

**PRODUCT MONOGRAPH**

**Metastron™**  
Strontium [<sup>89</sup>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 [<sup>89</sup>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 [<sup>89</sup>Sr] Chloride for intravenous injection.

Each millilitre of the product contains 13.4 - 20.1 mg of Strontium Chloride. The radioactive concentration is 37MBq, 1mCi/mL and the specific activity 3.33-5.00MBq, 90-135uCi/mg Sr. The pH of the solution is 4-7.

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:  $^{88}\text{Sr}(n, \gamma)^{89}\text{Sr}$

Half life: 50.5 days

Type of decay:  $\beta^-$

1.463 MeV 100%

Range of  $\beta^-$  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<sup>1</sup>. Two primary tumours predominate in metastasizing to bone; breast, the most common cancer in women<sup>2</sup>, and prostate, a common cancer in men<sup>2</sup>. Management of pain in prostate cancer patients is particularly difficult. Over 50% have bone metastases at diagnosis<sup>3</sup> and survival times are relatively long. Surgical orchidectomy and/or hormone therapy can limit the rate of disease progression and reduce pain temporarily<sup>4</sup>. 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<sup>5</sup>. 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<sup>6,7</sup> 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<sup>8</sup>. 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.

"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<sup>10</sup>. 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**

The use of "Metastron" is contraindicated in patients who are significantly incontinent.

#### **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. 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.

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.

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.

Where an assessment of the risk/benefits ratio suggests use of this product in lactating mothers, nursing should be stopped.

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.

#### **PRECAUTIONS**

The normal precautions taken when handling radioactive material should be observed.

#### **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 1 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<sup>11</sup>.

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.<sup>9</sup> 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	
	cGy/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<sup>11</sup>

**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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2. In: **Cancer Facts and Figures - 1988**, New York: American Cancer Society Inc., 1988.
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4. Stoll B.A. **Hormonal Therapy - Pain Relief and Recalcification.** In: **Bone Metastasis**, editors Stoll B.A. and Parbhoo S., New York: Raven Press, 1983.
5. Salazar O.M. et al. Single Dose Half Body Irradiation for Palliation of Multiple Bone Metastases from Solid Tumours, final RTOG report. **Cancer**, 1986; 58: 29-36.
6. Maxfield J,R. Use of Radioactive Phosphorus and Testosterone in Metastatic Bone Lesions from Breast and Prostate. **Southern Medical Journal**, 1958; 51: 320-328.
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8. Blake G.M. et al. Sr-89 Therapy: Strontium Kinetics in Disseminated Carcinoma of the Prostate, **Eur. J. Nucl. Med.**, 1986; **12: 447-454.**
9. Blake G,M. et al. Strontium-89 therapy: Measurement of absorbed dose to skeletal metastases, **J. Nucl. Med.**, 1988; **29 (4):549-557.**
10. Robinson R,G. et al. Treatment of metastatic bone pain with Strontium-89, **Nucl. Med. Biol.**, 1987; **14 (3): 219-222.**
11. International Commission of Radiological Protection. **Radiation Dose to Patients from Radiopharmaceuticals (Publication 53)**, Oxford, Pergamon Press, 1988; 171.