Medical Services Advisory Committee

Public Summary Document

Application No. 1140 - Matrix Induced Autologous Chondrocyte Implantation and Autologous Chondrocyte Implantation

Sponsors/Applicants:	**Genzyme, Biotech Regulatory Solutions and Device Technologies Australia**
Date of MSAC consideration:	**51st MSAC meeting, 2 December 2010**

1. Purpose of Application

On 12 May 2009, Genzyme Australasia Pty Ltd requested that MSAC undertake an assessment of Matrix Induced Autologous Chondrocyte Implantation and Autologous Chondrocyte Implantation (MACI/ACI) for the treatment of focal hyaline knee lesions greater than $2cm^2$.

Genzyme Australasia previously made an application to MSAC for an assessment of ACI, which was suspended because the use of Tisseel (the fibrin glue used as a bonding agent for the implant) was not registered by the Therapeutic Goods Administration for this indication.

Due to the relevance of this application to other parties with a commercial interest in MBS funding for MACI/ACI, the Department of Health and Ageing allowed Biotech Regulatory Solutions and Device Technologies Australia to be included as co-applicants in October 2009 and December 2009 respectively.

Although not requested by Genzyme, MSAC assessed MACI/ACI for knee lesions of all sizes given it better represents current Australian clinical practice and evidence relates to use in all sizes of lesions. MSAC found that more evidence is needed to define the patient group to likely to derive the most benefit from MACI/ACI.

2. Current arrangements for public reimbursement

MACI/ACI is performed in private hospitals and is not currently funded on the MBS. The procedure was previously claimed by some practitioners under MBS items 49563 and 49557, but the profession was instructed to cease this practice in 2006 because MACI/ACI was outside of the policy intent for the use of these MBS items.

Data on the previous claiming of MACI/ACI under MBS item numbers 49563 and 49557 was used to inform the anticipated volume of services in MSAC's financial analysis of the procedure. Noting that the use of MACI/ACI was precluded under these items in 2006, the MBS item descriptors are as follows:

> 49563
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> *KNEE, arthroscopic surgery of, involving 1 or more of: meniscus repair; osteochondral graft; or chondral graft - not associated with any other arthroscopic procedure of the knee region.* (Fee $766.50)

49557

KNEE, diagnostic arthroscopy of (including biopsy, simple trimming of meniscal margin or plica) - not being a service associated with any other arthroscopic procedure of the knee region. (Fee $262.50)

Genzyme proposed two MBS items, using the fees for MBS items 49563 and 49557.

Genzyme proposed the following descriptor for the first surgical procedure (the biopsy):

KNEE, arthroscopic surgery of, involving a biopsy for preparation of Autologous Chondrocytes Implantation or Matrix-induced Autologous Chondrocytes Implantation - not associated with any other arthroscopic procedure of the knee region (Anaes.) (Assist.)

ANKLE, arthroscopic surgery of, involving a biopsy for preparation of Autologous Chondrocytes Implantation or Matrix-induced Autologous Chondrocytes Implantation - not associated with any other arthroscopic procedure of the ankle region (Anaes.) (Assist.)

Genzyme proposed the following descriptor for the second surgical procedure (the MACI/ACI implantation):

KNEE, arthroscopic surgery or arthrotomy of the knee region, involving: Autologous Chondrocytes Implantation or Matrix-induced Autologous Chondrocytes Implantation - not associated with any other arthroscopic procedure or arthrotomy of the knee region (Anaes.) (Assist.)

ANKLE, arthroscopic surgery or arthrotomy of the ankle region, involving: Autologous Chondrocytes Implantation or Matrix-induced Autologous Chondrocytes Implantation - not associated with any other arthroscopic procedure or arthrotomy of the ankle region (Anaes.) (Assist.)

The comparators for MACI/ACI were Mosaicplasty and Microfracture.

The primary MBS item number for Mosaicplasty is 49563. This item has an MBS fee of $766.50. The MBS item descriptor is shown above.

The primary MBS item number for Microfracture is 49561. This item has an MBS fee of $648.50. The MBS item descriptor is:

KNEE, ARTHROSCOPIC SURGERY OF, involving 1 or more of: partial or total meniscectomy, removal of loose body or lateral release; where the procedure includes associated debridement, osteoplasty or chondroplasty - not associated with any other arthroscopic procedure of the knee region.

3. Background

Chondral injuries involve damage to the hyaline cartilage. Injuries in which there is damage of both the hyaline cartilage and underlying bone are known as osteochondral injuries. Damage to hyaline cartilage can bring about secondary events such as pain and swelling of the joint, caused by cartilage fragments released by shredding into the synovium. However, patients do not always experience pain because articular cartilage is both aneural and avascular. It is hypothesised that the presence of pain is a result of the increased load on the subchondral bone resulting from damage or loss of overlying cartilage. This can lead to decreased mobility and pain on movement. In some circumstances, deformity and constant pain can result.

The ACI procedure involves culturing chondrocytes obtained from a biopsy of normal cartilage and implanting them into the defect with the aim of the chondrocytes synthesising cartilage to repair the defect. Fibrin glue is used to attach the implant and acts as a sealant.

The MACI procedure, which is sometimes referred to as a second generation ACI, is an ACI technique that does not use a periosteal patch or artificial collagen to contain the implanted chondrocytes. Instead, the cultured chondrocytes are seeded directly onto a collagen scaffold, or matrix, prior to implantation. With MACI, the second surgical stage is determined using a limited surgical approach or arthroscopy. The MACI procedure may be performed in a tourniquet-controlled bloodless field.

MSAC considered that in a typical MACI/ACI procedure, the following MBS items would be claimed (if MACI/ACI were publicly funded):

- 17610 – Pre-anaesthesia consultation
- 21382 – Initiation of anaesthesia
- 49557 – Biopsy
- 61 – Anaesthesia
- 51300 – Biopsy assistance
- 49563 – MACI/ACI
- 23063 – Anaesthesia
- 51303 – MACI/ACI assistance

The following AR-DRG would be claimed:

- I18Z – Hospital stay

Patients with private health insurance would claim the following Prostheses List item:

- ORT01 – Autologous chondrocytes implant and matrix

MSAC noted that MACI and ACI are only performed in appropriately equipped facilities in major centres by orthopaedic surgeons who specialise in joint surgery, and in particular chondroplasty procedures.

Although a new MBS item was proposed for MACI/ACI by Genzyme, existing MBS items could be used if this were to receive public funding. MSAC noted that several surgical procedures for treating focal chondral lesions are currently funded on the MBS.

MSAC noted that ACI or MACI are additional options for chondroplasty and may be of value as either first or second line procedures.

MACI/ACI is used in the Australian setting as a first-line surgical treatment, following failure of conservative therapy to improve the condition. MSAC noted expert opinion (15 October 2010) that MACI implants are performed overseas as a second-line surgical procedure after failed microfracture.

Patients being considered for MACI/ACI must first undergo diagnostic imaging (typically by Magnetic Resonance Imaging) to confirm they are eligible for the procedure.

4. Clinical need

MACI/ACI would be considered for patients with full thickness chondral or osteochondral defects in an otherwise healthy knee (knees and ankles are the most common joints treated with ACI).

Procedures such as mosaicplasty and microfracture are publicly funded interventions that are currently used in Australia to treat patients presenting with chondral defects. MACI/ACI is intended for a population that already has access to treatment via these procedures.

MSAC noted that any restrictions would relate to the patients' suitability for the procedure. Patients receiving MACI/ACI must be 15-55 years old with a focal chondral lesion surrounded by normal cartilage in a normal joint. Widespread arthritis, rheumatoid arthritis or active autoimmune connective tissue diseases are contraindications for this procedure. Surgeons may further exclude patients from treatment based on a high Body Mass Index.

MSAC estimated that approximately 1000 patients per annum receive some form of hyaline knee cartilage repair, but the proportion of these patients receiving MACI/ACI is uncertain.

5. Comparator

MACI/ACI would typically be performed after a patient had presented with ongoing knee pain or swelling despite conservative treatment. Suitability for the procedure is confirmed through diagnostic imaging before the procedure is undertaken. MSAC noted that MACI/ACI is also used as a second-line surgical treatment following failure of other procedures, although this is not the clinical scenario in the majority of cases in Australia.

If MACI/ACI were listed, it would substitute for some instances of mosaicplasty and microfracture, which are commonly performed treatments for chondral defects and are listed on the MBS. Therefore these treatments were chosen as comparators for MSAC's assessment.

MSAC considered mosaicplasty, microfracture and debridement are appropriate comparators for MACI/ACI.

6. Scientific basis of comparison

The primary source of evidence for MSAC's advice was an Assessment Report produced by a contracted evaluator group. The Assessment Report comprised of a scientific literature review that was informed by an Advisory Panel of clinical experts and a consumer representative who ensured that the assessment considered relevant issues and appropriately reflected the Australian setting.

MSAC found that a significant body of evidence was identified, although the level of evidence was not to a high standard. The evidence consisted of 10 systematic reviews – 3 health technology assessments, five randomised control trials (RCTs), one pseudo-randomised trial, 12 non-randomised comparative studies, and 39 case series eligible for appraisal. .

MSAC noted that the safety data were not the main focus of the comparative evidence used for this assessment. However, the incidence of adverse events per patient was able to be calculated from the safety data supplied. Three non-randomised comparative studies and one randomised controlled study with inappropriate comparisons were treated as level IV studies and their study arms included for safety data only.

MSAC found inconsistent reporting in all treatment options but that three reviews found ACI does not pose additional risks, and major complications are rare and comparable between techniques.

MSAC noted that a variety of functional and imaging outcome measures were used to measure clinical effectiveness, making comparisons between studies difficult. They also noted that there were no studies available that gave comparative evidence about the long-term effectiveness (>5 years) of MACI/ACI. MSAC agreed there was not sufficient evidence to conclude that MACI/ACI is superior to other treatments.

7. Safety

For the majority of adverse events reported, there were no obvious differences in incidence rates between the MACI/ACI and comparator procedure groups. Procedure failure rate was the most commonly reported adverse event, and demonstrated an incidence rate of 9.5% in the ACI/MACI population, and 11.9% in the comparator procedure population.

Major morbidities such as infection and deep vein thrombosis were rare in both the MACI/ACI and comparator groups, and there were no reported deaths as a result of any of the procedures in either group.

While noting inconsistent reporting in the literature, MSAC agreed that the safety of MACI/ACI appeared to be comparable to other procedures for the treatment of chondral defects in the knee. Procedure failure was the most commonly reported adverse event, but was at a rate similar to the comparator procedures. MSAC noted that MACI/ACI and its comparative procedures have extensive rehabilitation time and patients will typically receive only one chondroplasty procedure.

8. Clinical effectiveness

MSAC found that clinical effectiveness studies had many different outcome measures, but noted that the focus should be on functional rather than imaging outcome measures as these were more relevant to quality of life following the procedure. The most commonly reported functional outcome measures were the Lysholm and Tegner scores. Of the eight studies that reported Lysholm scores, six reported no significant difference in the effectiveness of MACI/ACI over time compared with comparator procedures. However, one study reported that MACI/ACI was more effective over time compared with microfracture and mosaicplasty. Similarly, of the five studies that reported Tegner scores, four studies reported no significant difference in the effectiveness of MACI/ACI over time compared with comparator procedures. One study reported that MACI was more effective over time compared with microfracture.

Most studies that assessed quality of life and pain scores reported that these outcomes were not significantly different following MACI/ACI compared with comparator procedures. However, one study did report that the improvement in pain scores following ACI was significantly better compared with debridement.

Imaging outcomes reported in a limited number of studies revealed no significant difference in the quality of articular cartilage repair following MACI/ACI compared with comparator procedures. Similarly, one study reported that at five years follow-up, there was no significant difference in the frequency of radiographic changes that were indicative of osteoarthritis in MACI/ACI patients compared with patients who underwent microfracture.

MSAC found that clinical effectiveness evidence relying on functional outcome measures suggests that MACI and ACI are no better than microfracture or mosaicplasty in the short term, and imaging results up to five years post-procedure suggest no changes indicative of longer term incremental benefits such as a reduction in radiological changes indicative of osteoarthritis compared to alternative interventions.

MSAC found that the bulk of evidence on functional outcomes suggests no difference in outcomes within the period of follow-up. The bulk of evidence on quality of life and pain scores suggests no difference in outcomes within the period of follow-up. Imaging outcomes at five years are not necessarily indicative of long-term benefit (such as reduced osteoarthritis).

MSAC noted that the application suggested MACI/ACI may potentially be more effective for patients with large chondral lesions (>2cm^2), but found that this was not supported by high quality evidence.

9. Economic evaluation

In the absence of conclusive effectiveness data, a cost analysis was conducted to compare the different costs associated with each of the three procedures.

MSAC noted that the cost model in the assessment report assumes rehabilitation costs are the same across all surgical options (noting the MACI/ACI require extensive (up to 12 months) rehabilitation.

The cost analysis found that both MACI and ACI are significantly more expensive than either microfracture or mosaicplasty for the repair of knee hyaline cartilage damage. The main cost of MACI/ACI, chrondocyte cell culture ($11,400) and Tisseel sealant ($380), results in a much higher unit cost for MACI and ACI procedures, estimated at $14,083. The unit cost of mosaicplasty is $2,639 and the unit cost of microfracture is $1,405. Therefore MACI/ACI are 10 times more expensive than microfracture and over five times the cost of mosaicplasty.

MSAC noted the average co-payment would be $1,028.95 per MACI/ACI procedure. Patients without private health insurance will also be liable for the full cost of the chondrocyte culturing and implantation, which is estimated at $11,400.

MSAC noted that all MBS items associated with MACI/ACI are performed in an inpatient setting. Therefore, any out-of-pocket costs associated with these items will not contribute towards the Extended Medicare Safety Net (EMSN). Consequently, out-of-pocket contributions for MACI/ACI are unlikely to impact on the EMSN.

MSAC noted the costs related to the isolation and culture of chondrocytes were the main contributors to the differences in cost between MACI/ACI and the comparators. Another contributing factor is that MACI/ACI is a two-stage surgical procedure also requiring a preliminary diagnostic arthroscopy; the comparators requiring only one procedure.

Evidence suggests there is no difference in effectiveness between MACI/ACI and the comparators, whereas the additional cost per MACI/ACI procedure is substantial. Due to these factors, no formal cost effectiveness analysis was undertaken.

10. Financial/budgetary impacts

MSAC estimated that approximately 1000 patients per annum receive some form of hyaline knee cartilage repair, but the proportion of these patients receiving MACI or ACI is uncertain. MSAC noted that as MACI/ACI is an established procedure, the number of patients receiving the treatment would be unlikely to increase significantly if public funding were available.

MSAC noted the total cost to the MBS was estimated at $1.27 million to $9 million per annum. This is an incremental cost to the MBS of $365,123 to $2.58 million per annum.

The population receiving chondral repair procedures was estimated at 1000 patients per year, with a potential 7000 patients per year estimated in the sensitivity analysis. Applying the cost of MACI/ACI to this population, assuming full substitution, resulted in an estimated budgetary impact of $14 million to $90 million per annum.

MSAC noted that the total net budgetary impact for this procedure was calculated based on full substitution of MACI/ACI for all other chondral repair procedures. However, MSAC considered full substitution for this procedure was unlikely.

11. Other significant factors

MSAC noted that the natural history of hyaline cartilage damage is unknown and that the need for surgical intervention in this indication is not clear. MSAC's assessment found that neither MACI, ACI, nor the comparator procedures have been reliably shown to be superior to non-surgical treatments in properly constructed randomised trials, and noted the lack of evidence in relation to long term functional outcomes of these procedures.

MSAC noted the suggestion that MACI and/or ACI may potentially be more effective for patients with large chondral lesions (>2cm^2), but concluded this was not supported by high quality evidence. MSAC also considered whether MACI/ACI should be limited to use as a second-line treatment (following failure of another intervention), but noted that the use of MACI or ACI as a second-line treatment was neither common practice in Australia nor supported by evidence.

MSAC also noted that MACI and ACI are only performed in appropriately equipped facilities in major centres by orthopaedic surgeons who specialise in joint surgery, and in particular chondroplasty procedures. Therefore, patients in rural and remote areas, and those without private health insurance, may have difficulty accessing this procedure.

MSAC further noted that long-term studies would be required to assess the development of osteoarthritis following treatment with the MACI/ACI procedure.

MSAC concluded that ACI/MACI are alternatives to currently funded arthroplasty procedures, and safety is comparable to other procedures, but there is no convincing evidence of greater benefit to patients in the short to medium term.

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

MSAC considered the strength of the evidence, related primarily to the knee joint, of the use of Matrix Induced Autologous Chondrocyte Implantation (MACI) and Autologous Chondrocyte Implantation (ACI) as first-line treatments for focal hyaline cartilage lesions. MACI and ACI are two-step procedures for replacing damaged cartilage with true hyaline cartilage where chondral cells from the patient are cultured (in vitro) and then reimplanted into the focal defect, either within a matrix (MACI) or using a periosteal/collagen flap (ACI) which is adhered with fibrin glue. MACI and ACI are alternatives to currently funded arthroplasty procedures -- mosaicplasty and microfracture -- which are one-step procedures.

MSAC noted that the natural history of hyaline cartilage damage is unknown and that the need for surgical intervention in this indication is not clear. It is estimated that approximately 1000 patients per annum receive some form of hyaline knee cartilage repair, but the proportion of these patients receiving MACI or ACI is uncertain.

While noting inconsistent reporting in the literature, MSAC agreed that the safety of MACI/ACI appeared to be comparable to other procedures for the treatment of chondral defects in the knee. Procedure failure was the most commonly reported adverse event, but was similar to the comparator procedures. MSAC noted that MACI/ACI and its comparative procedures have extensive rehabilitation time and patients will typically receive only one chondroplasty procedure.

MSAC found that clinical effectiveness evidence relying on functional outcome measures suggests that MACI and ACI are no better than microfracture or mosaicplasty in the short term, and imaging results up to five years post-procedure suggest no changes indicative of longer term incremental benefits such as a reduction in radiological changes of osteoarthritis compared to alternative interventions. The assessment found that neither MACI or ACI nor the comparator procedures have been reliably shown to be superior to non-surgical treatments in properly constructed randomised trials, and noted the lack of evidence in relation to long term functional outcomes of these procedures.

MSAC noted the suggestion that MACI and/or ACI may potentially be more effective for patients with large chondral lesions (>2cm^2), however this was not supported by high quality evidence. MSAC also considered whether MACI/ACI should be limited to use as a second-line treatment (following failure of another intervention), but noted that the use of MACI or ACI as a second-line treatment was neither common practice in Australia nor supported by evidence.

MSAC found that there was insufficient evidence to support a full economic evaluation of MACI or ACI. MSAC found that both MACI and ACI are significantly more expensive than either microfracture or mosaicplasty for the repair of knee hyaline cartilage damage. MSAC found that the unit cost of the MACI and ACI procedures was estimated at $14,083; the unit cost of mosaicplasty is $2,639; and the unit cost of microfracture is $1,405. Therefore MACI and ACI are 10 times more expensive than microfracture and over five times the cost of mosaicplasty. The costs related to the isolation and culture of chondrocytes was the main contributor to the difference in cost.

The total net budgetary impact for this procedure had been estimated between $11 million and $90 million depending on uptake and substitution of MACI/ACI for the comparative surgical treatments. However, MSAC considered full substitution for this procedure unlikely.

MSAC also noted that MACI and ACI are only performed in appropriately equipped facilities in major centres by orthopaedic surgeons who specialise in joint surgery, and in particular chondroplasty procedures. Therefore, patients in rural and remote areas, and those without private health insurance, may have difficulty accessing this procedure.

13. MSAC's advice to the Minister

MSAC does not support public funding for matrix-induced autologous chondrocyte implantation or autologous chondrocyte implantation for the treatment of chondral defects in the knee and other joints, due to the increased cost compared to existing procedures and the lack of evidence showing short term or long-term improvements in clinical outcomes.

14. Context for Decision

This advice was made under the MSAC Terms of Reference:

"MSAC is to:

Advise the Minister for Health and Ageing on medical services including those that involve new or emerging technologies and procedures and, where relevant, amendment to existing MBS items, in relation to:

- the strength of evidence in relation to the comparative safety, effectiveness, cost-effectiveness and total cost of the medical service;
- whether public funding should be supported for the medical service and, if so, the circumstances under which public funding should be supported;
- the proposed Medicare Benefits Schedule (MBS) item descriptor and fee for the service where funding through the MBS is supported;
- the circumstances, where there is uncertainty in relation to the clinical or cost-effectiveness of a service, under which interim public funding of a service should be supported for a specified period, during which defined data collections under agreed clinical protocols would be collected to inform a re-assessment of the service by MSAC at the conclusion of that period;
- other matters related to the public funding of health services referred by the Minister.

Advise the Australian Health Minister's Advisory Council (AHMAC) on health technology assessments referred under AHMAC arrangements.

MSAC may also establish sub-committees to assist MSAC to effectively undertake its role. MSAC may delegate some of its functions to such sub-committees."

15. Linkages to Other Documents

MSAC's processes are detailed on the MSAC Website at: www.msac.gov.au.

The MSAC Assessment Report is available at

http://www.msac.gov.au/internet/msac/publishing.nsf/Content/app1140-1