019

11 DOSIMETRY

The estimated radiation doses that would be received by normal healthy adults from the intravenous administration of 1 MBq of strontium-89 are given in the table below. Data are taken from Publication 53 of the ICRP (International Commission on Radiological Protection, Radiation Dose to Patients from Radiopharmaceuticals, Pergamon Press 1987).

Radiation doses to normal adults from the intravenous injection of strontium-89

Organ	**Absorbed radiation dose mGy/MBq**
Bone surfaces	17.0
Red bone marrow	11.0
Lower large intestine wall	4.7
Bladder wall	1.3
Testes	0.78

When osseous metastases are present significantly enhanced localisation of the radiopharmaceutical will occur with correspondingly higher doses to the metastases relative to other organs.

The absorbed dose to vertebral metastases has been measured in a group of 10 patients with widely varying extends of disease*****. The minimum, maximum and mean doses in this group are listed below.

Radiation dose to vertebral metastases from intravenous injection of strontium-89

	Absorbed radiation dose mGy/MBq
Minimum	60
Maximum	610
Mean	230

*Blake, G M *et al* Strontium-89 therapy: Measurement of absorbed dose to skeletal metastases. J Nucl Med 1988; 29(4), 549-557.

The Effective Dose for strontium-89 is 465 mSv per 150 MBq (ICRP 80, 1998).

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Metastron is an aqueous solution for intravenous injection and should be used without dilution. See section 4.2.

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