PRODUCT MONOGRAPH

METASTRON™
Strontium [^{89}Sr] Chloride

37 MBq per mL

Therapeutic Radiopharmaceutical

For the palliation of pain in patients
suffering from bone metastases

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NAME OF DRUG

Metastron™
Strontium [^{89}Sr] Chloride

THERAPEUTIC OR PHARMACOLOGICAL CLASSIFICATION

For the palliation of pain in patients suffering from bone metastases

DESCRIPTION

"Metastron" is supplied in single dose vials containing 150 MBq, 4mCi in 4ml of aqueous solution at the activity reference date stated on the label. It is provided as a sterile, aqueous solution of Strontium [^{89}Sr] Chloride for intravenous injection.

Each millilitre of the product contains 10.9 - 22.6 mg of Strontium Chloride. The radioactive concentration is 37MBq, lmCi/mL and the specific activity 2.96 – 6.17 MBq, 80-167 μCi/mg Sr. The pH of the solution is 4-7.5.

The injection is sterilized by autoclaving, it contains no bactericide.

The reference date, lot reference number, volume, radioactive concentration and total radioactive content for each batch are stated on the container labels.

All activities quoted are to the reference date stated on the labels.

NUCLEAR DATA

Production process: $^{88}Sr(n.\gamma)^{89}Sr$

Half life: 50.5 days

Type of decay: β^-

1.463 MeV 100%

Range of β^- from Strontium-89 in tissue 0.8 cm

RADIOACTIVITY

The volume of "Metastron" to be administered is calculated by reference to the radioactive concentration at 1200 hrs. GMT on the day of administration. The activity at this time may be calculated by multiplying the assay value given on the vial label by the appropriate factor from the following table.

Decay of Strontium-89:

Day*	Factor	Day*	Factor
-28	1.47	0	1.00
-26	1.43	2	0.97
-24	1.39	4	0.95
-22	1.35	6	0.92
-20	1.32	8	0.90
-18	1.28	10	0.87
-16	1.25	12	0.85
-14	1.21	14	0.83
-12	1.18	16	0.80
-10	1.15	18	0.78
- 8	1.12	20	0.76
- 6	1.09	22	0.74
-4	1.06	24	0.72
-2	1.03	26	0.70

*Days before (-) or days after the reference date as stated on the container label.

CLINICAL PHARMACOLOGY

Bone metastases from malignant tumours are frequently a source of deep unremitting pain, often causing exhaustion and despair in both patient and family[1]. Two primary tumours predominate in metastasizing to bone; breast, the most common cancer in women[2], and prostate, a common cancer in men [2]. Management of pain in prostate cancer patients is particularly difficult. Over 50% have bone metastases at diagnosis[3] and survival times are relatively long. Surgical orchidectomy and/or hormone therapy can limit the rate of disease progression and reduce pain temporarily[4]. Local or wide field radiotherapy is usually effective in relieving pain as metastases develop, but with certain drawbacks. Local radiotherapy treats a small number of painful sites, avoiding significant bone marrow irradiation but frequently unmasking other sites of pain, whereas wide field radiotherapy usually provides widespread relief from pain but at the expense of significant acute and sub-acute toxicity[5]. Pain control by analgesics such as aspirin, codeine, morphine or their like, is frequently both incomplete and, in the case of the narcotics, associated with unpleasant debilitating side effects.

Radionuclide pain palliation with intravenous phosphorus-32 was examined over a number of years[6],[7] but it suffered from two drawbacks; only approximately 30% of the phosphorus-32 was retained in the body, and bone marrow toxicity was significant.

Strontium-89 once injected, however, imitates calcium *in vivo*, localising in proliferating bone[8]. In addition, Strontium-89 is efficiently retained in metastatic bone lesions, whereas it is lost from normal bone with an initial half-life of 14 days.

Strontium-89 excretion pathways are two-thirds urinary and one-third fecal in patients with bone

metastases. Urinary excretion is higher in people without bone lesions. Urinary excretion is greatest in the first two days following injection.

"Metastron" is thus able to deliver a palliative radiation dose selectively and simultaneously to all skeletal metastases whilst delivering only a relatively small dose to bone marrow. The mean absorbed radiation dose to vertebral metastases in a group of patients with widely varying extents of skeletal disease is quoted under Radiation Dosimetry below.

The efficacy of "Metastron" has been demonstrated in a double blind clinical trial which compared advanced prostate cancer patients receiving "Metastron" with those receiving stable Strontium Chloride; "Metastron" was proven to be effective at the 99% confidence level.

Clinical trials have concentrated on demonstrating the response rate to "Metastron" in prostate cancer patients who have previously received conventional therapies for bone metastases, including radiotherapy, but whose pain has returned. A single dose of Strontium-89 has been shown to provide improvement in pain in approximately 75% of these patients with complete freedom from pain in approximately 20%. Onset of pain relief occurred typically between 10 and 20 days following administration and could improve for a further 2 - 3 weeks. Duration of relief averaged 6 months with a range of 4 - 12 months, and treatment could be repeated as required after intervals of at least 3 months, provided haematology values are satisfactory.

Similar results were reported in an independent study by Robinson, et al[10]. In both these clinical

studies bone marrow toxicity was found to be mild.

INDICATIONS

"Metastron" is indicated for the palliation of pain in patients suffering from bone metastases.

CONTRAINDICATIONS

Metastron therapy is contraindicated in patients with known hypersensitivity to the aqueous solution of Strontium Chloride or any component of Metastron.

WARNINGS

Use of the product in patients with evidence of seriously compromised bone marrow from previous therapy or disease infiltration is not recommended unless the potential benefit of the treatment outweighs the risks. Metastron should be used with caution in patients with low platelet counts and low white blood cell count and following values can be considered in general: Leukocytes >3000/µl, platelets >100,000/µl and haemoglobin (Hb) >90 g/l. Mild haematological toxicity is often observed following administration of the product. Platelet levels commonly fall to about 70% of pre-treatment levels, with a nadir at typically 4 to 6 weeks post-injection, and then steadily recover. It is recommended that the haematology of patients should be monitored at least once every other week. In considering repeat administration of Metastron the patient's haematological response to the initial dose, the current platelet levels and any other evidence of marrow depletion should all be carefully considered.

Metastron is not indicated for use in patients with cancer not involving bone.

Selection criteria for re-treatment should repeat the rationale outlined for the first administration and include bone scintigraphy and hematologic and renal assessment

A cytotoxic agent may be administered to a patient who has previously received Metastron provided the haematological parameters are stable or have returned to pre-administration levels.

It is recommended that the presence of bone metastases is confirmed, for example with a technetium-99m labelled MDP bone image, prior to therapy. Calcium therapy should be discontinued at least two weeks before "Metastron" administration.

A small number of patients have reported a transient increase in pain at 36 to 72 hours post-injection. This was usually mild and always controllable by analgesics.

In view of the expected time of onset of pain relief (10 to 20 days), it is not recommended that "Metastron" be administered to patients with very short life expectancies.

Pregnant Women

Since adequate reproduction studies have not been performed in animals to determine whether this drug affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus, this radiopharmaceutical preparation should not be administered to pregnant or nursing women unless it is considered that the benefits to be gained outweigh the potential hazards.

If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving this drug. Use of Metastron in

women of childbearing age should be deferred until the possibility of pregnancy has been ruled out. Women should use appropriate contraceptive methods to avoid pregnancy. If the patient is considering becoming pregnant, a nuclear medicine specialist or medical physicist should be consulted to determine if residual Metastron poses any potential risk to the fetus.

Nursing Women

Because Strontium acts as a calcium analog, its secretion into human milk is likely. It is recommended that nursing be discontinued by mothers about to receive intravenous Strontinum-89 Chloride. Hence where an assessment of the risk/benefits ratio suggests use of this product in lactating mothers, nursing should be stopped.

Pediatrics

Adequate studies do not exist to support the use in children. As in pregnancy and lactating mothers, the benefit to risk ratio should be assessed before consideration is given to the use of this product in this age group.

Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

Fertility

At the dosage levels at which Metastron is administered no changes in semen quality are expected, as Strontium chloride is a salt, and strontium is rapidly taken up by bone tissue. Therefore foetal damage is not expected and barrier method of contraception is not required for men.

A calcium-like flushing sensation has been observed in patients following a rapid (less than 30 second injection) administration. Calcium-like flushing sensation should not occur if the compound is infused slowly.

PRECAUTIONS

The normal precautions taken when handling radioactive material should be observed. It is important that information concerning this treatment and the associated safety precautions are given to the patient, relatives and hospital staff.

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.

Metastron is excreted primarily by the kidneys. Careful consideration of the benefit risk ratio in patients with renal impairment is required since an increased radiation exposure is possible.

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.

Metastron contains a radioactive component and should be administered only by physicians and other health care professionals (HCPs) qualified by training in the safe use and handling of therapeutic radionuclides. It should be administered only by physicians and HCPs qualified in the management of bone metastases. Appropriate management of therapy and complications is only possible when the presence of bone metastasis has been confirmed prior to therapy and treatment

facilities are readily available.

After use, all materials and its container, should be decontaminated or treated as radioactive waste and disposed of in accordance with the conditions specified by the local competent authority. Contaminated materials must be disposed of as radioactive waste via an authorised route.

ADVERSE REACTIONS

Undesirable effects reported with Metastron include bone marrow depression, transient exacerbation of bone pain and hot flush.

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)

Blood and lymphatic system disorders

Very common: Bone marrow depression, including serious thrombocytopenia, serious leukopenia, reduced haemoglobin or low red blood cell count

General disorders and administration site conditions

Very common: Pain exacerbated (transient)

Vascular disorders

Common: Flushing

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.

DOSAGE AND ADMINISTRATION

"Metastron" is supplied in a single dose vial ready for intravenous injection. The normal dose is 111-150 MBq per injection calculated at 2 MBq/kg. Repeat administration should not be performed within 3 months of the previous "Metastron" injection.

RADIATION DOSIMETRY

The estimated radiation doses that would be received by normal, healthy adults from the intravenous administration of l mCi or 1MBq of Strontium-89 are given in the table below. Data are taken from the ICRP publication "Radiation Dose to Patients from Radiopharmaceuticals" ICRP 53[11].

Radiation Doses To Normal Adults From The Intravenous Injection Of Strontium-89

Organ	Absorbed Radiation Dose

	mGy/MBq	rad/mCi
Bone Surfaces	17.0	63.0
Red Bone Marrow	11.0	40.7
Lower Large Intestine Wall	4.7	17.4
Upper Large Intestine Wall	1.8	6.7
Bladder Wall	1.3	4.8
Adrenals	0.78	2.9
Kidney	0.78	2.9
Pancreas	0.78	2.9
Testes	0.78	2.9

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 extents of disease.[9] 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	rad/mCi
Minimum	6	220
Maximum	61	2260
Mean	23	850

Effective dose equivalent (EDE). The effective dose equivalent for Strontium-89 is 435mSv per 150MBq*.

*Further information may be obtained by reference to the ICRP publication "Radiation Dose to Patients from Radiopharmaceuticals" ICRP 53[11]

EXPIRY

The product should not be used later than 4 weeks following the activity reference date.

STORAGE

Store at room temperature.

REFERENCES

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

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11. International Commission of Radiological Protection. **Radiation Dose to Patients from Radiopharmaceuticals** (**Publication 53),** Oxford, Pergamon Press, 1988; 171.