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Australia and New Zealand Horizon Scanning Network

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Horizon Scanning Technology Prioritising Summary

OP-1 Putty

October 2004
(Updated November 2005)



ASERNIP/S

**Australian
Safety
and Efficacy
Register
of New
Interventional
Procedures -
Surgical**



**Royal Australasian
College of Surgeons**



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The production of this Horizon scanning prioritising summary was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), a sub-committee of the Medical Services Advisory Committee (MSAC). HealthPACT comprises representatives from health departments in all states and territories, the Australia and New Zealand governments; MSAC and ASERNIP-S. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

This Horizon scanning prioritising summary was prepared by staff from the Australian safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S).

**Name of Technology:**

OP-1 putty

Purpose and Target Group:

OP-1 putty is an alternative to bone autograft and allograft in patients requiring lumbar spinal fusion or long bone fusion. It is especially useful where autologous bone and bone marrow harvest are not feasible, such as for patients with diabetes or osteoporosis. It may therefore be applicable for the treatment of spinal disorders such as spinal canal stenosis and degenerative spondylolisthesis, or long bone non-union.

Stage of Development (in Australia):

- Experimental
- Investigational
- Nearly established
- Established
- Established but changed indication or modification of technique
- Should be taken out of use

The OP-1 Putty is not listed or registered in the Australian Register of Therapeutic Goods (ARTG).

International Utilisation:

COUNTRY	LEVEL OF USE		
	Trials underway	Limited use	Widely Diffused
United States	✓		

Impact Summary:***Background***

Arthrodesis, the fusion of bones across a joint space, is the treatment for a variety of spinal disorders and long bone non-unions. Traditionally, the most effective technique for achieving fusion has involved placing an autogenous bone graft between adjacent bone surfaces. The autogenous bone graft then matures, often fusing the surfaces together (Heiple *et al.* 1987). Autogenous bone grafts, especially in the spine, have been associated with an array of morbidities such as chronic pain, hypersensitivity, fracture, hernia and cosmetic deformity (Cockin *et al.* 1971, Younger *et al.* 1989). Furthermore, spinal autogenous bone grafts have a failure rate of between 10 and 40% (Vaccaro *et al.* 2002) and are not viable in all patients. They are often contraindicated in patients who smoke, have osteoporosis or are diabetic.



In attempt to avoid complications associated with autogenous bone grafts, allograft bone has been used. In comparison to autogenous bone grafts, allograft bone tends to have decreased fusion rates with higher rates of graft reabsorption. Allograft bone can also be associated with host immunologic rejection and the transfer of infectious disease (Damien *et al.* 1991).

OP-1 (Osteogenic Protein 1), also known as BMP-7 (Bone Morphogenetic Protein 7), is an osteoinductive growth factor specific to bone formation. It works by recruiting stem cells from the surrounding tissue to promote bone formation. As OP-1 is a protein, it can be used as a solution or in conjunction with other absorbable products. One form of OP-1 is a putty is made up of recombinant human osteogenic protein-1 (rather than demineralised bone matrix found in other putties), a purified Type 1 bovine bone collagen and carboxymethylcellulose (CMC). The powdered mixture is reconstituted at the time of surgery by the addition of saline to form putty. The mixture which resembles slurry is designed to allow accurate delivery of OP-1, avoiding unwanted bone growth from misplaced protein. The collagen then provides an osteoconductive scaffold on which bone can grow, potentially fusing the adjacent bone together (Stryker Biotech, 2004).

Clinical Need and Burden of Disease

The epidemiological impact of disorders that result from compression of the spinal canal or of long bone non-union in Australia is currently unknown. However, it is known that back and disc problems are a significant cause of ill health within the community, with increased prevalence in the older adult. Figures from the Australian Bureau of Statistics show that 16% of 16-24 year olds and 32% of 55-64 year olds have required medical attention for back and disc problems between July 2002 and June 2003 (Australian Bureau of Statistics, 2001). Back and disc problems including, spinal canal stenosis, cause patients substantial discomfort and subsequently impact heavily on employment and social abilities (Gore DR, 1998). Long bone non-unions are often the result of trauma or osteotomy. Patients are often disabled to some degree, a consequence of which tends to be an increase in obesity. This impacts not only on the immediate well-being of the patient, but also contributes to an increase in rates of cardiovascular disease and diabetes, which can lead to reduced productivity through diminished employment, and increased medical costs.

Estimated Speed, Geographic and Practitioner Use Patterns of Diffusion in the Health System

OP-1 putty was approved by the FDA under the Humanitarian Device Exception program on April 7, 2004. Under the FDA OP-1 putty is indicated as an alternative to bone autograft in compromised patients (patients for whom autologous and bone marrow harvest are not feasible eg. Smokers, diabetics, osteoporosis) requiring revision intertransverse lumbar spinal fusion. The Humanitarian Device Exception program stated that this is a device intended to benefit fewer than 4000 people in the United States per year. Two pilot studies in the United States, one of which involved 12 patients and the other 36 patients, have been published by Vaccaro *et al.* (2003, 2004). FDA approved clinical trials are currently



underway. The approved multicentered trials are potentially recruiting 312 patients across the United States and Canada.

Two clinical trials have been reported in Australia (Speck and Pike 2000, McCombe and Walsh 2001), one of which was suspended due to poor clinical results (McCombe and Walsh 2001). On May 3, 2001 the Australian Therapeutic Goods Administration approved OP-1 Implant as a drug indicated for the treatment of long bone non-union.

Existing Comparators

- OP-1 in forms other than a putty
- Autogenous bone graft
- Allograft bone graft
- Fusion by synthetic implant

Estimated Cost Impact

The costs associated with this new product are not available. The cost of surgery involving autogenous or allograft bones in Australia is also not available. However, reimbursement fees as stated by the Medicare Benefits Schedule for bone grafts to femur, tibia, humerus, radius, ulna or spine without internal fixation are approximately \$625, \$469, \$469, \$313, \$313 and \$899 respectively (Item numbers 48200, 48206, 48212, 48218, 48224, 48642). The reimbursement for spinal fusion at one level is approximately \$900 (Item number 48660), increasing when more than one level is affected, and internal spinal fixation with a synthetic product is approximately \$470 (Item number 48678). Reimbursement for the harvesting of grafts (autogenous) is approximately \$116 for a small quantity, \$195 for a large quantity and \$313 for vascularised pedicle (Item numbers 47726, 47729 & 47732).

According to the HIC, for the 2002/2003 financial year there were 2185 claims to Medicare for bone grafts to the long bones and spine, 2851 claims for harvesting of grafts, 985 claims for spinal fusions at one or more than one level (Item Numbers 48600, 48663, 48666, 48669, 48672, 48675) and 66 claims for internal spinal fixation with a synthetic product (Item number 48678) (<http://www.hic.gov.au>).

Efficacy and Safety Issues

List of Studies Found

Total number of studies	4
Randomised controlled trials	1
Non-randomised comparative studies	2
Case series studies	1

The studies included in this summary are highlighted in bold in the reference list.

Safety and efficacy data were evaluated from studies where it was stated that OP-1 was used in the form of putty (mixed with CMC and type 1 bovine bone collagen). Data on OP-1



putty exist from one randomised controlled trial, preliminary data from two comparative studies and one case series.

The randomised controlled trial involved 36 patients, reviewed after an average 12 months. Success (20% improvement in the Oswestry score) was reported in 18/21 (86%) OP-1 putty patients compared to 8/11 (73%) autograft patients. Similar results were reported in SF-36 scores. Fourteen of 19 (74%) OP-1 putty patients and 6/10 (60%) autograft patients achieved successful posterolateral fusion (Vaccaro *et al.* 2004).

In the comparative studies, Speck and Pike (2000) compared autogenous bone graft to OP-1 putty in 12 patients. Each patient served as their own control, with one side of the lumbar spine treated with OP-1 putty and the other with an autogenous bone graft. On publication of the preliminary results, 5 of the maximum 12 patients had been enrolled. The follow-up period ranged from 3 to 12 months, with all patients exhibiting development of bone on both the autograft and the OP-1 sites. No further publication could be found at this time. The historical comparative study between autograft and OP-1 putty for spinal fusion conducted by Vaccaro *et al.* (2003) showed clinical success in 9/12 (75%) OP-1 putty patients. Radiologic fusion at 12 months occurred in 6/11 (55%) OP-1 putty patients, which was similar to the 45% reported in autograft patients. One OP-1 putty patient underwent revision posterior lumbar fusion with internal fixation due to pseudarthrosis 8 months post procedure. Ten of the 11 (91%) OP-1 putty patients had bridging bone between the transverse processes.

Adverse events identified among patients who received OP-1 putty for spinal fusion included: pseudarthrosis, increased back pain, donor site pain and surgical complications. No side effects attributable to the OP-1 product were reported. There were also no reports of systemic toxicity, ectopic bone formation or recurrence of spinal stenosis. Data on adverse events and complications for patients who received autograft alone (historical controls) were not provided.

McCombe and Walsh (2001) conducted a case series attempting to repair non-union tibial fractures with OP-1 putty. This study, however, was suspended after five patients due to poor clinical results and failure of bone formation. Of the five patients, 1/5 (20%) had outstanding results and 1/5 (20%) acceptable results but 3/5 (60%) had poor results, with 2/3 patients reporting a worsening of symptoms. Serial radiographs failed to show significant bone formation up to 12 months.

There is limited evidence for the safety and efficacy of OP-1 putty as an alternative to bone autograft/allograft. The studies conducted have indicated that the procedure may enable effective spinal fusion, although data from the case series suggest OP-1 putty may not be suitable for the treatment of long bone non-union.



2005 UPDATE

A search of relevant databases, online journals and the Internet was conducted in November 2005, following the recommendation in November 2004 that OP-1 putty be monitored for assessment in 12 months time. One new source of evidence on the safety and efficacy of this intervention has been located in the literature. Vaccaro et al. (2005) conducted a case series study to evaluate the safety and efficacy of OP-1 putty as an adjunct to iliac crest autograft in posterolateral lumbar fusions in 12 patients. A total of eight patients out of the nine (89%) who completed the 24 month follow up were successfully treated (20% improvement in the Oswestry score and functional improvement as demonstrated by the SF-36 outcome analysis). Radiologic fusion was attained in five patients (50%) at 24 months. Seven patients were noted to have bridging bone between the transverse processes on their antero-posterior radiographs. All patients did not experience any progression of their spondylolisthesis while one patient was diagnosed with pseudoarthrosis and underwent a revision posterior lumbar fusion.

The authors reported that 25% of patients experienced moderate pain at the donor site and all patients were pain-free at 24 months. There were no incidences of systemic toxicity, ectopic bone formation or recurrence of spinal stenosis. No side effects were attributed to the use of OP-1 putty.

This study did not demonstrate that OP-1 putty combined with autograft was more efficacious when compared to autologous bone graft alone (historical control) in achieving arthrodesis in degenerative spondylolisthesis.

Reference:

1) Vaccaro AR, Patel T, Fischgrund J, Anderson DG, Truumees E, herkowitz H, Phillips F, Hilibrand A, Albert TJ. A 2-year follow-up pilot study evaluating the safety and efficacy of op-1 putty (rhbmp-7) as an adjunct to iliac crest autograft in posterolateral lumbar fusions. *European Spine Journal* 2005; **14** (7): 623-629.

Ethical Issues

No issues were identified from the retrieved material.

Cultural or Religious Considerations

The collagen in OP-1 putty is manufactured bovine bone collagen. This may be an issue for some cultural or religious groups.

Other Issues

Vegetarians may also have concerns with the bovine derived bone collagen.

**Conclusion:**

Limited evidence exists on the safety and efficacy of OP-1 putty. Long-term safety and efficacy data from randomised controlled trials will be required before this procedure can be widely accepted.

2005 Update: OP-1 Putty appears have generated significant interest within the Australian healthcare system; a Horizon Scanning Report on this product will be produced.

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|---|--|
| <input checked="" type="checkbox"/> Horizon Scanning Report | <input type="checkbox"/> Full Health Technology Assessment |
| <input type="checkbox"/> Monitor | <input type="checkbox"/> Archive |

References:

Australian Bureau of Statistics. National health survey – summary of results.

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Stryker Biotech. Frequently asked questions

<http://www.stryker.com/orthobiologics/us/professionals/op1/spine/op1puttyfaq.htm>

Accessed August 2004. Last updated 2004-10-14

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Vaccaro AR, Patel T, Fischgrund J, Anderson DG, Truumees E, Herkowitz H, Phillips F, Hilibrand A, Albert TJ. A pilot safety and efficacy study of OP-1 putty (rhBMP-7) as an adjunct to iliac crest autograft in posterolateral lumbar fusions. *European Spine Journal* 2003; 12:495-500.

Younger EM, Chapman MW. Morbidity at bone graft donor site. *Journal of Orthopaedic Trauma* 1989; 3:192-5.

Sources of Further Information:

Vaccaro AR, Anderson DG, Toth CA. Recombinant human osteogenic protein -1 (Bone morphogenetic protein-7) as an osteoinductive agent in spinal fusion. *Spine* 2002; 27(16S):59-65.

RCT in progress:

Gerszten PC and William CW. A prospective, randomised, controlled, multicenter, pivotal study of OP-1 putty in uninstrumented posterolateral fusion. This study is being conducted at the University of Pittsburg and is intended to establish the safety and efficacy of OP-1 putty. This will be determined by the rate of complications, neurological status, fusion success and time to fusion, when compared to the control group (autograft). Study Period: 23/01/04 to 31/12/04.

Search Criteria:

A search of MEDLINE, PubMed and Cochrane Library, Current Controlled Trials metaRegister, UK National Research Register, International Network for Agencies for Health Technology Assessments, relevant online journals and the Internet was conducted in September 2004.



Search terms used were: 'OP-1 putty', 'spinal fusion putty', 'Osteogenic Protein 1 or OP-1 and carboxymethylcellulose or CMC', 'Bone Morphogenetic Protein 7 or BMP-7', 'OP-1 implants' and 'rhOP-1 and bovine and CMC'.

This Horizon Scanning Prioritising Summary was prepared by Ms Lynette Cufone from the NET-S Project, ASERNIP-S for the Health Policy Advisory Committee on Technology (Health PACT), on behalf of the Medical Services Advisory Committee (MSAC) and the Australian Health Ministers' Advisory Council (AHMAC).