Samarium^{153}-lexidronam for bone pain due to skeletal metastases

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Final assessment report

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The Medicare Services Advisory Committee is an independent committee which has been established to provide advice to the Commonwealth Minister for Health and Aged Care on the strength of evidence available on new medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform Government decisions about which new medical services should attract funding under Medicare.

This report was prepared by the Medicare Services Advisory Committee (MSAC). The report was endorsed by the Commonwealth Minister for Health and Aged Care on 9 August 1999.

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MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

Contents

Tables

Executive summary

The procedure

Samarium^{153}-lexidronam pentasodium (^{153}Sm-lexidronam) is a therapeutic radiopharmaceutical. It is a complex consisting of a metal component (isotope Samarium^{153}, which emits a medium energy β-particle and an imagable γ-photon) and a ligand (ethylene diamine tetramethylene phosphonic acid—EDTMP). The complex is a 'bone-seeker', that is, it has an affinity for skeletal tissue and concentrates in areas of increased bone metabolic activity, for example, metastatic bone lesions. ^{153}Sm-lexidronam is given slowly through an intravenous line over a period of one minute. Following systemic administration, ^{153}Sm-lexidronam concentrates in areas of bone growth, especially the layer of osteoid undergoing mineralisation.

Medicare Services Advisory Committee — role and approach

The Medicare Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister for Health and Aged Care on the evidence relating to the safety, effectiveness and cost-effectiveness of new medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. The medical literature on the new technology is searched and the evidence is assessed and classified according to the National Health and Medical Research Council (NHMRC) four-point hierarchy of evidence. A supporting committee with expertise in this area evaluates the evidence and provides advice to MSAC.

Assessment of Samarium^{153}-lexidronam for bone pain due to skeletal metastases

Many clinical studies have been undertaken on ^{153}Sm-lexidronam to date and this assessment is based on the best available data, that is, randomised controlled trials (RCTs). The main clinical data has been obtained from two ^{153}Sm-lexidronam RCTs and three Strontium^{89} RCTs.

There is a lack of clinical trial data directly comparing ^{153}Sm-lexidronam with Strontium^{89}. Therefore, the comparative effectiveness has been assessed using placebo as the common comparator. The comparability of the placebo arms in ^{153}Sm-lexidronam trials and Strontium^{89} trials is justified.

Clinical need

Bone metastases are common in carcinoma of the prostate, breast and lung, and are often manifested by multiple lesions with significant pain and pathologic fracture. The prevalence of prostate, breast and lung cancer was about 14,500 per 100,000 population in Australia with about 36 per cent (5,300) of these patients suffering from bony metastases[1]. Patients with intractable multiple lesion bone pain are usually at the end-stage of cancer, with a short life expectancy. The primary aim of clinical management is to control the pain and provide a better quality of life for patients and their families.

^{153}Sm-lexidronam is expected to be used as a second-line 'add-on' treatment to standard clinical management strategies, such as opioid and narcotic analgesics, when chemotherapy, hormone therapy and external-beam radiotherapy have failed or are unsuitable.

Safety

^{153}Sm-lexidronam appears, from the available evidence, to be no worse than Strontium^{89} in terms of haematological toxicity and other adverse events. However, it should be noted that, though the prognosis and life expectancy of end-stage cancer patients are generally poor and the majority of patients will receive a single dose, repeated treatment of ^{153}Sm-lexidronam remains an issue. In particular, the toxicity associated with repeated injection of ^{153}Sm-lexidronam should be investigated.

Effectiveness

It is demonstrated that ^{153}Sm-lexidronam is at least as effective as Strontium^{89} in relieving bone pain due to skeletal metastases from carcinoma of the prostate. ^{153}Sm-lexidronam has also been demonstrated to be effective in relieving bone pain due to skeletal metastases from carcinoma of the breast.

Decreased use of analgesics following ^{153}Sm-lexidronam administration was demonstrated in one of the two RCTs[2]. However, no comparison could be made with Strontium^{89} due to the different endpoints used in reporting results.

Cost-effectiveness

As ^{153}Sm-lexidronam seems as effective as Strontium^{89} in pain relief and no worse than Strontium^{89} in terms of toxicity, a cost minimisation analysis is appropriate. However, as the proposed fee for ^{153}Sm-lexidronam is much lower than that for Strontium^{89} and insufficient costing data has been provided, an economic analysis has not been conducted.

Recommendation

On the basis of evidence supporting its safety, effectiveness and cost-effectiveness, the supporting committee for this application recommends that ^{153}Sm-lexidronam be subsidised for the relief of bone pain in patients with skeletal metastases (as indicated by a positive bone scan) from the following malignancies:

i. carcinoma of the prostate, where hormonal therapy has failed; or

ii. carcinoma of the breast, where hormonal therapy and chemotherapy have failed;

and either:

a. the disease is poorly controlled by conventional radiotherapy; or

b. conventional radiotherapy is inappropriate, due to the wide distribution of sites of bone pain.

Introduction

The Medicare Services Advisory Committee (MSAC) has assessed Samarium^{153}-lexidronam pentasodium (^{153}Sm-lexidronam) injection for relief of bone pain in patients with skeletal metastases confirmed by a positive bone scan. MSAC evaluates new health technologies and procedures for which funding is sought under the Medicare Benefits Schedule (MBS) in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multi-disciplinary expert body, comprising members drawn from disciplines such as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health administration and health economics.

This report summarises the assessment of current evidence for ^{153}Sm-lexidronam injection for the treatment of bone pain in patients with skeletal metastases.

Background

Samarium^{153}-lexidronam

The procedure

^{153}Sm-lexidronam is a therapeutic radiopharmaceutical. It is a complex consisting of a metal component (isotope Samarium^{153}, which emits a medium energy β-particle and an imagable γ-photon) and a ligand (ethylene diamine tetramethylene phosphonic acid—EDTMP). The complex is a 'bone-seeker', that is, it has an affinity for skeletal tissue and concentrates in areas of increased bone metabolic activity, for example, metastatic bone lesions. The pathophysiology of pain in patients with bone neoplasia and also the mechanism of ^{153}Sm-lexidronam in pain relief are still unknown. However, it is believed that ^{153}Sm-lexidronam may interfere with or destroy cells elaborating the pain-producing substances (prostaglandins, kinins, growth factors etc).

^{153}Sm-lexidronam is available as a sterile solution of 2.0 GBq/mL in a 3 mL, rubber-stoppered glass vial, ie each vial contains 6 GBq. ^{153}Sm-lexidronam is given slowly through an intravenous line over a period of one minute. The recommended dosage is 37 MBq/kg. Sufficient fluid intake is strongly suggested before and six hours after injection. The half-life of ^{153}Sm-lexidronam is 1.9 days. Urinary excretion will be complete six hours after injection.

As indicated in the Product Information and supported by the Therapeutic Goods Administration (TGA) delegate, ^{153}Sm-lexidronam can be administered repeatedly at a minimum interval of eight weeks, if necessary.

Following systemic administration, ^{153}Sm-lexidronam concentrates in areas of bone growth, especially the layer of osteoid undergoing mineralisation. The ratio of distribution in bone lesion to normal bone is about 5:1.

Intended purpose

^{153}Sm-lexidronam injection is proposed for the relief of bone pain in patients with skeletal metastases as indicated by a positive bone scan.

^{153}Sm-lexidronam is expected to be used as a second-line 'add-on' treatment to standard clinical management strategies such as opioid and narcotic analgesics when chemotherapy, hormone therapy and external-beam radiotherapy have failed or are unsuitable. It is administered in an out-patient setting in nuclear medicine facilities or radiation oncology departments. It should be administered by suitably qualified and licensed medical specialists.

It is advisable that patients are first assessed by a radiation oncologist to ensure that external-beam radiotherapy is inappropriate.

Clinical need / burden of disease

Bone metastases are common in carcinoma of the prostate, breast and lung, and are often manifested by multiple lesions with significant pain, and pathologic fracture. The prevalence of prostate, breast and lung cancer was about 14,500 per 100,000 population in Australia with about 36 per cent (5,300) of these patients suffering from bony metastases[1]. Patients with intractable multiple lesion bone pain are usually at the end-stage of cancer, with a short life expectancy. The primary aim of clinical management is to control the pain and provide a better quality of life for patients and their families.

Existing procedures

Currently, the clinical management strategy for bony metastases includes:

- chemotherapy or hormone therapy;
- opioid narcotic analgesics;
- external-beam radiotherapy, ie localised skeletal radiotherapy and hemi-body radiation therapy (HBRT); and
- systemic administration of radiotherapeutic agents, eg Strontium^{89} injection.

Chemotherapy or hormone therapies may be effective in controlling the malignancy but even responding cases eventually become refractory to treatment. Narcotic analgesics often require dosage increments over time and are associated with constipation and other adverse effects. External-beam radiotherapy is effective in most patients with localised bone lesions. However, its application is limited in cases where extensive bony lesions are involved. Radiotherapeutic agents such as Strontium^{89} have been used for palliation of osteoblastic skeletal metastases.

Comparator

Strontium^{89} is the only systemically administrable radiotherapeutic agent that has a therapeutic mechanism similar to that of ^{153}Sm-lexidronam. Strontium^{89} is currently listed on the MBS for a similar indication as that applying to ^{153}Sm-lexidronam, though not as broad as that for ^{153}Sm-lexidronam. Therefore, Strontium^{89} is considered to be an appropriate comparator for ^{153}Sm-lexidronam in the treatment of bone pain due to skeletal metastases.

The differences between ^{153}Sm-lexidronam and Strontium^{89} are summarised in Table 1. The main difference is that ^{153}Sm-lexidronam has a broader indication.

Estimated utilisation

Of the 5,300 patients per year in Australia who are estimated to suffer from bony metastases, 75 per cent (3,975 patients) will be successfully treated by chemotherapy, hormone therapy and / or external-beam radiotherapy. Therefore, there will be about 1,325 patients per year that require ^{153}Sm-lexidronam, or about 2,000 treatments, if more than one treatment is required per patient per year.

Table 1 Differences between 153Sm-lexidronam and Strontium89

^{153}SM-LEXIDRONAM	STRONTIUM^{89}
Indicated for the relief of bone pain in patients with skeletal metastases as indicated by a positive bone scan.	Indicated for painful bony metastases from carcinoma of the prostate where hormone therapy has failed and either: the disease is poorly controlled by conventional radiotherapy; or conventional radiotherapy is inappropriate, due to the wide distribution of sites of bone pain.
no restriction on the origin or the type of cancer	restricted to prostate cancer
no restriction regarding previous treatment	indicated for those who have failed chemotherapy or hormone therapy, and conventional radiotherapy
shorter half-life: 1.9 days	longer half-life: 50.6 days
emits lower energy, mean β particle energy 0.23MeV	emits higher energy, mean β particle energy 0.60MeV
effect peaks 4 to 8 weeks, lasts up to 4 months	effect peaks at 6 weeks, lasts up to 3–6 months
recommended dosage: 37 MBq/kg	recommended dosage: ≤ 2 MBq/kg
repeated treatment given at intervals of no less than 8 weeks	repeated treatment given at intervals of no less than 3 months

This estimation does not take into consideration the likely market share of Strontium^{89}, which is indicated for nearly half of the potentially eligible patients for ^{153}Sm-lexidronam (among 5,300 patients with bony metastases, 2,500 have prostate cancer, ie 2,500 / 5,300 = 47%). Therefore, 2,000 ^{153}Sm-lexidronam treatments per year is likely to be an overestimation.

If ^{153}Sm-lexidronam is proved to be at least equally effective, with a similar adverse effect profile, some replacement in the market by Strontium^{89} is expected. In addition, the shorter half-life of ^{153}Sm-lexidronam may be an advantage in allowing a more rapid haematological recovery if the patient experiences significant myelosuppression with radioisotope treatment.

Marketing status of the therapeutic procedure

^{153}Sm-lexidronam is registered on the Australian Register of Therapeutic Goods (ARTG) for the relief of bone pain in patients with metastatic bone lesions demonstrated on radionuclide bone scan. The registration number is AUST R 62521. The proposed indication assessed by MSAC is within the indication approved by the Therapeutic Goods Administration (TGA).

Current reimbursement arrangement

Currently there is no specific MBS item number for ^{153}Sm-lexidronam.

Approach to assessment

In its assessment, MSAC undertook a review of the literature available on ^{153}Sm-lexidronam in the treatment of bone pain due to skeletal metastases and convened a supporting committee to evaluate the evidence of the treatment and provide expert advice.

Review of literature

Literature search strategy

The medical literature was searched to identify relevant studies and reviews for the period between 1966 and September 1998. Searches were conducted via Medline, HealthStar, Toxline, Cancerlit, Pascal, Biosis, Derwent, SciSearch, Elsevier Biobase, Embase, Current Contents and Cochrane Library.

The search terms used included 'samarium', 'samarium^{153}', 'samarium^{153} EDTMP', 'strontium', 'strontium^{89}'and 'bone pain due to skeletal metastases', 'palliative therapy' and 'randomised controlled trial'.

Articles selected were those that reported on randomised controlled trials (phase III) comparing ^{153}Sm-lexidronam and placebo in patients with bony metastases, randomised controlled clinical trials (phase III) comparing Strontium^{89} and placebo in patients with bony metastases and phase I/II trials for assessing safety. General reviews and dose optimisation studies were excluded.

Among the 75 citations identified, 30 publications were requested after applying the inclusion and exclusion criteria described above. From these, the evidence presented in six publications was assessed and classified according to the NHMRC-revised hierarchy of evidence shown in Table 2.

TGA evaluation reports on ^{153}Sm-lexidronam and Strontium^{89} were also reviewed, in which the efficacy and adverse effects were analysed.

Table 2 Designation of levels of evidence

I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly designed randomised controlled trial.
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies or interrupted time series with control group.
III-3	Evidence obtained from comparative studies with historical control, two and more single arm studies or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pre-test and post-test.

Source: NHMRC[3]

Characteristics of the studies

The characteristics of the trials are summarised in Table 3. Both ^{153}Sm-lexidronam trials[2,4] recruited patients with a life expectancy of at least four months, and reported the results on the 'intention-to-treat' population.

There is a lack of clinical trial data directly comparing ^{153}Sm-lexidronam with Strontium^{89}. Therefore, the comparative effectiveness has been assessed using placebo as the common comparator. The comparability of the placebo arms in ^{153}Sm-lexidronam trials and Strontium^{89} trials is justified. The placebo used in the trials was normal saline with or without an inactive agent to colour the solution for the purpose of blinding.

^{153}Sm-lexidronam versus placebo arm

Two RCTs[2,4] are included in this arm. The trial conducted by Resche et al was a randomised dose comparison trial without placebo control, and is therefore excluded from further discussion[5]. However, it is worth noting that the trial concluded the 1.0mCi/kg dose of ^{153}Sm-lexidronam is safe and effective for pain relief. It should be noted that analgesics were continued in both ^{153}Sm-lexidronam and placebo groups.

Strontium^{89} versus placebo arm

Three RCTs[6,7,8] were included in this arm. It should be noted that analgesics were continued in both Strontium^{89} and placebo groups.

The quality and validity of the three Strontium^{89} trials are considered. The need to select the best available Strontium^{89} trials to enable a comparison with ^{153}Sm-lexidronam is also recognised. It is noted that all three Strontium^{89} trials included used treatment regimes outside the TGA's recommendations, which became effective in October 1995.

In two RCTs[7,8] the dosage employed exceeded the approved 100–150MBq per administration, and in two RCTs[6,7] a repeat treatment was given at four to five weeks in contrast to the recommended interval of ≥ 3 months. It was revealed in the TGA clinical evaluation report for Strontium^{89} that increasing dosage to up to 400MBq per administration may not alter clinical effectiveness, though it could attribute to platelet toxicity.

It is also recognised that, although these studies were all randomised trials in design, there was a lack of rigour in terms of analysing results on 'intention-to-treat' population and avoiding bias in assessing subjective endpoints, such as pain score[7]. The trial conducted by Porter was a two-phase RCT designed to assess the effectiveness of Strontium^{89} as adjunctive treatment to local external-beam radiotherapy (LRT)[8]. Patients were randomly allocated to Strontium^{89} therapy or placebo in the second phase following LRT within seven days. Nevertheless, the difference in pain relief may arguably reflect the difference between Strontium^{89} and placebo, though the trial provided more accurate information on toxicity of adjunctive treatment with Strontium^{89}.

Representativeness

It appears that the trial population is representative of patient groups in respect of whom funding is sought under the MBS.

Expert advice

A supporting committee with expertise in internal medicine, radiation oncology and nuclear medicine was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for supporting committees, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations for nominees. Membership of the supporting committee is provided at Appendix B.

Table 3 Characteristics of the clinical trials

Trial	Study design	Quality	Subjects	Drug dose	Outcome
Serafini AN[4], 1998	RCT (phase III), multicentre, double blind, 'head-to-head' placebo controlled Follow-up: 4 months	NHMRC Level II 6/6	n=118 median age: 65 (24–83), prostate cancer: 80, breast cancer: 21 lung cancer: 6 other cancer: 11 previous treatment: surgery (85–95%), hormone (82–85%), radiation (73–77%), chemotherapy (23–38%). concomitant treatment: analgesics	single injection ^{153}Sm 0.5mCi/kg, n=40 1.0mCi/kg, n=39 placebo, n=39	area under pain curve (visual/ analog); physicians' assessment (PGA); analgesic use
Quick D[2], 1997 (abstract)	RCT (phase III), multicentre, double blind, 'head-to-head' placebo controlled Follow-up: 4 months	NHMRC Level II 4/6	n=152 median age: ? (46–86), prostate cancer: 152 previous treatment: not reported concomitant treatment: analgesics	single injection ^{153}Sm 1.0mCi/kg, n=101 placebo, n=51	area under pain curve (visual/analog); pain score; analgesic use
Lewington VJ[6], 1991	RCT (phase III), multicentre, double blind, 'head-to-head' placebo controlled Follow-up: 5 weeks	NHMRC Level II 5/6	n=32 (27 evaluated) median age: ? (64–79) prostate cancer: 32 previous treatment: hormone, radiation. concomitant treatment: analgesics	injection every 5 weeks ^{89}Sr 150MBq n=12 placebo (^{88}Sr) n=15	clinical response (5 Grades): G1: deteriorated G2: no change G3: some improvement G4: substantial improvement G5: pain-free
Buchali K[7], 1988	RCT, double blind, 'head-to-head' placebo controlled Follow-up: up to 3 years	NHMRC Level II 2/6	n=49 mean age: 67 (64–79) prostate cancer: 32 previous treatment: not reported concomitant treatment: analgesics	monthly injection ^{89}Sr 3x75MBq n=25 placebo n=24	pain relief survival
Porter AT[8], 1993	RCT (phase III), multicentre, double blind, 'head-to-head' placebo controlled Follow-up: 21 months	NHMRC Level II 5/6	n=126 median age: 71 (48–86) prostate cancer: 126 previous treatment: surgery, hormone. Patients underwent radiotherapy after randomisation, then to receive ^{89}Sr or placebo within 7 days. concomitant treatment: analgesics	single injection ^{89}Sr 400MBq n=67 placebo (^{88}Sr) n=59	pain relief analgesic use quality of life survival

?: Could not be determined from study

Results of assessment

No systematic reviews of ^{153}Sm-lexidronam were retrieved. This systematic review is based on RCTs, with the main clinical data obtained from two ^{153}Sm-lexidronam RCTs[2,4] and three Strontium^{89} RCTs[6,7,8].

Is it safe?

Haematological toxicity

^{153}Sm-lexidronam

The haematological toxicity profile of ^{153}Sm-lexidronam was based on RCTs[2,4,5] and on an 'intention-to-treat' population. It includes 95 per cent Confidence Interval and predictive values of the differences (Table 4). As reported in RCTs[2,4,5], and additional data submitted to the TGA, the main toxicity of systemic administration of ^{153}Sm-lexidronam was reversible haematological toxicity.

Table 4: Adverse events of systemic 153Sm-lexidronam treatment

Adverse event	^{153}Sm-lexidronam (1.0mCi/kg) n=193	Placebo n=85	Difference (95% CI), p value
Haemoglobin, at 7 weeks			
Grade* 0–2 toxicity	160 (83%)	73 (86%)	
Grade 3 toxicity	17 (9%)	6 (7%)	2% (-4%, 8%), p=0.41
Grade 4 toxicity	3 (1.5%)	1 (1%)	1% (-0.4%, 3%), p=0.68
Platelet, at 4 weeks			
Grade 0–2 toxicity	168 (87%)	80 (94%)	
Grade 3 toxicity	10 (5.2%)	0	5% (3%, 7.6%), p<0.00001
Grade 4 toxicity	1 (0.5%)	0	0.5% (-0.5%, 1.5%), p=0.16
White blood cell (WBC), at 4 weeks			
Grade 0–2 toxicity	164 (85%)	80 (94%)	8% (4%, 12%), p<0.00001
Grade 3 toxicity	(8%)	0	
Grade 4 toxicity	0	0	
Febrile neutropenia	0	0	
Bleeding	0	0	

*National Cancer Institute Common Toxicity Criteria:
Grade 2: Hb 8.0–9.4g/dl; platelet 50–74x109/L; WBC 2.0–2.9x109/L;
Grade 3: Hb 6.5–7.9g/dl; platelet 25–49x109/L; WBC 1.0–1.9x109/L; and
Grade 4: Hb <6.5g/dl; platelet <25x109/L; WBC<1.0x109/L.

A report from the US Food and Drug Administration (FDA)[9] indicated that the most common adverse effects based on two four-week RCTs[2,4] submitted to FDA by Cytogen Corporation shown in table 5.

Though the total incidence of ^{153}Sm-lexidronam-related anaemia, thrombocytopenia and leucocytopenia was significantly higher than that in the placebo group, severe toxicity with clinical significance was seen in only 5 per cent and 8 per cent of patients treated

with ^{153}Sm-lexidronam for Grade 3 platelet toxicity and Grade 3 white blood cell (WBC) toxicity, respectively.

Toxicity associated with repeated treatment with ^{153}Sm-lexidronam

It is noted that, though the prognosis and life expectancy of end-stage cancer patients are generally poor and the majority of patients will receive a single dose, repeated treatment with ^{153}Sm-lexidronam remains an issue. In particular, the toxicity associated with repeated injections of ^{153}Sm-lexidronam should be investigated.

All three RCTs[2,4,5] employed a single administration of ^{153}Sm-lexidronam, so it is uncertain whether ^{153}Sm-lexidronam is safe when given repeatedly. Unfortunately, there is limited data on toxicity of repeat dosing except in animal experiments. The available clinical data were from two unpublished phase I trials submitted to the TGA and a phase I/II study by Alberts et al[10]. ^{153}Sm-lexidronam administration at 1mCi/kg to 2mCi/kg per dose was repeated at six to eight week intervals for four doses. In the unpublished trials, the lowest WBC count ($1.4x10^9$/L) and the lowest platelet count ($35x10^9$/L) were recorded; both occurred after the first dose. No febrile neutropenia or haemorrhage occurred. Alberts et al reported an increased cumulative toxicity over repeated treatment[10]. Forty four per cent of patients experienced Grades 1 and 2 haematological toxicity after the first dose and this increased to 70 per cent by the third dose. However, the severity of the toxicity did not warrant termination of the treatment.

Strontium^{89}

Haematological toxicity of Strontium^{89} is summarised in Table 6, based on RCTs[6,7,8].

Strontium^{89} treatment significantly increased ≥ Grade 2 platelet toxicity, the incidence of haemorrhage, and Grades 1–3 WBC toxicity. The severity of the myelosuppression seen may be related to the high dose-intensity of Strontium^{89} used in the early studies.

The increased adverse events caused by ^{153}Sm-lexidronam[2,4,5] or Strontium^{89} [6,7,8] are compared in Table 7.

Death

Overall, deaths were measured at 6 per cent in the placebo group (n=85), and 12 per cent in the ^{153}Sm-lexidronam 1.0mCi/kg group (n=193). As noted in the TGA report, a higher rate of deaths in the ^{153}Sm-lexidronam group may be explained by a longer observation period for the majority of patients, as up to 59 per cent of patients in the placebo group crossed over to ^{153}Sm-lexidronam treatment after four weeks. Further, according to the investigators, all deaths were due to the progression of the disease and not related to ^{153}Sm-lexidronam.

Other adverse events

Other adverse events were reviewed in the TGA clinical evaluation and appear to be insignificant.

In conclusion, ^{153}Sm-lexidronam appears to be no worse than Strontium^{89} in terms of haematological toxicity.

Table 5 Adverse Effects of ^{153}Sm-lexidronam treatment based on two four-week RCTs

Adverse Effects	^{153}Sm-lexidronam (n=199)	Placebo (n=90)	Difference (95%CI,p)
Thrombocytopenia	69.3%	8.9%	60.5% (54.3%, 66.6%), p<0.00001
Leucocytopenia	59.3%	6.7%	52.6% (46.6%, 58.7%), p<0.00001
Decrease in haemoglobin	40.7%	23.3%	17.4%(9.5%,25.2%), p<0.000014
Transient pain increase	7%	6%	1.5%(-2.7%,5.7%), p=0.49

Table 6 Haematological toxicity of Strontium89

Adverse event	Strontium^{89}	Placebo	Difference (95% CI), p value
Platelet	n=104	n=98	
Grade 1 toxicity	(15.4%)	12 (12.2%)	3.4% (-36.%, 9.9%), p=0.36
Grade 2 toxicity	(18.2%)	4 (4.1%)	14.2% (8.3%, 20.1%), p<0.00001
Grade 3 toxicity	15 (14.4%)	1 (1%)	13.4% (8.4%, 18.4%), p<0.00001
Grade 4 toxicity	7 (6.7%)	1 (1%)	5.7% (2%, 9.4%), p=0.0024
WBC	n=92	n=83	
Grade 1 toxicity	(25%)	12 (14.4%)	10.5% (2.3%, 18.8%), p=0.012
Grade 2 toxicity	(18.5%)	1 (1.2%)	17.3% (11.4%, 23.1%), p<0.00001
Grade 3 toxicity	(7.6%)	0	7.6% (3.8%, 11.4%), p=0.000019
Grade 4 toxicity	1 (1.1%)	0	1% (-0.4%, 2.6%), p=0.16
Haemorrhage*	10 (14.9%)	3 (5.1%)	9.8% (2.6%, 17.1%), p=0.0075
Infection*	9 (13.4%)	7 (11.9%)	1.6% 9-6.6%, 9.8%), p=0.71

* only reported in RCT[8]

Table 7 Comparative Safety of 153Sm-lexidronam and Strontium89

Events	^{153}Sm-lexidronam	Strontium^{89}
Thrombocytopenia		
Platelet toxicity		
Grade 2 (50–74x10^9/L)	60.5%*	14.2%*
Grade 3 (25–49x10^9/L)	5%*	13.4%*
Grade 4 (<25x10^9/L)	0.5%	5.7*
Leucocytopenia		
WBC toxicity		
Grade 2 (2.0–2.9x10^9/L)	52.6%*	17.3%*
Grade 3 (1.0–1.9x10^9/L)	8%*	7.6%*
Grade 4 (<1.0x10^9/L)		1%
Decrease in haemoglobin		
Grade 2 (8.0–9.4 g/100mL)	17.4%*	
Grade 3 (6.5–7.9 g/100mL)	2%	n/a
Grade 4 (<6.5 g/100mL)	1%	
Transient pain increase	1%	9.8%*
Haemorrhage	0	1.6%
Infection	n/a	

* Compared with placebo control, the difference was statistically significant.

Is it effective?

Main outcome measures

The two RCTs of ^{153}Sm-lexidronam versus placebo employed similar outcome measures, while the RCTs of Strontium[89] versus placebo adopted different outcome measurements. In order to compare ^{153}Sm-lexidronam with Strontium[89], the common endpoints of 'pain relief' (or at least partial improvement) and 'analgesic use' have been employed.

Other outcome measures

'Quality of life' and 'survival' were also reported in Strontium[89] trials, but not in ^{153}Sm-lexidronam trials.

Results

Main outcome measures

Pain relief

Pain relief was measured either by patients or physicians.

In two RCTs[2,4], patients' daily score of pain on a scale of 0 to 10 was combined as an overall pain score every seven days, and computed to generate the pain curve. The area under the pain curve (AUPC) for each treatment group was then compared. In addition, physicians' clinical evaluation and global assessment (PGA) on pain relief was also reported. It was based on a six-point scale on the following categories:

- worse, an increased amount of pain and discomfort;
- no change;
- slight relief, some pain and discomfort;
- moderate relief, a noticeable improvement in pain and discomfort;
- marked relief, pain is vastly improved and does not cause discomfort; and
- completely better, total absence of pain and no disruption of normal daily activities.

In three of the RCTs[6,7,8], pain relief was measured and reported in different ways (see Table 8 for details). The proportion of patients with at least slight pain relief is categorised as 'partial pain relief' and reported in this initial assessment.

It is recognised that the result of pain relief should be interpreted with caution, as it is inevitably a subjective outcome measure, and pain threshold varies greatly among patients. Nevertheless, all the RCTs included were double blind in design, and took efforts to limit potential bias.

It is noted that in ^{153}Sm-lexidronam trials, ^{153}Sm-lexidronam was given as a single injection. In the Strontium[89] trials, a repeated injection at an interval of four to five weeks

was administered, except in one RCT[8] in which Strontium[89] was administered as a single injection. The recommended repeated treatment interval in Australia is ≥ 8 weeks for ^{153}Sm-lexidronam, and ≥ 3 months for Strontium[89] treatment. The results are summarised in Table 8.

Table 8 Main outcomes

Trial	Pain relief	Analgesic use
(^{153}Sm vs placebo) Serafini AN[4]	Pain relief (including slight to complete improvement), based on PGA at 4 weeks: ^{153}Sm: 62% (24/39), p<0.016 placebo: 41% (16/39) at 16 weeks: ^{153}Sm: 41% (16/39), p<0.0001 placebo: 3% (1/39)	decreased use in ^{153}Sm group, the difference from the placebo group was not significant at 4 weeks (p>0.093).
(^{153}Sm vs placebo) Quick D[2] (abstract)	Substantial relief (much better or completely better), based on visual analog scale (VAS) and pain descriptor scale (PDS) at 4 weeks: ^{153}Sm: 55.8% (53/95), p<0.001 placebo: 32.6%(15/46)	decreased use was by 37% in ^{153}Sm group, and increased by 26% in placebo group (p<0.05)
(^{89}Sr vs placebo) Lewington VJ[6] *	Pain relief (≥ Grade 3),assessed by the numerical weighting system (Grades 1–5) at 5 weeks: ^{89}Sr: 67% (8/12), p<0.01 placebo: 20% (3/15) Substantial relief (≥ Grade 4) at 5 weeks: ^{89}Sr: 41.6% (5/12), p<0.01 placebo: 6.7% (1/15) complete relief (Grade 5) at 5 weeks: ^{89}Sr: 33.3% (4/12), p<0.01 placebo: 0%	decreased use of analgesics is included in the grading system, which was significantly different from the placebo group.
(^{89}Sr vs placebo) Buchali K[7] *	Pain relief, based on patients' report, no details given at ? years ^{89}Sr: 28% (7/25), p=0.06 placebo: 45.8% (11/24)	not reported
(^{89}Sr vs placebo) Porter AT[8] *	Partial relief, (>50% improve), based on pain severity score (0–4) & frequency score (0–4) for each initial pain site at 4 months: ^{89}Sr: 83% (56/67), p=0.43 placebo: 78% (46/59) at 6 months: ^{89}Sr: 82% (55/67), p<0.0001 placebo: 49% (29/59) complete relief, (pain free) at 4 months: ^{89}Sr: 58% (39/67), NS placebo: 58% (34/59) at 6 months: ^{89}Sr: 42% (28/67), p=0.06 placebo: 30% (18/59)	Reduced analgesic use by at least 50% at 4 months ^{89}Sr: 23% p<0.05 placebo: 0% at 6 months ^{89}Sr: 30% p=0.036 placebo: 18% discontinued analgesic use at 4 months ^{89}Sr: 10% p=0.024 placebo: 3% at 6 months ^{89}Sr: 17% p=0.024 placebo: 5%

* results are re-calculated on 'intention-to-treat' population.
?: unable to identify from study when results were reported

Comparison of ^{153}Sm-lexidronam and Strontium89 in pain relief

To compare the effectiveness of ^{153}Sm-lexidronam with Strontium[89] in pain relief via the common comparator, the comparability of the placebo groups used in ^{153}Sm-lexidronam

versus placebo trials and Strontium[89] versus placebo trials have been examined and presented in Table 9.

Table 9 Comparison of ^{153}Sm-lexidronam and Strontium^{89} in pain relief[a]

^{153}Sm-lexidronam[b]			Strontium^{89}[c]		
Trial	**^{153}Sm 1.0mCi/kg**	**Placebo**	**Placebo**	**Strontium^{89}**	
Serafini AN[4] at 4 weeks	62% (24/39)	41% (16/39)	20% (3/15)	67% (8/12)	Lewington VJ[6] at 5 weeks
Quick D[2] (abstract) at 4 weeks	55.8% (53/95)	32.6% (15/46)	45.8% (11/24)	28% (7/25)	Buchali K[7] at ? weeks
			49% (29/59)	82% (55/67)	Porter AT[8] at 6 months
		pooled 36.5% (31/85) pooled 43.9% (43/98) difference:7.4% (2.6%–14%) Odds ratio: 0.73 (0.48–1.12) P=0.15			

a. The common endpoint used is partial pain relief.
b. For ^{153}Sm-lexidronam trials, results at four weeks after a single injection are used because detailed results at 16 weeks were not available in one RCT[2].
c. For Strontium^{89} trials, results reported at the end of the trials were used, as no common reporting time could be identified.
NB. Patients enrolled in both ^{153}Sm-lexidronam with Strontium^{89} trials had previous hormone therapy, chemotherapy, local radiotherapy, and were receiving analgesics.

It is demonstrated that there is no statistically significant difference between the placebo groups used in ^{153}Sm-lexidronam trials and Strontium^{89} trials. Therefore, the approach of using placebo control as a common comparator to compare ^{153}Sm-lexidronam with Strontium^{89} is justified.

The results of the clinical effectiveness comparison of ^{153}Sm-lexidronam and Strontium^{89} in pain relief are based on evidence generated from RCTs using meta-analysis. A random effect model is used due to a statistically significant heterogeneity within both trial groups. The quality of the randomised Strontium^{89} trials included is as discussed previously. However, it should be noted that the comparative effectiveness between ^{153}Sm-lexidronam and Strontium^{89} is not based on 'head-to-head' comparative RCTs but an indirect comparison. Therefore the resulting evidence is of low level (NHMRC Level III-3).

Results from meta-analysis

	^{153}Sm-lexidronam versus placebo arm[2,4]	**Strontium^{89} versus placebo arm[6,7,8]**
Pain relief	Odds ratio: 2.52	Odds ratio: 2.49
(partial)	(1.42–4.46)	(0.46–13.47)
	p=0.0015	p=0.29
	Risk difference	Risk difference
	22.5%	20.3%
	(9.3%–35.7%)	(-15.3%–55.9%)
	p=0.00087	p=0.26

The meta-analysis showed that 22.5 per cent more patients with additional ^{153}Sm-lexidronam treatment achieved pain relief to some degree, compared to the placebo group with analgesic only.

The decreased overall effectiveness of Strontium[89] is due to the conflicting results observed in RCT[7]. This is confirmed by cumulative meta-analysis. If the Buchali et al trial was excluded, a significant improvement in pain relief would be achieved in 35.4 per cent more patients in the Strontium[89] group compared with placebo, $p<0.00001$ (odds ratio 5.2, 95% CI: 2.5–10.8, $p=0.00001$)[7].

Given that the results of the placebo groups from both ^{153}Sm-lexidronam and Strontium[89] arms are equivalent, it appears that 2.2 per cent (22.5% – 20.3%=2.2%) more patients treated with ^{153}Sm-lexidronam achieved pain relief to some degree when compared with Strontium[89] treatment. However, the difference between ^{153}Sm-lexidronam and Strontium[89] treatment in relieving bone pain due to skeletal metastases is not statistically significant ($p=0.62$).

Comparison of ^{153}Sm-lexidronam and Strontium[89] in analgesic use

The trial conducted by Serafini et al[4] failed to demonstrate a decreased use of analgesics following ^{153}Sm-lexidronam treatment, while the trial conducted by Quick et al[2] showed a significantly reduced use of analgesics in ^{153}Sm-lexidronam treated patients[2,3]. Two of the three Strontium[89] trials[6,8] also observed a significant reduction in analgesics consumption. However, no common endpoint could be used to make a precise comparison.

Other outcomes

The ^{153}Sm-lexidronam trials did not report patients' 'quality of life' or 'survival' data. One Strontium[89] trial[8] showed that at three months a significant improvement in 'quality of life' was achieved in patients treated with Strontium[89], in terms of both alleviation of pain and improvement in physical activity ($p<0.05$), and in the overall estimate ($p=0.006$).

The 'survival rate' at two years post-Strontium[89] treatment was significantly higher than that of the placebo group, ie 46 per cent versus 4 per cent[7]. However, confounding factors such as stage of the disease, natural history, and the extension of metastases were identified, and the result was undermined. In one RCT[8] the median survival time was longer in the placebo group (34 weeks) in comparison with the Strontium[89] group (27 weeks). However, the difference was not statistically significant.

Effectiveness in relief of bone pain due to skeletal metastases from cancer other than prostate origin

Based on the available publications, the majority of patients that received ^{153}Sm-lexidronam treatment suffered from bony metastases from prostate cancer. ^{153}Sm-lexidronam has also been used for the management of bone pain due to skeletal metastases associated with other cancers, eg breast and lung cancers. However, published information, especially high quality data, is limited.

Across the two ^{153}Sm-lexidronam RCTs referenced in this report[4,5], 288 out of 373 patients had prostate cancer, 57 had breast cancer, eight had lung cancer, and 20 had other malignancies. However, the trial results were reported as an overall outcome without addressing subgroups of patients with different cancers. Although the mechanism of action of ^{153}Sm-lexidronam in the treatment of bone pain due to skeletal metastases may be less relevant to the type of primary cancer, the available treatment options and strategies are vastly different for cancers of various origins. Therefore, the

clinical effectiveness of ^{153}Sm-lexidronam in managing bony metastases from breast and lung cancer should be addressed, both to identify the clinical place of ^{153}Sm-lexidronam for the management of bony metastases from these cancers and to justify the indication and any restrictions that might be applicable for ^{153}Sm-lexidronam treatment.

A number of controlled/uncontrolled clinical studies have been retrieved, in which patients with prostate cancer, breast cancer, lung cancer and other cancers were recruited. The characteristics and the reported results are summarised in Table 10.

The data revealed:

- ^{153}Sm-lexidronam appears to be at least as effective as Strontium^{89} in managing painful bone metastases.
- ^{153}Sm-lexidronam is most frequently used for the treatment of bony metastases from prostate cancer, and has also been used for managing bony metastases from cancers of the breast, lung and of other origins.
- Data from two RCTs[4,5] suggest that ^{153}Sm-lexidronam is at least as effective in the treatment of bone pain due to skeletal metastases of breast cancer compared with those of prostate cancer.
- There is insufficient data to demonstrate that ^{153}Sm-lexidronam can benefit patients with bone pain due to skeletal metastases from lung cancer.
- The pain relief effect lasts for at least four weeks after a single injection and can be sustained up to 16 weeks[4].
- It is unclear what previous treatment was received by patients with prostate cancer, breast cancer or lung cancer. Therefore, it is difficult to define at what stage of disease or treatment ^{153}Sm-lexidronam is indicated for patients in each group from the data.
- There is a lack of data to confirm an improvement in patients' quality of life, though this is a likely consequence of pain relief. There is no evidence to indicate any benefit in survival.

Table 10 153Sm-lexidronam—managing bone pain due to skeletal metastases from various cancer types

Study	Quality	Cancer origin	Treatment	Outcome (pain relief)
Resche I et al[5], 1997	Level II	prostate: n=75 breast: n=36 lung: n=2 others: n=9	previous treatment: surgery 78–81%, hormone 84–86%, radiation 76–84% chemo 27–36% ^{153}Sm treatment (single injection) ^{153}Sm 0.5mCi/kg, n=55 1.0mCi/kg, n=59	patients with breast cancer seemed to respond better to 1.0mci/kg dosage (80%) than to 0.5mCi/kg dosage, while the difference in dose response among prostate cancer patients was less profound; no greater myelotoxicity seen though breast cancer patients likely had chemotherapy previously overall outcome: ^{153}Sm is effective for relief from bone pain due to skeletal metastases

Table 10 153Sm-lexidronam—managing bone pain due to skeletal metastases from various cancer types (cont.)

Study	Quality	Cancer origin	Treatment	Outcome (pain relief)
Serafini AN et al[4], 1998	Level II	prostate: n=80 breast: n=21 lung: n=6 others: n=11	previous treatment[a]: surgery 85–95% hormone 82–85%, radiation 73–77%, chemo 23–38% ^{153}Sm treatment (single injection) ^{153}Sm 0.5mCi/kg, n=40 1.0mCi/kg, n=39 placebo n=39	compared with prostate cancer, patients with breast cancer showed greater treatment response, less response seen in patients with lung cancer and other cancers
BA-105[b11]	Level IV	breast: n=23	previous treatment not clear ^{153}Sm treatment dose ascending, dose repeating study	pain relief seen in 9 (39%) patients with 5 (22%) reduced opioids no withdrawal due to toxicity
BA-107[b8]	Level IV	prostate: n=21 breast: n=1	previous treatment not clear ^{153}Sm treatment dose ascending study (up to 1.5mCi/kg)	no efficacy data reported, overall profile of toxicity presented
Turner JH et al[13], 1989	Level IV	prostate: n=10 breast: n=15 others: n=10	previous treatment hormonal 25 chemo 19 radio 21 none 2 ^{153}Sm treatment 740 MBq (11 patients had second dose)	overall results were reported without specifically addressing breast cancer subgroup 22 patients achieved pain relief
Turner JH et al[14], 1991	Level IV	prostate: n=11 breast: n=9 others: n=3	previous treatment hormonal 20 chemo 10 radio 15 none 3 ^{153}Sm treatment 740 MBq (11 patients had second dose)	overall results were reported without specifically addressing breast cancer subgroup 14 patients achieved pain relief
Albert AA et al[10],1997	Level III-2	prostate: n=56 breast: n=12 lung: n=7 others: n=7	previous treatment chemo 9 radio 36 none 37 ^{153}Sm treatment 0.75, 1.5, 3 mCi/kg (35 patients had more than one dose)	overall results were reported without specifically addressing breast cancer subgroup 78–95% patients achieved adequate pain control; the longest duration of efficacy was 56 days at a dose of 1.5mCi/kg

a. the range of % represents % of patients in 1.0mCi/kg group and 0.5mCi/kg group
b. data submitted to the TGA, no publication details available

What are the economic considerations?

Costs per treatment associated with ^{153}Sm-lexidronam are as follows:

^{153}Sm-lexidronam, including delivery:	$1,659.00
storage, administration and disposal:	$54.00
contingency fee (10% unit cost):	$166.00
medical consultation fee (MBS 110 or 104):	(up to) $112.65
Total:	**$1,991.65**

Costs per treatment associated with the comparator, Strontium^{89} are as follows:

Strontium^{89}, including delivery (MBS 16105):	$2,995.00
storage, administration and disposal:	$78.00
contingency fee (5% unit cost):	$149.75
medical consultation fee (MBS 110 or 104):	(up to) $112.65
Total:	**$3,335.40**

If ^{153}Sm-lexidronam is considered to be at least as effective as Strontium^{89}, then a cost minimisation analysis is appropriate. Given that the proposed fee for ^{153}Sm-lexidronam is much lower than the fee for Strontium^{89} listed on the MBS ($1,991.65 versus $3,335.40) and the lack of costing data, an economic analysis has not been conducted.

In the majority of patients, a single dose of ^{153}Sm-lexidronam is expected. However, ^{153}Sm-lexidronam can be administered repeatedly at intervals of ≥ 8 weeks. Strontium^{89} is recommended for repeated dosing at intervals of ≥ 3 months. Depending on the patients' life expectancy, the number of treatments required per year could be up to 6.5 and 4.3 for ^{153}Sm-lexidronam therapy and Strontium^{89} therapy respectively. In recognising that this could represent the worst scenario, expert opinion was sought. It is concluded that treatment comprising repeated administration of ^{153}Sm-lexidronam and Strontium^{89} is likely to involve three doses and two doses respectively. The resulting total treatment costs are therefore:

Likely scenario:

^{153}Sm-lexidronam: $1,991.65 x 3 = $5,974 per patient per year; and

Strontium^{89}: $3,335.40 x 2 = $6,670 per patient per year.

Worst scenario:

^{153}Sm-lexidronam: $1,991.65 x 6.5 = $12,946 per patient per year; and

Strontium^{89}: $3,335.40 x 4.3 = $14,342 per patient per year.

Other considerations

Although ^{153}Sm-lexidronam was approved by the TGA for the treatment of metastatic bone lesions, this assessment suggested that the indication of ^{153}Sm-lexidronam should be restricted to painful bony metastases from carcinoma of the prostate or the breast, as there are insufficient data, at the present time, to support its use for other disease sites.

The adverse events associated with repeated dosing of ^{153}Sm-lexidronam should be monitored, as there is limited clinical experience.

Conclusions

Safety

^{153}Sm-lexidronam appears, from the available evidence, to be no worse than Strontium^{89} in terms of haematological toxicity and other adverse events. However, it should be noted that, though the prognosis and life expectancy of end-stage cancer patients are generally poor and the majority of patients will receive a single dose, repeated treatment of ^{153}Sm-lexidronam remains an issue. In particular, the toxicity associated with repeated injections of ^{153}Sm-lexidronam should be investigated.

Effectiveness

It is demonstrated that ^{153}Sm-lexidronam is at least as effective as Strontium^{89} in relieving bone pain due to skeletal metastases from carcinoma of the prostate. In addition, ^{153}Sm-lexidronam has also been demonstrated to be effective in relieving bone pain due to skeletal metastases from carcinoma of the breast.

Decreased use of analgesics following ^{153}Sm-lexidronam administration was demonstrated in one of the two RCTs[2]. However, no comparison could be made with Strontium^{89} due to the different endpoints used in reporting results.

Cost-effectiveness

As ^{153}Sm-lexidronam seems as effective as Strontium^{89} in pain relief and no worse than Strontium^{89} in terms of toxicity, a cost minimisation analysis is appropriate. However, as the proposed fee for ^{153}Sm-lexidronam is much lower than that of Strontium^{89} and insufficient costing data has been provided, an economic analysis has not been conducted.

Other considerations

Although ^{153}Sm-lexidronam was approved by the TGA for the treatment of metastatic bone lesions, this assessment suggests that the indication of ^{153}Sm-lexidronam should be restricted to painful bony metastases from carcinoma of the prostate or the breast, as there are insufficient data, at the present time, to support its use for other disease sites.

The adverse events associated with repeated dosing of ^{153}Sm-lexidronam should be monitored, as there is limited clinical experience.

Recommendation

On the basis of evidence supporting its safety, effectiveness and cost-effectiveness, the supporting committee for this application recommends that ^{153}Sm-lexidronam be subsidised for the relief of bone pain in patients with skeletal metastases (as indicated by a positive bone scan) from the following malignancies:

i. carcinoma of the prostate, where hormonal therapy has failed; or

ii. carcinoma of the breast, where hormonal therapy and chemotherapy have failed;

and either:

a. the disease is poorly controlled by conventional radiotherapy; or

b. conventional radiotherapy is inappropriate, due to the wide distribution of sites of bone pain.

Appendix A MSAC terms of reference and membership

The terms of reference of MSAC are to advise the Commonwealth Minister for Health and Aged Care on:

- the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness; and
- references related either to new and/or existing medical technologies and procedures.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	Expertise
Professor David Weedon (Chair)	pathology
Ms Hilda Bastian	consumer health issues
Dr Ross Blair	vascular surgery (New Zealand)
Mr Stephen Blamey	general surgery
Dr Paul Hemming	general practice
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Mr Alan Keith	Assistant Secretary, Diagnostics and Technology Branch, Commonwealth Department of Health and Aged Care (from 3 May 1999)
Dr Richard King	gastroenterology
Dr Michael Kitchener	nuclear medicine
Professor Peter Phelan	paediatrics
Dr David Robinson	plastic surgery
Ms Penny Rogers	Assistant Secretary, Diagnostics and Technology Branch, Commonwealth Department of Health and Aged Care (until 3 May 1999)
Associate Professor John Simes	clinical epidemiology and clinical trials
Dr Bryant Stokes	neurological surgery, representing the Australian Health Ministers' Advisory Council (from 1 January 1999)
Dr Doris Zonta	population health, representing the Australian Health Ministers' Advisory Council (until 31 December 1998)

Appendix B Supporting committee

Supporting committee for MSAC application 1016
Samarium^{153}-lexidronam for bone pain due to skeletal metastases

Dr Richard King (Chair) MBBS, FRACP Director, General Medical and Emergency Medicine, Southern Health Care Network, Victoria	member of MSAC
Mr Ian Burnard Consumer Representative	nominated by the Australian Cancer Society
Dr Graeme Dickie MBBS, MBA, FRACP, FRACR Clinical Associate Professor, University of Queensland; Deputy Director, Division of Oncology, Royal Brisbane Hospital	nominated by the Australian and New Zealand Association of Physicians in Nuclear Medicine
Assoc Prof Gillian Duchesne BSc (Hons), MB, MD, FRCR, FRACR Associate Professor, University of Melbourne; Radiation Oncologist, Peter MacCallum Cancer Institute	nominated by the Royal Australasian College of Radiologists
Dr Peter Ellis MBBS, FRACP, Mmed (Clin Epi) Research Fellow, Royal Prince Alfred Hospital, Sydney	nominated by the Royal Australasian College of Physicians
Dr John Primrose MBBS (Hons), FRACR Senior Medical Adviser, Commonwealth Department of Health and Aged Care	adviser to MSAC

Abbreviations

AIHW	Australian Institute of Health and Welfare
ARTG	Australian Register of Therapeutic Goods
AUPC	area under the pain curve
EDTMP	ethyl diamine tetramethylene phosphonic acid
FDA	US Food and Drug Administration
HBRT	hemi-body radiation therapy
LRT	local external-bean radiotherapy
MBS	Medicare Benefits Schedule
MSAC	Medicare Services Advisory Board
NHMRC	National Health and Medical Research Council
PGA	physicians' clinical evaluation and global assessment
RCTs	randomised controlled trials
TGA	Therapeutics Goods Administration
WBC	white blood cell

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