Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1466 – Vertebroplasty for severely painful osteoporotic vertebral fractures

Applicant: Interventional Radiology Society of Australasia

Date of MSAC consideration: MSAC 78th Meeting, 3 April 2020

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

The Department of Health received a revised application from Interventional Radiology Society of Australasia (IRSA) to request Medicare Benefits Schedule (MBS) relisting of vertebroplasty for severely painful osteoporotic thoracolumbar vertebral fractures of 3 weeks duration or less.

The revised application was based on additional information provided by the applicant following the June 2019 MSAC Stakeholder Meeting for vertebroplasty.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to its safety, clinical effectiveness and cost-effectiveness, MSAC supported public funding for vertebroplasty for severely painful thoracolumbar osteoporotic fracture of 3 weeks duration or less as suggested during the MSAC Stakeholder Meeting on Vertebroplasty held on 7 June 2019. MSAC also advised that a prospective registry be developed to monitor this listing. This should include reporting on the centre and state where each procedure was performed, whether the patient was hospitalised or not at the time the decision to perform the procedure was made, the length of hospital stay if hospitalised, and any associated adverse events requiring further medical or hospital attention.

The MSAC-supported descriptor was:

VERTEBROPLASTY, performed by an interventional radiologist, for the treatment of a painful osteoporotic thoracolumbar vertebral compression fracture, where:

a) pain is severe (numeric rated pain score ≥7 out of 10);
b) symptoms are poorly controlled by analgesic therapy, namely opiates;
c) fracture duration is ≤3 weeks; and
d) there is MRI (or SPECT-CT if MRI unavailable) evidence of acute vertebral fracture.

Not to be performed more than once on the same fracture, but may be repeated for a new fracture of the same vertebra if the subsequent fracture meets the above criteria and vertebroplasty is medically indicated.

The same fee is payable for a single procedure involving one or more vertebra.

Consumer summary

The Interventional Radiology Society of Australasia applied for public funding through the Medicare Benefits Schedule (MBS) for vertebroplasty to treat patients with severely painful osteoporotic thoracolumbar vertebral fractures of 3 weeks duration or less.

Vertebroplasty is a procedure in which acrylic cement is injected into a bone of the spine to treat a break (fracture) where the bone was already weakened due to osteoporosis, and where the break has resulted in pain and limited mobility affecting quality of life.

MSAC accepted that vertebroplasty has a benefit in a small population of patients by helping them regain their mobility sooner and reducing pain in the short term. However, MSAC noted that the cost-effectiveness of vertebroplasty is uncertain. MSAC also considered that the procedure might be used in patients for whom there is no evidence of any benefit. Therefore, MSAC advised that the use of vertebroplasty be limited to those patients with recent and severely painful fractures of a certain type and location. The Committee also suggested that this use is monitored through a registry for at least two years, so that information can be collected about who is receiving the treatment and the costs associated with that treatment. This will provide data that MSAC can review in the future to ensure that the procedure is being used appropriately according to these specified criteria.

MSAC's advice to the Commonwealth Minister for Health

MSAC supported the relisting of vertebroplasty on the MBS, but only for patients with severely painful osteoporotic thoracolumbar vertebral fractures of a duration of 3 weeks or less.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this was a reconsideration of vertebroplasty. Vertebroplasty was previously listed on the MBS as an interim-funded service (items 35400 and 35402) from 2005 to 2011. MSAC reviewed this service in April 2011 and did not support continued public funding based on two randomised controlled trials (RCTs) that did not appear to support vertebroplasty. MSAC considered this application for relisting vertebroplasty in November 2018 and in March 2019, but did not support MBS funding at that time.

MSAC agreed with the applicant that the eligible population for vertebroplasty should be people with a severely painful osteoporotic thoracolumbar vertebral fracture of 3 weeks duration or less rather than 6 weeks or less, and that this period should refer to the duration of the fracture rather than the duration of pain. MSAC noted that many such patients will have poor prognosis and considered that the long-term data for vertebroplasty have not been adjusted for competing risk of death. In addition, it is known that, due to the nature of the condition, the pain experienced by such patients who do not receive vertebroplasty will also reduce over time to converge towards the earlier pain reductions experienced following vertebroplasty. Therefore, this intervention should be viewed as acute pain relief for early mobility purposes rather than long-term pain relief.

MSAC considered that the additional materials from the applicant since its previous consideration, including the pre-MSAC response, largely recapitulated previously documented information and opinion. MSAC also noted that its previous requests for more informative analyses of existing data could not be fulfilled. Accordingly, MSAC was satisfied that it had appropriately exhausted all avenues to improve the evidence base to inform its advice, and thus retained moderate confidence that vertebroplasty has a benefit of likely clinical importance in a small population of patients with clearly identifiable clinical need.

MSAC remained of the view, that consistently across the VAPOUR trial and the Cochrane Review, there is evidence that vertebroplasty results in a reduction in pain and improved disability and disease-specific quality of life compared with placebo. In addition, there are imprecise estimates of the magnitude of these benefits due to the small size of the studies and the nature of the outcomes assessed.

MSAC also retained its conclusion that there is weak evidence to support the applicant's claims of improved benefit of vertebroplasty in patients with osteoporotic thoracolumbar fractures and/or fractures of three weeks duration or less, as they primarily relied on subgroup analyses performed in the VAPOUR trial. In this regard, MSAC noted that, in the conclusions of the Diamond 2020 paper (re-presenting in more detail the VAPOUR subgroup analysis in patients with osteoporotic fractures of three weeks duration or less), the VAPOUR investigators also acknowledged that these results were "limited by being an exploratory sub-group analysis".

MSAC considered that the results of Hsieh et al. (2019) suggested important signals in relation to the safety of vertebroplasty. Leakage of the cement used in the procedure occurred commonly (66.7%). Although this rarely led to severe consequences of local neurological impingement and pulmonary embolism, the risk of pulmonary embolism increased with increasing volume of cement injected into the vertebra. The latter is an important signal because there has been a trend over time towards increasing volume of cement injected in vertebroplasty procedures.

MSAC noted that the comparative cost-effectiveness of vertebroplasty was not formally estimated because no revised economic evaluation was provided that reflects the revised circumstances of the request and its concerns with the previous economic evaluation had not been addressed. However, the economic evaluation did suggest that the cost-effectiveness of vertebroplasty was largely driven by claims for later cost off-sets and would be more favourable if only hospitalised patients were eligible for vertebroplasty. MSAC considered this to be useful information, because it suggested that the most cost-effective population had already been identified, and to add this further requirement to an MBS item descriptor could instead have the perverse incentive of hospitalising more patients for the sole purpose of receiving vertebroplasty.

MSAC considered that, despite this uncertain cost-effectiveness, the financial impact is small because of the small population. At the individual patient level, there are discernible benefits for some patients in terms of improved mobility and reduced pain in the short term. Currently this procedure is available, but patients have to pay out of their own pocket, thus making access an equity issue, recognising that the fee proposed is consistent with other similar procedures. Therefore, MSAC recommended listing with the following restrictions: one MBS item per patient per procedure (not one for each fracture), limited to severely painful osteoporotic thoracolumbar vertebral fracture with a duration of ≤3 weeks, but allowing for treatment of a subsequent fracture in the same vertebra where eligible and appropriate.

Because of the remaining uncertainty, and to reduce the likelihood of leakage beyond the proposed MBS-eligible population, MSAC also advised that a prospective registry be developed to monitor this listing. This should include reporting on the centre and state where each procedure was performed, whether the patient was hospitalised or not at the time the decision to perform the procedure was made, the length of hospital stay if hospitalised, and any associated adverse events requiring further medical or hospital attention.

4. Background

Vertebroplasty was previously listed on the MBS as an interim funded service (items 35400 and 35402) from 2005 to 2011. MSAC reviewed this service in April 2011 and did not support continued public funding. The interim listings were removed from the MBS in 2011.

An application for relisting vertebroplasty for severely painful osteoporotic vertebral fractures of less than 6 weeks duration on the MBS was submitted to MSAC after publication in October 2016 of a randomised controlled trial (VAPOUR) conducted in Australia. The request for MBS listing has since been updated by the applicant as being for vertebroplasty for severely painful osteoporotic thoracolumbar vertebral fractures of 3 weeks duration or less.

At its November 2018 meeting, MSAC did not support public funding for vertebroplasty for severely painful osteoporotic vertebral fractures of less than either 3 or 6 weeks duration. MSAC considered that there may be a small clinical benefit, but was uncertain of its clinical significance, and so considered that the cost-effectiveness is highly uncertain with substantial risk of use beyond the proposed patient population.

At its March 2019 meeting, MSAC reconsidered the application and deferred its advice regarding public funding of vertebroplasty. MSAC considered that a stakeholder meeting, to provide a broader clinical perspective and patient input, could inform the uncertainties in the application. MSAC also considered that an independent meta-analysis of the individual patient data (IPD) from all relevant randomised trials would be informative to further address uncertainties, particularly to clarify any consequences of the identified clinical heterogeneity across these trials on the observed effects of vertebroplasty (see Public Summary Document (PSD) Application No. 1466, Nov 2018/March 2019).

The MSAC Stakeholder Meeting for vertebroplasty was held on 7 June 2019 and the minutes have been published on the MSAC website (see Final Stakeholder Meeting Minutes Application No. 1466, June 2019).

5. Prerequisites to implementation of any funding advice

No new information has been provided on this aspect. As such this remains unchanged; see PSD Application No. 1466, Nov 2018/March 2019 p9.

6. Proposal for public funding

The applicant proposed amending the item descriptor to further restrict the proposed population to patients with severe pain from a fracture of 3 weeks duration or less (Table 1). This has changed from the initial submission, which was for fractures of less than 6 weeks duration.

The February 2020 Departmental Overview noted that the applicant's requested MBS item descriptor did not specify that patients must have a thoracolumbar fracture, which would

mean that patients with other types of vertebral fracture would also be eligible for vertebroplasty. The Departmental Overview therefore suggested insertion of the word "thoracolumbar" before the first use of the word "vertebral" in the descriptor below to reinforce this intent expressed during the Stakeholder meeting.

Table 1 Applicant revised requested MBS item with Departmental Overview amendment

Category 3—therapeutic procedures
VERTEBROPLASTY, performed by an interventional radiologist, for the treatment of a painful osteoporotic thoracolumbar vertebral compression fracture, where a) pain is severe (numeric rated pain score ≥7 out of 10); b) symptoms are poorly controlled by analgesic therapy, namely opiates; c) severe pain duration is ≤3 weeks; and d) there is MRI (or SPECT-CT if MRI unavailable) evidence of acute vertebral fracture. Not to be performed more than once on the same fracture. (Anaes.) MBS Fee: $700

Source: Table 1, p3 of the February 2020 Departmental Overview

7. Summary of public consultation feedback/consumer Issues

Twenty-three responses were previously received in the consultation feedback; see PSD Application No. 1466, Nov 2018/March 2019 p10.

A MSAC Stakeholder Meeting for vertebroplasty was held on 7 June 2019 with members of MSAC, clinicians with experience and expertise in geriatric medicine, interventional radiology and spinal surgery; representatives of the applicant; representatives from consumer organisations; and representatives from the Department of Health. See Final Stakeholder Minutes Application No. 1466, June 2019.

8. Proposed intervention's place in clinical management

With the exception of further refining the eligible population, the clinical management algorithm for the proposed intervention remained unchanged; see PSD Application No. 1466, Nov 2018/March 2019 p10.

9. Comparator

The comparator remained 'intensified and extended conservative medical therapy' (represented by placebo/sham injection in the available clinical evidence).

10. Comparative safety

Summary of new comparative safety data for consideration
New comparative evidence included a subgroup analysis of patients with fracture duration ≤3 weeks from the VAPOUR trial (published manuscript Diamond et al. 2020), the American Society for Bone and Mineral Research (ASBMR) Task Force Report (Ebling et al. 2019), and one meta-analysis (Lou et al. 2019). The applicant's "advice to ESC December 2019" also summarised the publication by Yang et al. (2016). The February 2020 Departmental Overview identified additional relevant evidence - one retrospective study (Hsieh et al. 2019), and one prospective study (Mazzantini et al. 2019) - although these additional studies do not provide direct evidence for comparative safety.

The published manuscript by Diamond et al. (2020) presents a subgroup analysis of 93 patients with fracture duration ≤3 weeks from the VAPOUR trial to support the claim that there was no difference in new fracture incidence on 60-month radiographs between the vertebroplasty (3/46 patients) and placebo (2/47 patients) groups.

The authors of the ASBMR Task Force Report (Ebeling et al. 2019), based on the evidence reviewed, were uncertain whether vertebroplasty increased the risk of new symptomatic/ radiographic vertebral fractures or related serious adverse events (AEs). Serious AEs reported across the studies reviewed in the Report included osteomyelitis requiring surgical drainage, rib and pedicle fractures, thecal sac injury, vasovagal reactions, acute asthma exacerbation, cord compression requiring immediate decompression, hypoxia and respiratory failure. Cement leakage was reported in up to 78% of cases, but the ASBMR Task Force Report was not able to determine the rate of significant sequelae as a consequence of cement leakage or embolism, due to the small number of these events.

The meta-analysis by Lou et al. (2019) stated that slightly higher rates of new vertebral fractures were found in the vertebroplasty group (116 fractures in 706 patients [16.43%]) compared to the control group (111 fractures in 701 patients [15.83%]). The difference was not statistically significantly different (relative risk [RR] = 0.97; 95% confidence interval [CI]: 0.63, 1.49). The November 2019 Departmental Overview noted that these results correspond with results observed in the 2018 Cochrane Review (Buchbinder et al. 2018). A summary of the similarities and differences in the analyses and findings by Lou et al. 2019 and the 2018 Cochrane Review are shown below in Table 2.

Table 2 Similarities and differences between the meta-analyses in Lou et al. (2019) and the 2018 Cochrane Review – safety outcomes

	Fracture type	Trial N	Patient N		RR (95% CI)	I^2	Included trials
			Vert	Control			
Occurrence of new vertebral fractures							
Lou et al. 2019	Clinical or radiographic	11	706	701	0.97 (0.63, 1.49)	NR	Firanescu 2018, Leali 2016, Clark 2016, Yang 2016, Hansen 2015, Chen 2014, Blasco 2012, Farrokhi 2011, Klazen 2010, Rousing 2009, Buchbinder 2009
2018 Cochrane Review	Clinical	6	418	422	1.29 (0.46, 3.62)	70%	Buchbinder 2009; Leali 2016; Farrokhi 2011; Yang 2016; Chen 2014; Blasco 2012
	Radiographic	8	411	393	1.14 (0.71, 1.84)	67%	Buchbinder 2009; Clark 2016; Yang 2016; Blasco 2012; Klazen 2010; Rousing 2009; Firanescu 2018; unpublished VOPE data from Hansen 2015
Comment	*The Lou et al. (2019) analysis combined new clinical and radiographic fractures (11 trials), while the 2018 Cochrane Review considered these separately (6 and 8 trials, respectively).* *None of the analyses showed a statistically significant difference in the occurrence of new fractures with vertebroplasty of control (placebo or conservative/usual care).*						

MD=mean difference; NA=not applicable; NR=not reported; Vert=vertebroplasty
Source: Figure 5, Lou et al. 2019; Analyses 5.1 and 5.2, 2018 Cochrane Review

Hsieh et al. (2019) retrospectively reviewed 3175 patients treated with vertebroplasty and analysed the clinically significant complications after cement leakage. Of the total 3812 vertebroplasty procedures performed, cement leakage was found in 2542 vertebrae (66.7%). Four of 26 patients with cement leakage into the spinal canal (type-C posterior) needed

surgical decompression. Nine of 153 patients with leakage via the segmental vein (type S leak) needed postoperative oxygen support due to pulmonary embolism. The risk factor for a pulmonary cement embolism was higher volume of polymethyl methacrylate (PMMA) injected, and the risk factor for neurological deficit was type-C posterior cement leakage into the thoracic spine. The incidence of pulmonary cement embolism was significantly increased with increasing volume of PMMA injected (PMMA injection < 3.5 cc: 0%; 3.5-7.0 cc: 0.11%; > 7.0 cc: 0.9%; p<0.01).

Mazzantini et al. (2019) prospectively studied the occurrence of vertebral fracture after vertebroplasty in 141 osteoporotic patients with vertebral fracture treated with glucocorticoid therapy (n=70) or not treated with glucocorticoid therapy (n=71). At 24 months, the proportion of patients with new vertebral fractures was 44.3% in the glucocorticoid group and 22.6% in the non-glucocorticoid group (RR=1.96; 95% CI: 1.19, 3.26).

Overall, the February 2020 Departmental Overview considered that both publications demonstrate potential harms associated with vertebroplasty; the risk of pulmonary cement embolism (Hsieh et al. 2019) and the risk of new fractures in patients also taking glucocorticoids (Mazzantini et al. 2019).

In its pre-ESC response to the February 2020 ESC meeting, the applicant claimed that:

- the publication by Hsieh et al. 2019 is not relevant to the application. The application notes that 3175 patients were treated by orthopaedic surgeons from Taiwan between 2001 and 2011 and that the publication is 8 years after this period. The applicant's critical appraisal of the study claimed that the surgeons used inappropriate imaging, vertebroplasty technique, patient selection and the wrong PMMA.
- the publication by Mazzantini et al. (2019) is not randomised evidence and is not relevant. The study reported a higher incidence of vertebral fractures following corticosteroid therapy. The applicant stated it is well known that steroids increase the risk for incident osteoporotic fractures with or without vertebroplasty.

11. Comparative effectiveness

Summary of new comparative effectiveness data for consideration
The applicant provided a subgroup analysis of 93 patients with fracture duration ≤3 weeks from the VAPOUR trial that reported a statistically significant advantage for vertebroplasty over placebo at all time points, with the exception of difference in mean Roland-Morris Disability Questionnaire (RDQ) score at 1 month, which indicated an advantage for vertebroplasty that was not statistically significant (published manuscript Diamond 2020). These results are provided in Table 3.

Table 3 Results for the subgroup with fracture duration ≤3 weeks from VAPOUR

Follow-up	Day 3	Day 14	Month 1	Month 3	Month 6
Proportion of patients with NRS pain score <4					
Vertebroplasty n/N (%)	14/43 (33%)	21/41 (51%)	22/40 (55%)	21/39 (54%)	28/38 (74%)
Placebo n/N (%)	3/43 (7%)	9/45 (20%)	7/45 (16%)	12/41 (29%)	19/40 (48%)
Difference (95% CI) p-value	26 (10, 42) 0.0029	31 (12, 50) 0.002	39 (21, 58) 0.0001	25 (4, 46) 0.008	26 (5, 47) 0.018
Mean NRS pain score					
Vertebroplasty mean (SD)	N=43; 4.8 (2.4)	N=41; 3.8 (2.6)	N=40; 3.7 (2.7)	N=39; 3.1 (3.1)	N=38; 2.1 (2.6)
Placebo mean (SD)	N=43; 7.2 (2.0)	N=45; 5.6 (2.8)	N=45; 5.5 (2.5)	N=41; 4.5 (3.0)	N=40; 3.5 (2.6)
Difference (95% CI) p-value	2.4 (1.5, 3.4) <0.0001	1.9 (0.7, 3.0) 0.0019	1.9 (0.7, 3.0) 0.0014	1.4 (0.1, 2.8) 0.042	1.4 (0.3, 2.6) 0.017
Mean RDQ score					
Vertebroplasty mean (SD)	N=44; 14.0 (6.5)	N=39; 13.1 (6.2	N=40; 12.9 (5.9)	N=39; 10.2 (7.5)	N=37; 9.0 (6.4)
Placebo mean (SD)	N=39; 17.1 (4.2)	N=44; 16.0 (6.3)	N=43; 15.4 (5.9)	N=39; 13.6 (6.2)	N=40; 12.5 (6.5)
Difference (95% CI) p-value	3.1 (0.7, 5.4) 0.011	2.9 (0.2, 5.6) 0.039	2.5 (-0.2, 5.1) 0.057	3.4 (0.3, 6.5) 0.034	3.4 (0.5, 6.4) 0.022

NRS=numeric rating scale; RDQ=Roland-Morris Disability Questionnaire
Source: Table 6, p9 of November 2019 Departmental Overview

The applicant also provided a subgroup analysis of 53 patients with thoracolumbar fracture duration ≤3 weeks from the VAPOUR trial reporting the same outcome measures (Table 4).

Table 4 Results for the thoracolumbar fractures ≤3 week subgroup from VAPOUR

Follow-up	Day 3	Day 14	Month 1	Month 3	Month 6
Proportion of patients with NRS pain score <4					
Vertebroplasty n/N (%)	12/29 (41%)	17/29 (59%)	17/27 (63%)	15/26 (58%)	19/25 (76%)
Placebo n/N (%)	2/24 (8%)	3/24 (13%)	1/25 (4%)	5/24 (21%)	8/21 (38%)
Difference (95% CI) p-value	33 (12, 54) 0.007	46 (24, 68) 0.001	59 (39, 79) <0.0001	37 (12, 62) 0.008	38 (11, 65) 0.009
Mean NRS pain score					
Vertebroplasty mean (SD)	N=29; 4.1 (2.3)	N=29; 3.4 (2.7)	N=27; 3.3 (2.7)	N=26; 2.8 (3.1)	N=25; 1.9 (2.3)
Placebo mean (SD)	N=24; 7.3 (2.0)	N=24; 6.1 (2.5)	N=25; 5.9 (1.7)	N=24; 4.7 (2.5)	N=21; 4.1 (2.3)
Difference (95% CI) p-value	3.2 (2.0, 4.4) <0.0001	2.7 (1.3, 4.2) 0.0004	2.6 (1.3, 3.9) 0.0002	1.8 (0.2, 3.4) 0.027	2.2 (0.9, 3.6) 0.002
Mean RDQ score					
Vertebroplasty mean (SD)	N=30; 12.2 (6.5)	N=27; 12.0 (6.6)	N=27; 11.2 (6.0)	N=26; 7.8 (7.1)	N=24; 7.8 (5.6)
Placebo mean (SD)	N=23; 17.4 (4.5)	N=23; 16.8 (6.1)	N=25; 15.7 (5.7)	N=23; 14.7 (4.8)	N=21; 13.3 (5.7)
Difference (95% CI) p-value	5.2 (2.0, 8.3) 0.002	4.9 (1.2, 8.5) 0.010	4.5 (1.2, 7.8) 0.008	7.0 (3.4, 10.5) 0.0002	5.5 (2.1, 8.9) 0.002

CI=confidence interval; NRS=numeric rating scale; RDQ=Roland-Morris Disability Questionnaire; SD=standard deviation
Source: Table 2, applicant's December 2019 advice to ESC

The findings from Yang et al. (2016) were summarised within the applicant's "advice to ESC December 2019". The study included 107 patients, all had ≤3 week fracture duration, 80% had thoracolumbar fractures and 5% had thoracic segment fractures. The study reported benefits in pain, quality of life and the Oswestry Disability Index (ODI) to 12 months. Visual analogue scale (VAS) pain scores showed significantly earlier reduction in the vertebroplasty group.

The applicant's "advice to ESC December 2019" also referenced a published rebuttal to the ASBMR Task Force report (Diamond 2019); a published review by Lamanna et al. (2019); and two published rebuttals in response to a current controversies paper by Buchbinder and Busija (2019) and the 2018 Cochrane Review by Buchbinder et al. (2018). These papers have been noted, but not summarised, as they do not provide any new comparative effectiveness data.

The key efficacy finding from the ASBMR Task Force Report was that percutaneous vertebroplasty provides no demonstrable clinically significant benefit over placebo or sham procedures, and results did not differ according to duration of pain. The report stated that it is uncertain whether vertebroplasty increases the risk of incident or radiographic vertebral fractures or related serious AEs. This efficacy finding was based on the 2018 Cochrane Review of vertebroplasty (Buchbinder et al. 2018), which included five trials with a total of 535 patients.

The meta-analysis by Lou et al. (2019) compared vertebroplasty versus placebo or conservative treatment. For comparison with placebo, five trials were included. However, the VAPOUR trial was considered clinically heterogeneous to the other trials due to earlier fracture duration and worse pain scores and was analysed separately while the other four trials were combined. While the VAPOUR trial indicated a significant advantage for vertebroplasty at 1-2 weeks and at 6-12 months, the combined analysis of the other four clinical trials indicated there was no statistically significant advantage for vertebroplasty compared to placebo. For comparison with conservative treatment, analysis of the seven included trials showed statistically significant advantages for vertebroplasty compared to conservative therapy at all time points. In the subgroup analyses comparing fracture duration of ≤6 weeks and >6 weeks, there were no statistically significant differences between the subgroup analyses for patients with fracture duration ≤6 weeks or >6 weeks across all time points.

The November 2019 Departmental Overview summarised the similarities and differences between the Lou et al. (2019) meta-analyses and the 2018 Cochrane Review (Buchbinder et al. 2018) for effectiveness outcomes (reduction in pain), shown below in Table 5.

Table 5 Similarities and differences between the meta-analyses in Lou et al. (2019) and the 2018 Cochrane Review – effectiveness outcomes

	Timepoint	Trial N	Patient N		MD (95% CI)	I^2	Included trials
			Vert	Control			
Reduction in pain, vertebroplasty versus sham injection							
Lou et al. 2019	1-2 weeks	4	217	210	0.01 (-0.48, 0.50)	0%	Kallmes 2009, Buchbinder 2009, Hansen 2016, Firanescu 2018 for 1-2 weeks and 1-3 months; Kallmes excluded for 6-12 months.
	1-3 months	4	215	208	-0.41 (-0.92, 0.10)	0%	
	6-12 months	3	145	144	-0.53 (-1.14, 0.08)	0%	
	1-2 weeks	1	55	57	-1.20 (-2.26, -0.14)		Clark 2016
	1-3 months	1	53	52	-1.30 (-2.56, -0.04)	NA	Clark 2016
	6-12 months	1	51	51	-1.30 (-2.54, -0.06)		Clark 2016
2018 Cochrane Review	1-2 weeks	5	272	267	-0.09 (-0.30, 0.12)	32%	Kallmes 2009, Buchbinder 2009, Hansen 2016, Firanescu 2018, Clark 2016
	1 month	5	269	266	-0.27 (-0.44, -0.10)	0%	
	3 months	4	198	196	-0.20 (-0.40, 0.00)	0%	Buchbinder 2009, Firanescu 2018, Clark 2016, Hansen unpublished
	6 months	3	171	168	-0.21 (-0.42, 0.01)	0%	Buchbinder 2009, Firanescu 2018, Clark 2016
	12 months	3	135	134	-0.17 (-0.41, 0.06)	0%	Buchbinder 2009, Firanescu 2018, Hansen unpublished
	24 months	1	29	28	-0.36 (-0.88, 0.17)	NA	Buchbinder 2009
Comment	*The 2018 Cochrane Review included the Clark et al. (2016) trial (VAPOUR) in its meta-analyses, while the Lou et al. (2019) publication considered this trial separately.* *None of the Lou et al. (2019) analyses showed a statistically significant advantage for vertebroplasty, while all of the Clark et al. 2016 analyses in the Lou et al. (2019) paper showed an advantage for vertebroplasty.* *For the 2018 Cochrane Review, there was a statistically significant advantage for vertebroplasty at 1 month, but not at any other time points.* *The 2018 Cochrane Review showed some heterogeneity at the 1-2 week time point (I^2=32%), all other analyses had I^2=0%, as did all analyses for Lou et al. (2019).*						
Reduction in pain, vertebroplasty versus conservative therapy/usual care							
Lou et al. 2019	1-2 weeks	6	308	304	-1.83 (-2.69, -0.97)	91%	Voormolen 2007; Klazen 2010; Farrokhi 2011; Blasco 2012; Chen 2014; Yang 2016
	1-3 months	6	311	301	-1.60 (-2.02, -1.18)	68%	Rousing 2009; Klazen 2010; Farrokhi 2011; Blasco 2012; Chen 2014; Yang 2016
	6-12 months	6	295	280	-1.33 (-1.71, -0.95)	63%	
2018 Cochrane Review	1-2 weeks	6	321	306	-1.33 (-2.26, -0.39)	96%	Voormolen 2007; Klazen 2010; Farrokhi 2011; Blasco 2012; Chen 2014; Yang 2016
	1 month	3	198	196	-2.06 (-3.35, -0.76)	96%	Chen 2014; Klazen 2010; Yang 2016
	3 months	6	321	306	-1.18 (-1.95, -0.40)	95%	Rousing 2009; Klazen 2010; Farrokhi 2011; Blasco 2012; Chen 2014; Yang 2016
	6 months	5	295	278	-1.05 (-1.82, -0.28)	94%	Klazen 2010; Farrokhi 2011; Blasco 2012; Chen 2014; Yang 2016
	12 months	6	315	297	-1.02 (-1.74, -0.30)	94%	Rousing 2009; Klazen 2010; Farrokhi 2011; Blasco 2012; Chen 2014; Yang 2016
	24 months	1	38	39	-0.45 (-0.90, 0.01)	NA	Farrokhi 2011
Comment	*Lou et al. (2019) and 2018 Cochrane Review used the same trials at the 1-2 week, 3 month and 12 month time points although for Lou et al. (2019) the analyses covered 1-3 months and 6-12 months.* *Patient numbers differed across these analyses as did the mean differences and 95% CIs, although all results favoured vertebroplasty with the exception of the 24 month analysis in the 2018 Cochrane Review.* *There was a high level of heterogeneity across all analyses.*						

MD=mean difference; NA=not applicable; Vert=vertebroplasty
Source: Table 8, p 11 of November 2019 Departmental Overview.

The November 2019 Departmental Overview also identified a randomised, non-blinded study (Xu et al. 2019) and a meta-analysis (Chen et al. 2019) relevant to the effectiveness of vertebroplasty. The study by Xu et al. (2019) compared targeted vertebroplasty and

traditional vertebroplasty in 42 patients aged between 50 and 87 years. The study report claimed "targeted percutaneous vertebroplasty" may achieve (1) less skin positioning fluoroscopy times, less total fluoroscopy times and dose, shorter operation time, which is more precise than traditional vertebroplasty; and (2) less incidence of cement leakage. The Departmental Overview noted that this was a non-blinded study with a small sample size, so results should be interpreted with caution.

The meta-analysis by Chen et al. (2019) compared unilateral and bilateral percutaneous vertebroplasty. A total of 9 studies including 627 patients were selected for inclusion (N=314 unilateral; N=313 bilateral). The meta-analysis showed no significant difference in visual analogue scale (VAS) (MD=−0.05, 95% CI [−0.24, 0.13]), Oswestry Disability Index (ODI) score (MD=0.03, 95% CI: [−0.57, 0.62]) and cement leakage (odds ratio=1.00, 95% CI: [0.67, 1.50]) between the unilateral group and the bilateral group. The surgery time of unilateral vertebroplasty was less than that of bilateral (MD = −8.42, 95% CI: [−13.17, −3.66]). Patients with bilateral vertebroplasty surgery have been injected with more cement than patients with a unilateral surgery (MD = −2.56, 95% CI: [−2.79, −2.33]).

In its pre-ESC response to the February 2020 ESC meeting, the applicant reiterated that:

- the VAPOUR trial was triggered by the MSAC outcome in 2011. Compared to the 2009 trials, the VAPOUR trial was designed to treat a different patient group with more severe symptoms, worse osteoporosis, mostly inpatients, and used a different technique called "vertebral fill". The applicant claimed the only other randomised trial to test early vertebroplasty (within 3 weeks of fracture) for patients with severe pain due predominantly (80%) to thoracolumbar fractures is Yang et al. 2016 which verifies the findings in the VAPOUR trial.
- no authors from VAPOUR or the other blinded trials since 2009 were invited to contribute to the ASBMR Taskforce review. The applicant also claimed that the authors have had no clinical experience with vertebroplasty since 2009, when they stopped referring patients for it. The VAPOUR trial has happened since then.
- the Lou et al. (2019) meta-analysis assessed VAPOUR separately from the other randomised trials of vertebroplasty due to clinical differences and presented its results as a separate sub-group. This follows the guidelines in the published Cochrane vertebroplasty protocol. The applicant requested MSAC reconsider its positive assessment of the Cochrane Review from the 2018 PSD on the basis that:
    - the applicant has published a methodologically rigorous analysis of the Cochrane Review containing criticisms which are methodologically sound and referenced
    - the independent assessment of the Cochrane Review by Thema Consulting found it of critically low quality on AMSTAR2 rating, and not aligned to the PICO of MSAC 1466
    - Lamanna 2019, written by a Melbourne group, noted the errors in analysis in the April 2018 Cochrane Review and questioned why these were not corrected in the November 2018version, after they had been pointed out in a written complaint to Cochrane.

In its pre-MSAC response, the applicant reiterated its request for the 2018 Cochrane Review (Buchbinder et al. 2018), and by extension the ASBMR (Ebling et al. 2019) publication, to be excluded from MSAC's considerations. The applicant also claimed that the pre-specified clinical endpoint chosen for the VAPOUR trial was used to define how many patients responded sufficiently favourably and how many did not. The applicant also provided two new publications for MSAC to consider:

- Diamond et al. (2020) presenting the subgroup analysis of 93 patients with fracture duration ≤3 weeks from the VAPOUR trial and a review of literature (i.e. publication of the unpublished subgroup analysis data provided to MSAC)
- Clark et al. (2020) letter to the editor of Internal Medicine Journal regarding the 2018 Cochrane review and the VAPOUR trial.

Clinical claim

A revised clinical claim was not provided as part of the reconsideration of Application 1466. The claim that vertebroplasty has superior effectiveness compared to conservative medical therapy in relation to pain relief, and non-inferior safety therefore remained unchanged; see PSD Application No. 1466, Nov 2018/March 2019 p13.

12. Economic evaluation

A revised economic evaluation was not provided as part of the reconsideration of Application 1466. This therefore also remained unchanged; see PSD Application No. 1466, Nov 2018/March 2019 p13. In its pre-ESC response to the February 2020 ESC meeting, the applicant reiterated is advice of "a median 5.5 day reduction in hospitalisation and daily bed costs provided by Ramsay health care of $800-$900 per night. Savings on hospitalisation costs would exceed the cost of vertebroplasty for inpatients."

13. Financial/budgetary impacts

Revised utilisation or cost estimates were not provided as part of the reconsideration of Application 1466. This remained unchanged despite the requested changes to the eligible population; see PSD Application No. 1466, Nov 2018/March 2019 p13.

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Whether to support the claim made in Diamond (2019), Clark (2019) and Lamanna (2019) that the Cochrane Review is not relevant to the requested listing and the focus should be on VAPOUR alone	Based on the totality of the information presented, including input from the stakeholder meeting, ESC considered that dismissing evidence from other trials and focusing on the VAPOUR trial alone was inappropriate.
Whether the points made in Clark (2019) counter the claim made by Buchbinder and Busija (2019) that vertebroplasty should not be performed	Research and publications stating opposing conclusions to the applicant's findings cannot be dismissed. ESC was of the view that all evidence of the comparative safety and effectiveness of vertebroplasty should be considered.
The impact of the safety outcomes identified in Mazzantini et al. (2019) and Hsieh et al. (2019)	ESC considered that these publications should not be overlooked; the comparative safety of vertebroplasty remains uncertain overall.
The case presented by the applicant is optimistic but not entirely without merit	While the effectiveness and economic case presented by the applicant is not strong, ESC acknowledged that improvements in functional mobility are biologically plausible. However, comparative effectiveness has not yet been demonstrated using this outcome measure. ESC noted the claims made by the applicant regarding choice, equity, and enhancing public system responsiveness.
Considerable uncertainty in available evidence	Key aspects of uncertainty include the evidence for the clinical and economic outcomes, the setting of use, likely procedure variation, potential harms, and potential use outside the proposed patient population. Consequently, ESC was of the view that the application has presented the best case scenario.
Implementation measures	Options are limited for the MBS to influence issues such as use outside the proposed patient population, referral process, practice variation, experience of providers and case-by-case considerations. Considerable discretion is likely to be left to providers. As such ESC advised MSAC to consider its previous decisions, potential problems and its risk tolerance, before deciding if the implementation risks are acceptable.
Financial impact	ESC advised that the estimated financial impact was relatively modest for the MBS, but there would be significant upward potential.

ESC discussion

ESC noted the narrowing of the proposed population since MSAC's most recent previous consideration of this application, to patients with thoracolumbar vertebral fractures with duration of ≤3 weeks and severe pain. ESC noted that the comparator, clinical claim and clinical management algorithm are otherwise unchanged since the previous consideration. ESC therefore focused on the new material provided since MSAC's most recent previous consideration.

ESC noted new data analyses provided by the applicant:

- VAPOUR trial data for patients with thoracolumbar fractures of ≤3 weeks duration, showing no statistically significant differences in the 10-point numeric rating scale

(NRS) pain scores or EQ-5D results between vertebroplasty and sham interventions groups at baseline
- an unpublished (Diamond et al.) subgroup analysis of patients with fractures of ≤3 weeks duration showing statistically significant differences between vertebroplasty and placebo, including the proportion of patients with NRS pain score <4 at day 14 (20% versus 51%; difference in proportions 31%, 95% CI: 12% to 50%), and the mean NRS pain scores at day 14 (3.8 versus 5.6; difference in means 1.9, 95% CI: 0.7 to 3.0).

ESC considered that the approach adopted in VAPOUR of converting continuous scores to a binary outcome may obscure findings in individuals whose pain score did not change.

ESC noted the new evidence provided for comparative safety: Mazzantini et al. (2019) and Hsieh et al (2019). Mazzantini et al. (2019) prospectively showed the risk of new vertebral fracture after vertebroplasty was high in absolute terms, and higher when associated with glucocorticoid use (44.3% in the glucocorticoid group and 22.6% in the non-glucocorticoid group). ESC noted that the population in this study was restricted to those with vertebroplasty and considered this appropriate. Hsieh et al. (2019) was a retrospective review of risk factors for neurological deficit and pulmonary cement embolism. ESC noted the applicant's concern that, although this paper is recent, the procedures reviewed were performed 5–8 years ago suggesting they may not reflect contemporary practice. ESC also noted that the pain duration categories (<2 weeks, 2 weeks to 3 months, >3 months) are different to the current application, making comparison difficult. In addition, many participants in the study waited a long time between fracture and vertebroplasty. ESC noted that two-thirds of patients in the study had leakage of cement, although only a small number needed surgical corrective treatment. ESC concluded that this evidence shows that the procedure is not risk-free.

ESC noted forest plots from Lou et al. (2019) in which data from the VAPOUR trial in terms of pain reduction at different time intervals was analysed separately from that of other randomised trials of vertebroplasty. ESC noted that, although the plot for the VAPOUR trial favours vertebroplasty, the analysis did not separate outcomes for the ≤3 week and >3 week subgroups.

ESC noted that the stakeholder meeting held in June 2019 raised a number of issues, in particular:

- variance of views expressed at the meeting, noting also that, due to absences, views not supportive of the application were not expressed in person at the meeting
- concern whether patients would be able to access treatment within 3 weeks, and the potential for this timeframe to create access issues
- how much the patient population should be restricted, including whether the procedure should be restricted to the four joints with the strongest evidence (T11–L2), given there is weaker evidence for the two vertebrae on either side of these
- both positive and negative patient experiences of the procedure
- expert opinion that there would need to be sufficient clinical overlap across patients enrolled in the trials for an individual patient data (IPD) meta-analysis to be meaningful.

ESC also considered that an IPD analysis may not be feasible if there is inadequate recording at the individual patient level across all studies of all parameters for which clinical heterogeneity is claimed to have a consequence for the size of the effect of vertebroplasty (eg

time between fracture and intervention) or across enough relevant outcome measures (eg measures of function as well as pain).

ESC noted that no new information was provided for the economic analysis despite ESC's previous suggestion that "multiple changes are needed to provide a more appropriate base case". ESC noted the applicant's pre-ESC response that an estimate of cost-savings from reduced hospital length of stay had already been provided. However, ESC considered that hospital cost-saving is only one of many economic considerations, and the estimate provided by the applicant may overestimate overall cost-saving because not all patients receiving vertebroplasty would have been hospitalised. ESC also considered that an average per day estimate would be unlikely to reflect the cost profile of a hospital episode (e.g. higher cost upfront with lower costs later), such that the relevant marginal costs of any reduced hospital length of stay would be less than this average estimate. ESC considered that the economic model did not support the applicant's claim of cost-saving.

ESC noted that issues previously identified with the economic model still remain: time horizon >1 year may be more appropriate; quality-adjusted life years (QALYs) are based on pain scores only, not functional effect; the incremental QALY benefit is very small so the incremental cost-effectiveness ratio (ICER) is very sensitive to changes in costs; and if fewer patients are treated in the hospital setting or if the cost per day is lower the ICER moves away from its stated dominance.

ESC noted that previously identified areas of uncertainty remain:

- the effect of the mix of hospital/outpatient setting on cost-effectiveness (noting that any tighter restriction of the eligible population to hospitalised patients only would likely have perverse consequences by creating incentives for extra hospitalisations)
- lack of a widely disseminated model of care, pathways and superior referral process for vertebral fractures
- the impact of analgesic use on QALYs
- a high chance of variability in procedure quality depending on operator experience
- limited generalisability of a single site trial
- use of spine MRI may not lead to the procedure
- considerable potential for use beyond the proposed patient population, but uncertainty about what will happen in practice
- limitations of the item descriptor and evidence, which mean that patients with potential to benefit may be different from those in whom benefit has been demonstrated.

ESC noted that one area of uncertainty that would favour the procedure relative to the comparator is the reduction in risks associated with opiate treatment.

ESC noted that no new information on the financial or budgetary impact was provided. ESC noted that the financial impact to the MBS is likely to be modest, with possible freed resources for other parts of the healthcare system. However, ESC noted that the financial impact may be higher than predicted as a result of osteoporosis burden, eligibility and uptake, use in other patients, and population ageing. ESC noted that infrastructure is in place for 400–500 procedures per year (noting financial estimates use lower procedure numbers).

ESC noted MSAC's questions to ESC that have been addressed by the Department:

- the potential for use in other patients – ESC noted the Department's suggestion to make the item descriptor more restrictive by specifying that the timeframe of ≤3 weeks relates to fracture duration, not pain duration
- whether to claim per episode or per fracture – ESC noted the Department's suggestion that claims should be limited to once per patient per episode, regardless of the number of fractures.

However, ESC considered that, while attempts to reduce uncertainties are desirable, these two proposed measures:

- do not directly address key uncertainties (e.g. effect of the rate of hospitalisation on cost-effectiveness)
- may increase rather than reduce the potential for use outside the proposed patient population
- may not be optimal in light of access, clinical evidence and an individual patient's capacity to benefit from the procedure.

ESC considered that the ongoing uncertainties with this application arise mostly as a consequence of multiple post hoc analyses of a single randomised trial in the context of evidence from a wider set of randomised trials, and the transferability of these findings to overall Australian clinical practice. These and other issues identified above would need to be addressed to ensure the safe, appropriate and cost-effective use of this procedure.

ESC noted the claims made by the applicant regarding choice, equity, and enhancing public system responsiveness. ESC also recalled that MSAC has previously accepted the clinical need in this patient group, recognising that severe pain and loss of function can accompany a vertebral fracture.

15. Other significant factors

Nil.

16. Applicant comments on MSAC's Public Summary Document

The Interventional Radiology Society of Australasia welcomes the decision to restore public funding for a highly selected patient group likely to benefit from early vertebroplasty. Most osteoporotic spinal fractures produce mild symptoms and do not need vertebroplasty. A sub-set of patients with early fractures and severe, uncontrolled pain receive substantial benefit from early vertebroplasty. In this patient group there is no other treatment option, other than escalating doses of opiate therapy and bed rest, which can be a challenging health problem for elderly patients.

We make the following observations about the MSAC assessment:

- The application took 3.5 years to complete.
- The VAPOUR trial, a randomised controlled trial published in the Lancet, was designed specifically to assess vertebroplasty in the pre-defined patient group of this application. We feel that the study could have benefited from a more considered analysis by the MSAC.
- The MSAC has recommended the formation of a prospective registry to identify *"whether the patient was hospitalised or not at the time the decision to perform the*

procedure was made, the length of hospital stay if hospitalised, and any associated adverse events requiring further medical or hospital attention".

At the MSAC meeting of March 2019 the applicant proposed that "audit" of the IRSA log-book could provide data to assist MSAC in review of an interim vertebroplasty item number in 5 years. MSAC has not responded to this option until now. It was not raised for discussion at the stakeholders meeting nor in any MSAC feedback to the applicant. IRSA did not undertake to create a separate registry. Whilst IRSA would be pleased to assist with audit data from its logbook, it should be noted that IRSA has no authority to mandate Interventional Radiologists to enter data to the IRSA log-book and that it may not capture all instances of the procedure being performed. It is presumed that the proposed data is confined to the subset of patients who receive Medicare funding for vertebroplasty, but IRSA is unclear about this. Data of operator location, state, and inpatient status would be more efficiently captured by MBS statistics – particularly if there were separate vertebroplasty item descriptors for inpatients versus day-only patients. IRSA recommends MSAC consider this option of these two item descriptors. Length of hospital stay is outside the scope of log-book audit data. Patients hospitalised with severely painful osteoporotic fractures are often transferred (with or without vertebroplasty) to other hospitals for rehabilitation and data from these second hospitalisations is time-consuming to obtain and impractical outside of a controlled trial.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website