NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Vertebroplasty and kyphoplasty for the treatment of osteoporotic vertebral fractures

A submission by Johnson & Johnson for the CONFIDENCE SPINAL CEMENT SYSTEM™

Multiple Technology Appraisal (MTA)

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Executive Summary

Background

Osteoporotic vertebral compression fractures (VCFs) are commonly caused by minor trauma, as a result of weakening of the internal structures of the vertebra by the underlying disease. VCFs occur most frequently in the elderly, with a reported prevalence of between 10–20% for females in this population. The effects of VCFs can be devastating in this particularly vulnerable patient group; many cause significant pain, and patients may find themselves unable to perform routine activities such as dressing and bathing. In addition, a study of around 7,000 patients found that those with VCFs are confined to bed nine times more frequently than those without. This can lead to anxiety, social isolation, and depression in approximately 40% of cases, significantly reducing patients' quality of life (QoL). Indeed the impact of VCFs on quality of life has been estimated to be similar to the impact of chronic obstructive pulmonary disease.

Current burden of hospitalised osteoporotic VCFs to the NHS

The economic burden associated with osteoporotic VCFs is significant; a 2003 study estimated the total UK cost at €14.7 million per year, while a 2006 study estimated an average cost per hospitalised fracture of £4,470. In England, approximately 6,300 patients are admitted each year for treatment of osteoporotic VCFs causing severe pain which is refractory to non-invasive management. These patients have an average length of stay of 12.6 days; using a cost of £232 per bed day, this conservatively indicates a cost to the NHS of approximately £18 million per annum. This excludes the cost of physical therapy, analgesia and any back braces or orthotics.

Available treatments

Current first-line therapy for VCFs in the UK is non-invasive management (NIM), consisting of a combination of analgesics, bed-rest, physiotherapy and bracing. The majority of osteoporotic VCFs will resolve without intervention within weeks (circa 6 weeks) with NIM in the community or primary care setting. However, patients with severe pain and disability which are refractory to conservative management are regularly admitted to hospital; it is in this group of patients that NICE currently recommends surgical intervention. Two interventions are available, vertebroplasty and kyphoplasty. Both of these involve stabilisation of the fracture by infusing spinal cement into the affected vertebrae; however, kyphoplasty also seeks to restore lost vertebral height by insertion of a balloon or other mechanical device prior to cement injection. Data gathered from Dr Foster Intelligence indicated that there were 473 vertebroplasty, 225 kyphoplasty and 6,375 NIM patients treated in the inpatient/day case setting between April 2010 and March 2011.

Benefits of High Viscosity Vertebroplasty Technology

Standard vertebroplasty has traditionally been conducted using low-viscosity cement, which has been associated with higher levels of cement leakage than kyphoplasty. The CONFIDENCE SPINAL CEMENT SYSTEM™ uses a high viscosity cement that

offers significant benefits over low-viscosity cement, providing a safety profile similar to kyphoplasty.

Base case

As per the NICE scope, this submission considers vertebroplasty, kyphoplasty and NIM for all patients with osteoporotic VCFs refractory to conservative management as the base case. However, this allows the incorporation of clinical trials using a broad spectrum of inclusion criteria within the evidence informing the economic model. Various trials used inclusion criteria allowing fractures up to 1 year old, with some trials using minimum pain requirements of as little as 3 on the VAS scale . This population may include patients who would not be expected to benefit from surgical intervention, and more recent trials, such as VERTOS II, and the ongoing trial VERTOS IV, use more stringent criteria. These criteria have been used to develop our recommended patient group for consideration for surgical intervention.

Recommended patient selection criteria

- Referred to secondary care for, and diagnosed with, an osteoporotic pathological fracture of the spine
- Presence of VCF confirmed by radiographic imaging
- Severe intractable pain (e.g. VAS≥5)
- Confirmation of focal tenderness at the level of the fracture site
- Equal to or less than 3 months from onset of VCF-related pain

A full discussion of the criteria for defining VCFs which are likely to benefit from surgical intervention is given in Section 3.8.1.1.

Target population

It was not possible to use all of the above criteria to select RCT data for an alternative evidence base, as this would have resulted in the inclusion of only one trial. It was therefore decided to use RCTs including fractures ≤3 months old only as the alternative evidence base, as this allowed consideration of patients closer to the group proposed to gain the most benefit from vertebroplasty and kyphoplasty, while retaining sufficient data to inform robust conclusions. This is referred to throughout the submission as the target population.

Systematic review

A systematic review was performed to identify relevant randomised controlled trials (RCTs) from the published literature regarding the clinical efficacy and safety of vertebroplasty (VP) and kyphoplasty (KP) compared with non-invasive management (NIM) in patients with osteoporotic VCFs. A total of 15 RCTs were identified, which were used to inform the RCT, comparative efficacy and economic sections.

RCT efficacy evidence

- One RCT comparing vertebroplasty and kyphoplasty found that both procedures gave significant pain relief, with no difference between the interventions. QoL was not considered in this study.

- Four RCTs compared vertebroplasty with NIM; patients receiving vertebroplasty had significantly greater pain relief and QoL improvements than patients receiving NIM in all trials except one. A significant reduction from the baseline pain score was observed following vertebroplasty in this trial; however, pain relief was not compared between the groups until 3 months post-operatively, at which point no significant difference was found. The QoL scores at baseline in this trial were significantly different between groups, and therefore could not be compared at follow-up.
- One RCT compared kyphoplasty with NIM, reporting significantly greater improvements in pain score and QoL with kyphoplasty than with NIM.

RCT efficacy evidence: invasive control procedure ("sham") studies

- Two RCTs compared vertebroplasty to an invasive control procedure ("sham"), finding no difference between the interventions. The design and conduct of these trials have been questioned by the wider scientific community, including one of the contributors to the Kallmes study, for a number of reasons, including:
  - One of the studies included injection of anaesthetic into the spine as a "sham" procedure, which may be considered to be equivalent to a facet-block injection, used as a treatment for back pain
  - Fractures up to a year old were included in these studies; acute fractures (up to 3 months old) are expected to benefit the most from surgical intervention
  - The pain threshold in the Kallmes et al study was low, requiring a VAS score of only ≥3. Changes in VAS score may be difficult to detect in patients with a baseline score <5(1).
  - It should be noted that the p value for the improvement in pain score in the Kallmes study was 0.06, in favour of vertebroplasty over the invasive control procedure ("sham"). Had 19 additional patients with similar results been enrolled, the p value would have been less than 0.05.
- The patient population included in these trials does not represent the population in whom surgical intervention would generally be considered. In comparison, the recent VERTOS II trial, and the ongoing VERTOS IV trial, use more stringent inclusion criteria which better represents the target population for surgical intervention.

Comparative efficacy from network meta analysis (NMA)

- A network meta-analysis (NMA) was performed using the RCTs identified by the clinical systematic review to examine the efficacy and safety of vertebroplasty, kyphoplasty and NIM for the treatment of osteoporotic VCFs.
- This considered both the base case (all patients) and the target population (fractures ≤3 months old).

NMA efficacy: base case

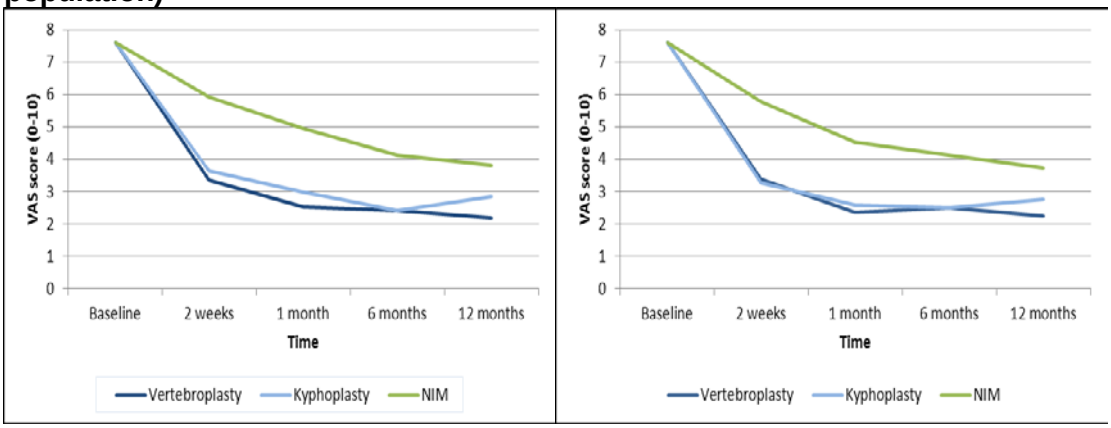
- The NMA showed that vertebroplasty and kyphoplasty were favoured over NIM at all time points considered for the VAS outcome (see Figure 1). Vertebroplasty and

kyphoplasty were both favoured over NIM for EQ-5D at 1 month; however, only kyphoplasty was favoured at 12 months post-procedure.

NMA efficacy: target population

- The NMA showed that vertebroplasty and kyphoplasty were favoured over NIM at all time points considered for the VAS outcome (see Figure 1). Vertebroplasty and kyphoplasty were both favoured over NIM for EQ-5D at 1 month; however, only kyphoplasty was favoured at 12 months post-procedure.

Figure 1: NMA calculated VAS score over time (left=base case, right=target population)



Safety

Cement leakage is a known adverse event associated with vertebroplasty and kyphoplasty; however, the vast majority of cement leakage events are asymptomatic and confer no clinical significance. While the occurrence of cement leakage in clinical studies ranges from around 8% to 72% depending on the technique and cement viscosity, only a very small fraction (circa 1%) are symptomatic and therefore clinically relevant. VCFs following intervention (refractures) have been suggested to be linked to the surgical intervention(2); however, the data suggest that there is no link between these.

- Studies reported that the reported cement leakage rates in the RCTs included in this submission were 9.1–72% for vertebroplasty with low-viscosity cement, 8.2% for vertebroplasty with high-viscosity cement, and 6.1–27% for kyphoplasty.
- The vast majority of leaks were asymptomatic; symptomatic cement leakage occurred in 4 of 408 patients for low-viscosity cement, 1 of 214 patients for kyphoplasty and 0 of 30 patients for high-viscosity vertebroplasty.
- Refracture rates were reported in a number of trials; however, only one trial applied statistical analysis to refracture rate. Klazen et al compared vertebroplasty and NIM, finding no significant difference in refracture rate between the treatments; the rate was also numerically lower in the vertebroplasty group.
- The NMA showed that there was no difference between treatments for refracture rate, while odds for cement leakage were highest for vertebroplasty with low-viscosity cement. Vertebroplasty using high-viscosity cement such as the

CONFIDENCE SPINAL CEMENT SYSTEM™ is associated with similar odds of cement leakage as kyphoplasty.

Cost-effectiveness

Methodology

- A simple 1-year treatment state model was developed in Microsoft® Excel®, where patients with a VCF receive either invasive or non-invasive treatment.
- A treatment state model was selected in place of a Markov model as the most appropriate methodology due to data not being available for the categorisation of patients into definable disease states.

Base case and target population

- **Base case:** The base case analysis considers the treatment of all patients with osteoporotic VCFs, regardless of the nature of these fractures. This all-patient analysis uses clinical evidence derived from all studies in the NMA, regardless of how patients were selected within each study. As described previously, patient selection criteria varied considerably, such that in some cases VCFs may have been ill-defined and across all studies may have been acute or chronic in duration. As such this analysis may include patients that would not be expected to benefit from surgical intervention, and more recent trials, such as VERTOS II, and the ongoing trial VERTOS IV, use more stringent criteria which more appropriately target the population likely to benefit.
- **Target population:** This analysis was performed in order to try to reflect the patient population that is expected to benefit most from surgical interventions. This analysis made use of clinical data from studies that considered patients with fractures ≤3 months old. As described in the NMA (Section 4), this body of evidence reflects a patient group closer to the 'ideal' selection criteria for the target population while retaining a sufficient evidence base.

Assumptions common to both analyses

- **Cost sources:** A bottom-up costing approach based on published data from Strom et al was used. This was deemed to be more appropriate than using Payment by Results national tariff costs which were not felt to be representative of the true costs of treatment; national tariff costs are informed by retrospective cost collection, which is subject to errors. In addition, vertebroplasty and kyphoplasty both map to the same HRG codes, and hence there is no differentiation in cost between the procedures. The costs themselves may not be truly representative of vertebroplasty and kyphoplasty specifically, as in excess of 140 different procedures map to the same HRG groups (see Section 5.2.4.3).
- **Utilities:** No studies were identified in the QoL SR that linked VAS to a utility score. As efficacy in the model is based on VAS, it was therefore necessary to perform a regression to convert the VAS to a utility score. Both VAS and EQ-5D data were captured in certain RCTs for the treatment of VCFs; it was felt that this offered the most appropriate and robust data set for use in our analysis as VAS scores were available from more studies and at a greater number of time points than modelling EQ-5D data directly (see Section 5.2.4.2). Four studies identified by the SR met the inclusion criteria for the NMA for the EQ-5D outcome. This

outcome was reported at 1 month in two of these trials, and at 1 and 12 months in the other two; this provided insufficient data to inform the EQ-5D outcome for the model at all time points (2 weeks, 1 month, 6 months and 12 months). It was therefore necessary to perform a regression based on the VAS and EQ-5D scores, to allow EQ-5D values to be determined for each time point. All time points in studies which reported both VAS and EQ-5D were used to inform the relationship between VAS and EQ-5D.

- **Comparators:** The comparators considered were vertebroplasty, kyphoplasty and NIM, as outlined in the NICE scope (see Section 5.2.1.3).
- **Evidence from invasive control procedure ("sham") studies:** Evidence from the vertebroplasty arms of the invasive control procedure ("sham") trials was used to supplement the body of clinical evidence for the vertebroplasty treatment modality, where appropriate. The invasive control arms of these trials were not considered to be clinically relevant treatment options for VCF treatment and were not considered as relevant comparators in the NICE scope. However, the cost-effectiveness of these arms has been modelled as a scenario for completeness.
- The invasive control procedures performed in the Kallmes and Buchbinder studies clearly cannot be considered as a form of non-invasive management, as both involve an invasive procedure. As such, data from these arms was not used to supplement the NIM evidence base in the base case and target population analyses. However, for completeness, the effect of pooling the invasive control procedure ("sham") arms with NIM has been considered in scenario analysis.

Scenarios

- In addition to the base case/target population analyses, which considered vertebroplasty, kyphoplasty and NIM in all patients, eight additional scenarios were modelled
- These scenarios varied the assumptions around the comparator interventions considered, extended the time horizon of the analysis, used alternative costing approaches to the base case/target population analyses, and used EQ-5D data taken directly from the NMA.

Cost-effectiveness: base case

- Vertebroplasty dominated kyphoplasty in the base case and all scenarios considered
- The ICER for vertebroplasty vs NIM was £4,392 in the base case, and ranged from £568–£13,595 in the scenarios considered
- The ICER for kyphoplasty vs NIM was £14,643 in the base case, and ranged from £2,539–£16,097 in the scenarios considered
- Vertebroplasty dominated the invasive control procedure ("sham") in the scenario where this was considered.
- When EQ-5D data were used directly to estimate patient benefits in a scenario analysis, vertebroplasty still dominated kyphoplasty, with an ICER of £5,516 vs NIM.

- Including the invasive control procedure ("sham") arms within the NIM group in the cost-effectiveness analysis was likely to bias the results against vertebroplasty, as the two trials including these arms showed no difference between vertebroplasty and the invasive control procedure ("sham"). Despite this, the ICER increased by only £590, to £4,982, demonstrating the robustness of the evidence for vertebroplasty outside of these trials.
- Based on probabilistic sensitivity analysis vertebroplasty is a cost-effective treatment compared to all other treatments above a willingness to pay (WTP) threshold of £5,000 per quality-adjusted life year (QALY).
- Vertebroplasty had a 99% chance of being cost-effective at a WTP threshold of £10,000 per QALY, and 100% at thresholds of £20,000 and £30,000 per QALY (in the analysis with kyphoplasty and NIM).
- Kyphoplasty had a 55% chance of cost-effectiveness at a willingness to pay threshold of £10,000 per QALY; this increased to 93% at a WTP threshold of £20,000 and 100% at a WTP threshold £30,000 per QALY (in a one-to-one analysis of kyphoplasty with NIM).
- The base case model considered a time horizon of 1 year; however, the benefits of surgical intervention may persist beyond this time. This was considered in scenario analysis, where vertebroplasty was dominant over kyphoplasty and was cost-effective over NIM, at a threshold of £20,000, with ICERs decreasing the longer the timeframe considered. These were £2,367 per QALY at 2 years, £1,033 per QALY at 5 years and £568 per QALY at 10 years in the scenario where the difference in QoL persisted.

Cost-effectiveness: target population

- Vertebroplasty dominated kyphoplasty in the target population and all scenarios considered.
- The ICER for vertebroplasty vs NIM was £4,755 in the target population, and ranged from £631–£14,718 in the scenarios considered.
- The ICER for kyphoplasty vs NIM was £15,006 in the target population, and ranged from £2,550–£16,497 in the scenarios considered.
- Based on probabilistic sensitivity analysis vertebroplasty is a cost-effective treatment compared to NIM above a willingness to pay (WTP) threshold of £5,000 per QALY.
- Vertebroplasty had a 99% chance of being cost-effective at a WTP threshold of £10,000 per QALY, and 100% at thresholds of £20,000 and £30,000 per QALY (in the analysis with kyphoplasty and NIM).
- Kyphoplasty had a 55% chance of cost-effectiveness at a willingness to pay threshold of £10,000 per QALY; this increased to 91% at a WTP threshold of £20,000 and 99% at a WTP threshold £30,000 per QALY (in a one-to-one analysis of kyphoplasty with NIM).

Budget Impact

From a budget impact perspective, three scenarios were modelled to examine the effects of an increase in the number of surgical procedures performed.

- Assuming no change in the number of each treatment performed (as NICE IPG guidelines already exist for the surgical interventions) resulted in a budget impact of zero.
- Assuming a positive recommendation from NICE for vertebroplasty, and not for kyphoplasty, and assuming that the number of vertebroplasty procedures grew by 25% over 5 years at the expense of kyphoplasty procedures, the cumulative net budget saving would be £238,012 over 5 years, a saving of approximately 1.1%.
- Assuming a positive recommendation from NICE for vertebroplasty and kyphoplasty, and assuming that the number of vertebroplasty and kyphoplasty procedures grows by 12.5% each over 5 years, with a 25% reduction in NIM procedures, the annual net budget impact would be £477,413 after 1 year and the cumulative net budget impact over 5 years would be £7,086,191.
- It should be noted that the analyses presented here have conservatively assumed that the non-surgical care received by NIM and surgical intervention patients would be equivalent. However, expert opinion suggests that NIM patients in clinical practice are likely to require more healthcare resources in the community care setting, such as pain management and post-respite care.

Conclusion

The clinical trial results for these interventions are varied, due to the range of inclusion criteria used; some trials may therefore have included patients that would not be expected to benefit from surgical intervention. However, in the subset of patients identified in this submission as the target population, it is clear that vertebroplasty and kyphoplasty are safe and clinically- and cost-effective treatment options for treating osteoporotic VCFs. Vertebroplasty was the dominant treatment strategy relative to kyphoplasty, and was cost-effective compared to NIM at a willingness to pay threshold of only £5,000. When EQ-5D data were used directly to estimate patient benefits in a scenario analysis, vertebroplasty still dominated kyphoplasty, with an ICER of £5,516 versus NIM. Both interventions are cost effective relative to NIM at willingness to pay thresholds below £20,000. This conservatively assumes that all benefit from vertebroplasty ceases after 1 year; in reality, the benefits of intervention are likely to be sustained beyond this time, decreasing the threshold at which cost-effectiveness is achieved. The ICER for vertebroplasty was below the WTP threshold of £20,000 per QALY in all scenarios considered, including using national tariff costs and pooling NIM with the invasive control procedure (“sham”) arms. The probability of vertebroplasty being cost-effective was 99% at a WTP threshold of £10,000 per QALY, and 100% at thresholds of £20,000 and £30,000 per QALY.

There are very few alternative treatment options to VP or KP for patients unresponsive to non-invasive management other than months of severe pain, restricted mobility and poor quality of life and depression in up to 40% of cases. It is reported that patients with VCFs are confined to bed nine times more often than those without VCFs, increasing their risk of further VCFs which can further complicate recovery. The impact of VCFs on quality of life (QoL) has been shown to be comparable with chronic obstructive pulmonary disease (COPD), a point which should not be underestimated.