Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1192 – Reduction of Mitral Regurgitation through Tissue Approximation using Transvenous / Transseptal Techniques

Applicant: **Abbott Vascular**

Date of MSAC Meeting: **29 – 30 November 2012**

1. Purpose of application

In August 2011, the Department of Health and Ageing received an application from Abbott Vascular requesting that the Medical Services Advisory Committee (MSAC) undertake an assessment for Medicare Benefits Schedule (MBS) listing of percutaneous reconstruction of an insufficient mitral valve through tissue approximation using transvenous/transeptal techniques. The submission related to a generic intervention, but was based on clinical evidence that related to a trademarked product, the MitraClip System. For the purposes of this summary, the term 'MitraClip' is therefore used to denote the intervention of interest.

The MitraClip system involves a catheter-based device being threaded via the femoral vein to the right atrium and passed into the left atrium via transseptal puncture. The device is then passed through the mitral valve into the left ventricle. When the clip is deployed, it essentially grasps the free edge of the anterior mitral valve leaflet and joins it to the posterior leaflet, creating a point of coaptation and a double orifice to restrict backflow of blood.

Percutaneous reconstruction of an insufficient mitral valve through tissue approximation using transvenous/transseptal techniques is indicated for patients suffering from clinically significant mitral regurgitation (MR) due to an insufficient mitral valve (i.e. mitral valve leaflets do not coapt properly, allowing backflow of blood from the left ventricle into the left atrium during systole). As a consequence there is decreased forward flow into the aorta and systemic circulation, requiring the heart to work harder to maintain an adequate forward stroke volume. Over time, left ventricular (LV) dilatation can occur. If left untreated MR can bring about irreversible LV systolic dysfunction, pulmonary oedema, congestive heart failure, thromboembolism resulting from atrial fibrillation, and in some cases sudden death. Clinical practice guidelines recommend mitral valve surgery as the only definitive treatment for MR, with surgical repair recommended over replacement whenever feasible. However, many patients have risk factors that render them unsuitable for surgery and these patients are only offered palliative medical therapy for management of symptoms.

2. Background

MitraClip is a novel technology which has not previously been considered by MSAC.

'*Percutaneous mitral valve repair utilising MitraClip®*', a prioritising summary of the technology, was presented to the Australia and New Zealand Horizon Scanning Network (ANZHSN) in August 2007 and updated in 2010.

3. Prerequisites to implementation of any funding advice

There are two Therapeutic Goods Administration (TGA) registrations for MitraClip listed by Abbott Vascular Division of Abbott Australasia Pty Ltd.

ARTG number	ARTG label name	Intended purpose
177709	MitraClip System - Mitral valve tissue repair system	A system of devices intended for the percutaneous reconstruction of an insufficient mitral valve through tissue approximation using transvenous/transseptal techniques.
189720	Clip Delivery System - Mitral valve clip	The MitraClip delivery system is intended for reconstruction of the insufficient mitral valve through tissue approximation. It is a component of the MitraClip System.

4. Proposal for public funding

The Applicant's proposed MBS item descriptor for the MitraClip system is:

Category3 – Therapeutic Procedures

MBS 38xxx

Percutaneous reconstruction of an insufficient mitral valve using transvenous/transseptal techniques for:

- Permanent placement of one or more tissue approximation devices, or
- Subsequent removal of one or more tissue approximation devices as a result of post percutaneous reconstruction recurrent mitral regurgitation requiring further surgical or medical management.

(Anaes.) (Assist.)

Explanatory notes

It is recommended that a 'heart team', comprising two cardiologists (a medical and an interventional cardiologist) and a cardiothoracic surgeon, provide approval regarding the patient's suitability for treatment.

This item may not be claimed if this device cannot be placed satisfactorily in the patient; and abandon surgery item may be claimed in this case.

Fee: to be determined

The MitraClip procedure is less likely to be successful in patients with:

- evidence of calcification or cleft of the grasping area;
- severe bileaflet flail or prolapse;
- lack of both primary and secondary chordal support, or
- a mitral valve orifice area of $\geq 4cm^2$.

MitraClip should not be implanted in patients with active endocarditis or other clinically significant infection, or in patients in whom MR is a result of rheumatic heart disease.

The MitraClip procedure is intended as a once in a lifetime intervention, delivered in a single procedure. If MR is unable to be satisfactorily reduced, the physician may remove the device completely, leaving the patient with the same therapeutic options as prior to the procedure, including surgical intervention. If MR recurs subsequent to an initially successful procedure, a second intervention with the MitraClip device is a treatment option. Surgical intervention may also be possible but this may be adversely affected by the extent of any damage inflicted on the mitral valve tissue from MitraClip placement or removal.

The assessment critique noted that the MitraClip device cannot be reused and that expert opinion suggested, in the event of MR recurrence, that valve tissue is often found to be substantially torn or fibrotic after MitraClip failure or removal. In this case, mitral valve repair would not be possible, necessitating surgical replacement of the mitral valve.

Patients are referred by a GP to a cardiologist, then to either an interventional cardiologist or a cardiothoracic surgeon. The assessment report proposed that a 'heart team', comprising two cardiologists (a medical and an interventional cardiologist) and a cardiothoracic surgeon, will provide approval regarding the patient's suitability for treatment with MitraClip.

To use MitraClip, physicians and hospital staff must complete a five day training program which includes coursework and 'hands on' use of a demonstration system (including a heart model). To qualify for the training program the physician must:

1. Be either an interventional cardiologist or cardiac surgeon with experience in transseptal technique and understanding or experience in structural heart disease.
2. Have a multidisciplinary team to support the procedure (including a dedicated echocardiographer (for patient screening and to be present during the procedure), and if the physician is an interventional cardiologist, a cardiac surgeon to provide support);
3. Have a cardiac surgeon to assist with the process.
4. Identify five suitable patients prior to training and have a reasonable volume of patients to maintain minimum skills levels and optimal patient outcomes.

5. Consumer Impact Statement

No feedback was received from consumers addressing potential advantages (or disadvantages) to consumers if treatment with MitraClip becomes available under the MBS.

6. Proposed intervention's place in clinical management

MitraClip is proposed as an alternative:

- for patients who are fit for surgery, to the currently subsidised surgical options of mitral valve repair or replacement; and
- for patients who are too ill for surgery, as an alternative to medical management. For some of these, this may mean a bridge to surgery.

The assessment report claimed both the RCT and 'real world' experiences demonstrate the clinical benefits of the MitraClip procedure, evidenced by rates of reduction in MR, improved LV dimensions and clinical improvements in NYHA functional class and quality of life through at least 12 months.

However, the assessment critique indicates that the clinical claim that MitraClip was non-inferior to mitral valve repair or replacement surgery was not supported by available evidence.

The basis of the assessment with regards to the comparison of MitraClip with mitral valve repair or replacement surgery was one direct RCT (Feldman et al 2011). Significant methodological limitations compromised the findings of this study:

- Inclusion of selected patient groups to increase likelihood of successful MitraClip treatment;
- Use of a non-inferiority analysis employing an unjustifiably wide margin for absolute risk difference between MitraClip and surgical treatment;

- Use of a clinical effectiveness outcome that potentially favoured MitraClip (i.e. freedom from MR grade 3+ or 4+);
- Use of a clinical safety outcome potentially not appropriate to be considered a major adverse event (i.e. requirement for transfusion of ≥2 units of blood);
- Failure to report or discuss adverse events in patients receiving surgery after MitraClip failure;
- Insufficient length of follow-up.

According to the critique, the effectiveness or safety of MitraClip relative to mitral valve repair or replacement surgery or to medical management could not be established in patient groups at high risk or unsuitable for conventional mitral valve surgery. Although the assessment report presented one comparative study reporting on apparent high-risk patients (Whitlow et al 2012), this study contained a heterogeneous comparator group without differentiating clinical outcomes and as such was not considered a valid comparative study for the purpose of this assessment. There was also some question as to whether all included patients had high-risk surgical profiles.

7. Other options for MSAC consideration

In their submission the Applicant amended the proposed intervention to read:

- Permanent placement of one or more tissue approximation devices; or
- Subsequent removal of one or more tissue approximation devices as a result of post percutaneous reconstruction recurrent mitral regurgitation requiring further surgical or medical management.'

The Applicant provided no explanation for this change.

In their submission the Applicant amended the heart team to two cardiologists (*a medical and an interventional cardiologist*) and a cardiothoracic surgeon but has provided no explanation for the additional cardiologist.

8. Comparator to the proposed intervention

Two comparators are relevant for the treatment of MR: mitral valve repair or replacement surgery; and medical management for patients who are unsuitable for surgery (or as a bridge to surgery).

The following table shows MBS items related to the surgical treatment of MR:

MBS item number	***MBS item descriptor***
38480	Valve repair, 1 leaflet Fee: $1,966.00
38481	Valve repair, 2 or more leaflets Fee: $2,238.15
38485	Mitral annulus, reconstruction of, after decalcification, when performed in association with valve surgery Fee: $801.85
38488	Valve replacement with bioprosthesis or mechanical prosthesis Fee: $1,874.00
38489	Valve replacement with allograft (subcoronary or cylindrical implant), or unstented xenograft

38490	Fee: $2,228.70 Sub-valvular structures, reconstruction and re-implantation of, associated with mitral and tricuspid valve replacement Fee: $544.20

MBS Medicare Benefits Schedule operating from 01 May 2012

9. Comparative safety

Principal evidence of the safety and effectiveness of the MitraClip device was derived from the endovascular valve edge-to-edge repair study (EVEREST) II RCT, and supported by published data from the EVEREST I and EVEREST II Roll-In clinical studies.

These studies evaluated the performance of the MitraClip device in patients eligible for mitral valve surgery with moderate-to-severe (3+) or severe (4+) chronic MR with symptoms, or asymptomatic patients with LV dysfunction or new onset of atrial fibrillation or pulmonary hypertension without regard to surgical risk status.

The results of the EVEREST II trial were reported by Feldman et al (2011). The results from the High-Risk Study, an arm of the EVEREST II trial, were reported by Whitlow et al (2012). The High Risk Study was a prospective single-arm study in patients assessed as having a surgical mortality risk of at least 12%.

However, the critique concluded that the assessment report did not report and analyse all relevant clinical safety outcomes reported by the RCT. As such, a more comprehensive analysis and interpretation was prepared and is presented in detail below.

The critique noted that with respect to comparative safety evidence from the included RCT, the assessment report stated that there was an absolute difference of -33 per cent between the MitraClip and surgical treatment groups in the rate of a composite measure of major adverse events at 30 day follow-up, with a one-sided upper limit (using a 97.5 per cent confidence interval) of -21 per cent (ITT analysis). This was significantly lower than the pre-specified -2 per cent margin the RCT authors stated was required to confirm greater safety of MitraClip ($p<0.001$).

However, when adverse events were examined individually, the only significant differences between the treatment groups were that surgery patients were significantly more likely than MitraClip patients to require mechanical ventilation for more than 48 hours after treatment ($p=0.02$), and require transfusion of two or more units of blood ($p<0.001$). It is debatable as to whether the requirement for transfusion of two or more units of blood should be considered in this composite measure of major adverse events. The RCT authors noted that when requirement for blood transfusion was excluded from the comparison of safety endpoints, no significant difference in the rate of total major adverse events was found between the treatment groups.

In the per protocol analysis of only those patients who had successful in-hospital procedural results, MitraClip patients had significantly fewer major adverse events at 30 day follow-up than surgery patients. This was the case regardless of whether requirement for blood transfusion was considered to be a major adverse event ($p<0.001$) or not ($p=0.001$).

With regards to adverse events related to the MitraClip device, 37 of 178 patients (21 per cent) who underwent the MitraClip procedure subsequently underwent mitral valve surgery during 12 months of follow-up; 17 of these patients had not received a MitraClip device during initial treatment. During mitral valve surgery, leaflet or chordae tears were noted in seven patients; it was not stated by the authors whether these tears were due to MitraClip placement or removal. No device embolisation or substantial mitral stenosis was observed.

While treatment with MitraClip is likely to be of comparable safety to mitral valve repair or replacement surgery, it can be reasonably argued that MitraClip did not demonstrate a clinically relevant safety benefit in the single included RCT study.

Comparative evidence in high-risk patients
The critique noted that all patients recruited into the RCT by Feldman et al (2011) had low- or moderate-risk surgical profiles and were deemed medically suitable to potentially undergo both MitraClip and mitral valve repair or replacement surgery. This selectivity precluded the RCT from informing this assessment regarding the relative effectiveness or safety of MitraClip against surgery in high-risk patients. The assessment report presented no other data that was considered eligible to inform the relative effectiveness or safety of MitraClip in comparison to surgery or medical management in high-risk patients.

The critique concluded that while treatment with MitraClip is likely to be of comparable safety to mitral valve repair / replacement surgery, it can be reasonably argued that MitraClip did not demonstrate a clinically relevant safety benefit in the single included RCT study.

10. Comparative effectiveness

Primary clinical effectiveness endpoints were reported in the EVEREST II trial results.

As a result of the issues identified below, the critique indicated that the clinical claim that MitraClip was non-inferior to mitral valve repair or replacement surgery was not supported by available evidence.

According to the critique, the assessment report did not provided a comprehensive assessment of the effectiveness and safety of the MitraClip device. The main areas of clinical uncertainty identified in the critique relate to significant methodological limitations in identifying, analysing and interpreting the clinical evidence regarding:

- Inadequate evidence search strategy;
- No uniform or systematic criteria for evidence selection;
- No critical appraisal of studies for methodological bias;
- No critical appraisal of appropriateness of study eligibility criteria, patient populations or interventions;
- No critical appraisal of appropriateness of study outcome measures or statistical analyses;
- Inadequate and inappropriate reporting, analysis and interpretation of clinical outcomes.

11. Economic evaluation

The economic evaluation of MitraClip used a cost-utility analysis.

The critique concluded that there were significant omissions from the methodology underpinning the economic model which affected the quality of the cost-effectiveness analysis of the MitraClip device in the assessment report. These omissions included the following:

- the report lacked an adequate description of the model;
- the Excel model provided did not explain the model inputs;

- premodelling studies were not conducted to transform the clinical data to match the intended population to receive MitraClip;
- many of the sources of data described in the model could not be verified;
- clinical effectiveness outcomes differ;
- adverse events post MitraClip were not reported;
- there was insufficient long-term follow-up (up to 5 years is expected post-surgery).

The economic model further adds to the economic uncertainty due to the following issues:

- the baseline risk of the groups (stratified by NYHA) differed between MitraClip and surgery intervention groups (these cohorts should be identical prior to intervention);
- the long term effectiveness of MitraClip is questionable given the inferiority result from the main clinical study reported in Feldman et al 2011;
- the model applied a lower mortality rate to the MitraClip group compared to the surgery arm; however Feldman et al 2011 found no significant differences;
- the data underpinning the medical management group in the model was not verifiable;
- the primary efficacy outcomes in Feldman et al 2011 were freedom from death, surgery and MR <2+ at 12 months. However utility weights were applied in the model based on stratification of NYHA class;
- a scaling factor was applied to the mortality estimates in the medical management group, increasing the overall mortality in this group. There was no basis for this assumption which could bias the results in favour of MitraClip;
- the surgery comparator group should have evaluated both repair and replacement in the comparator group as per the decision analytic pathway in the DAP. There is no distinction made between the two procedures;
- the model did not include any further MBS costs for the removal of a MitraClip in the event that the device failed, or any further MBS costs associated with the surgery being abandoned.

Base case cost-effectiveness results

With medical management as the comparator, on a per-patient basis over the lifetime horizon of up to 40 years, patients who were given MitraClip accrued an additional 1.62 discounted LYG and 2.10 QALYs. These benefits would cost the Australian health care system an additional $42,805 per patient. The incremental cost-effectiveness ratio (ICER) was therefore $20,382 per QALY gained and $26,415 per LYG gained.

However, the critique noted that the model inputs could not be verified. Therefore the estimated ICERs are highly uncertain. The increased QoL gains of MitraClip versus medical management remain highly uncertain due to appropriateness of the survival data used.

In regards to MitraClip versus surgery, the ICER for MitraClip was $295,993 per QALY gained and $216,290 per LYG gained. However, as the EVEREST II trial demonstrated superior efficacy of surgery relative to MitraClip, a cost-utility analysis comparing these interventions is questionable. The mortality rate used in the surgery group was double that of MitraClip group for the first month in the model, which may also be biasing the results in favour of MitraClip.

The fee proposed by the applicant was based on the repair of two leaflets (MBS item 38481). However, after PASC consideration it was determined that repair of an atrial septal defect

(ASD) via transcatheter approach (MBS item 38272) provides a more comparable basis for the item fee in terms of time and complexity. The assessment report noted that the similarities of the MitraClip procedure to an ASD closure stop at the intra-atrial septum and do not take into account the time/complexity of maneuvering a device in the left atrium, left ventricle, and mitral valvular apparatus. This suggests that the applicant considers the fee to be inadequate.

Although the proposed service is to be provided in-hospital, there will be pre and post-operative treatment which may impact on the MSN and EMSN. These costs have not been identified.

12. Financial/budgetary impacts

The critique found that the quality of the assessment report did not provide a sufficient basis for a comprehensive assessment of the overall financial implications of the MitraClip device. Significantly the methodology did not adequately identify the estimated patient numbers and financial impacts of the device:

- The estimated numbers of eligible patients reported in the assessment report were not the same estimates used in the final budgetary impact presented in Section E.5 of the critique of the assessment.
- No detail was provided on the methodology of the estimates and the sources are not verifiable.
- The financial impact data presented was not consistent with the model presented in Section D of the assessment report.
- The costs used in the economic model were not derived from current MBS costs.

The main issues of uncertainty in the financial implications of MitraClip are:

- Patient numbers for surgery were derived from prevalence estimates and the estimated number of patients for medical management from incidence estimates. The estimated number of patients is uncertain.
- The uptake rates reported in the assessment report are not discussed nor substantiated with any data to support this estimate.
- The overall costs presented in Section E.5 of the assessment critique were based on the Excel model which did not disaggregate the costs to identify which costs would have an impact on the MBS.
- The financial estimates do not include the additional MBS costs for treating adverse events.
- The financial estimates also do not include the additional MBS services required after a MitraClip procedure.
- Patient co-payments were not included.

The critique explained the problems with the Applicant's assumptions regarding patient volume, prevalence and incidence of MR. The assessment report indicated that the estimated number of eligible patients/year for the MitraClip procedure (before applying an uptake rate) was 150,000 per year. This equated to the 146,250 patients eligible to receive medical management and 3,750 patients eligible to receive surgery in the comparator groups. It went on to state that the current 2012 Australian population was taken from the ABS and a 1.3 per cent annual growth multiplier applied to generate future population estimates. Then indicated that the model assumed that 300,000 individuals have heart failure and half of these patients will have some form of MR, resulting in a population of 150,000 with MR. However, the critique noted that:

- the eligible population was not estimated from the ABS;
- an annual growth multiplier was not applied to generate the future population;
- the eligible population was derived using a starting population of 300,000 each year (no source provided);
- future incidence of MR or population growth over time was not taken into account;
- current prevalence estimates for MR were not taken into account (prevalence of moderate and severe MR est. to be 1.7%).

The critique noted that the assessment report used the current MBS items for valve surgery to determine the split between medical management and surgery. The Applicant assumed that the 3,800 patients who received valve surgery would comprise the group of patients eligible to receive surgery. This equated to 2.5 per cent of the starting population of 150,000. This implied that 97.5 per cent of all eligible patients are currently receiving medical management for their condition.

The critique noted that the Applicant has assumed that the 3,800 operations should be based on the prevalence figure of 150,000 with MR and used this to derive the 97.5 per cent which has implications to the overall financial projections. This assumed the same proportion of new cases would also receive surgery which is not appropriate

Number of patients likely to use the intervention

The assessment report estimated that 1,500 patients will use MitraClip in Year 1, increasing to 4,500 in Year 5. This was based on an uptake rate of 1% in Year 1, increasing 0.5% each year, with an assumed 3% uptake rate in Year 5. There was no explanation of these estimates. The critique noted that the patient estimates in the model differ from those in the assessment report. The discrepancy between the sources was not appropriate as the overall budgetary impact presented in Section B.5 is based on the Excel model.

The critique noted that, in the Excel model, the number of patients was derived from the prevalence rate for the MitraClip estimates and surgery. However, the total numbers of medical management patients was derived from the incidence figures. For example, the estimate of the number of patients in Year 1:

- Medical Management versus MitraClip:
  - MM: 8700 x 99% = 8613
  - MC: 146,250 x 1% = 1462
- Surgery versus MitraClip:
  - S: 3750 x (99%) = 3713
  - MC: 3750 x (1%) = 38

The assessment report also briefly discusses the Euro Heart Survey which was used to estimate the number of patients considered high risk. According to the study, out of 396 patients with severe MR (grade >3/4), a decision not to operate was taken in 49 per cent of patients. The report indicated that 3,988 valve repairs or replacement surgeries were claimed on the MBS in 2011, representing the 51 per cent who were 'assumed' not to be at a high risk from surgery. The report assumed this provides a potential population for MitraClip of 3,832. The critique queried why this breakdown was identified but not used in the actual estimates for the patient numbers in the assessment report or the Excel model.

The MitraClip procedure was designed as a once in a lifetime therapeutic intervention.

The number of patients eligible to receive MitraClip in the model was derived from overall MR prevalence and incidence figures.

The total incidence population was calculated as:

patients with heart failure (300,000) x newly diagnosed (10%) x severe MR (29%).

- 300,000 x 10% x 29% = 8,700

The total prevalent population was calculated as:

patients with health failure (300,000) x number with severe MR (50%) x eligible for surgery (2.5%) or ineligible for surgery (97.5%):

- 300,000 x 50% x 2.5% = 3,750
- 300,000 x 50% x 97.5% = 146,250.

The sponsor recommended cost of the MitraClip System is $**(redacted)** It is important to note that this is a cost per procedure regardless of how many clips are used in the procedure.

The critique lists the health care resources included in the economic evaluation which are identified in the table on the following page. The critique noted that the following require clarification:

- the Australian cost of the MitraClip procedure is a flat $**(redacted)** dollars (regardless of the number of clips used) and should be included in the economic model;
- Theatre costs should be disaggregated to individual unit costs;
- Identify how the cost of daily hospital based care was incorporated into the model;
- Identify and verify all the sources of adverse event data;
- Source costs for emergency CV surgery events, gastro-intestinal complication, blood transfusions and heart failure related hospitalisations from current MBS data (not UK);
- Provide details on how the costs were applied for the table of Pharmaceutical Benefits Scheme (PBS) drugs used in the model.

Item	Unit of measurement	Unit cost ($)	Source of cost	Cost in economic model ($)	
Intervention					
Direct intervention costs			Reported in assessment report as "local input"	$ (redacted)	See Note a
Specialist services					
Type of medical practitioner	Consultation				N/A
Hospital services					
ICU	One day		None provided	$2,200	See Note b
CCU	One day		None provided	$1,700	See Note b
Non ICU	One day		HCF private payer	$700	See Note b
Emergency CV surgery event	None reported		UK model project report	$2,962	See Note c
GI complications requiring surgery	None reported		UK model project report	$7,287	See Note c
Blood transfusion	None reported		UK model project report	$275	See Note c
Heart failure related hospitalisation rate	None reported		Flinders medical centre	$9,214	See Note c
Theatre costs surgery MitraClip	None reported		Excel spreadsheet	$12,758	See Note a
Theatre costs MitraClip	Hourly	$1,500	Assumption	$3,000	See note a
Theatre costs surgery	None reported		HCF private health insurance payer	$18,758	See Note a
Pharmaceuticals					
PBS drug, form and strength	Daily		MM: PBS, Australia MC: PBS, Australia S: PBS, Australian	$175.45 $171.50 $172.85	See Note d
Other relevant diagnostic services					
					N/A
Allied health services					
Community rehabilitation event	Daily	$575	Flinders medical centre	$5,750	See Note b
Managed rehabilitation	One visit	$140	Flinders medical centre	$700	See Note b

The assessment report calculated the cumulative budget impact on the Australian healthcare sector should MitraClip be incorporated into it, would be $66.2 million in year 1, decreasing to $45.9 million in year 5. However, the critique noted that the structure of the Excel model did not allow for the analysis of the overall budgetary impact solely on the MBS. There is potential for the net cost per year to the MBS to be greater than that identified in the assessment report. The market uptake rates do not match the rates used in the estimated patient numbers in Table E.2.1 of the assessment critique. The overall financial figures are not consistent with the estimates presented in the previous sections of the assessment critique in regards to patient numbers and overall costs. It is also not clear why the net cost to the MBS would be decreasing over time if the uptake rate is increasing.

Furthermore, the calculations of the financial implications assumed patient numbers using prevalence figures for the surgery group and incidence for the medical management group in the current scenario estimates.

Potential usage outside the requested listing

The potential usage outside the requested listing was not discussed in the assessment report. Nor were any other therapies that are likely to be co-administered identified. The critique indicated a potential for the MBS costs to be greater than estimated in the report based on the proposed MBS listing which outlines subsequent removal of the MitraClip in cases when the device has failed. This MBS listing could be used to remove the MitraClip from the valve, increasing the potential cost of overall MitraClip estimates. In the EVEREST II trial, 11% (20/178) of patients who received percutaneous implantation of the MitraClip subsequently underwent mitral valve surgery during 12 months of follow-up (Feldmand et al 2011, p.1401). There is also potential for the treatment of adverse events with PBS medicines and MBS services to be greater than the estimate in the assessment report given that only 30 days of adverse event data were used to inform the economic model in terms of adverse events.

The Assessment report calculated the economic evaluation for the MitraClip and medical management, and MitraClip and repair/surgery.

Results of the economic evaluation (MitraClip vs. Medical management)

Component	MitraClip	Medical management	Increment
Costs	$[redacted]	[redacted]	[redacted]
QALYs	4.04	1.94	2.1
LYG	5.33	3.71	1.62
Incremental cost-effectiveness ratio (cost per QALY)			**$20,382**
Incremental cost-effectiveness ratio (cost per LYG)			**$26,415**

Source: Table D6, p54 of the assessment report

Results of the economic evaluation (MitraClip vs. Repair/ surgery)

Component	MitraClip	Repair / surgery	Increment
Costs	$[redacted]	[redacted]	[redacted]
QALYs	6.83	6.77	0.06
LYG	7.96	7.88	0.08
Incremental cost-effectiveness ratio (cost per QALY)			**$295,993**
Incremental cost-effectiveness ratio (cost per LYG)			**$216,290**

Source: Table D9, p58 of the assessment report

However, as previously noted, the inputs for the economic model could not be verified. Therefore the estimated ICERs are highly uncertain. The increased quality of life gains of MitraClip versus medical management remain highly uncertain due to the appropriateness of the survival data used.

In regards to MitraClip versus surgery, the ICER suggests that MitraClip is not cost-effective (assuming a willingness to pay threshold of $50,000 per QALY). As the EVEREST II trial demonstrated superior efficacy of surgery relative to MitraClip, a cost-utility analysis comparing these interventions is questionable. The mortality rate used in the surgery group was double that of MitraClip group for the first month in the model, which may also be biasing the results in favour of MitraClip.

13. Key issues for MSAC from ESC

Main issues around the proposed eligible population for public funding and/or the proposed main comparator?

ESC discussed the proposed eligible population for MitraClip, including the frequency of use per patient over a lifetime. ESC noted that the EVEREST II trial compared endovascular mitral repair with open mitral valve surgery. Patients had to be candidates for open mitral valve surgery to be eligible to participate in the EVEREST II trial. However, it is proposed that MitraClip be considered for patients who are too ill for open mitral valve surgery, as an alternative to medical management. The applicant has provided the Everest II High Risk Study (Whitlow et al 2012) as evidence to support the use of MitraClip in this second subgroup. ESC recommended that MSAC give due consideration to the applicability of the evidence presented to the populations proposed and the appropriateness of the comparisons made, as the High Risk Study was a single arm study in the trial and the comparisons are based on a retrospectively identified comparator group who were either eligible for inclusion in the High Risk Study but did not enroll or were not anatomically eligible for MitraClip.

Main issues around the evidence and conclusions for safety?

ESC discussed the claim of superior safety of the MitraClip procedure compared to mitral valve surgery. Issues around the evidence of safety included:

- the results were based on one EVEREST II RCT by Feldman et al (2011), with supplementary data from EVEREST I (Whitlow et al 2012) and EVEREST II Roll-In studies; and
- the total major adverse events were:
  - based on 30 days follow up; and
  - included surgical patients receiving a transfusion of two or more units of blood.

ESC discussed as to whether receiving a blood transfusion should be categorised as a major adverse event. ESC noted that if blood transfusion is excluded from the list of major adverse events, percutaneous repair with MitraClip is of similar safety to surgical management.

ESC also questioned the merits of the composite safety measure (total major adverse events) used in the submission to compare safety but also noted the transfusion related pulmonary oedema was a trivial adverse event. ESC noted that there was uncertainty in the data presented around delayed adverse events such as endocarditis and dislodgement of the device over the longer term horizon.

ESC expressed concern at the lack of information in the Assessment Report regarding the rates of failure and/or removal of clips over time. ESC also noted that if patients unsuitable for surgery have the MitraClip procedure, there may be limited options for this patient group should the clips fail.

Main issues around the evidence and conclusions for clinical effectiveness?

The primary clinical effectiveness endpoints were reported in the EVEREST II trial results. The Assessment Report stated the RCT supports the contention that the MitraClip procedure is less effective at reducing MR than conventional mitral valve repair or replacement.

ESC questioned the following aspects of the comparative effectiveness assessment:

- Why the model has a time horizon of 40 years when presumably the majority of patients receiving MitraClip would be aged 60 years and over; and
- The basis for the incremental QALY gains claimed for MitraClip?

ESC suggested that the raw data from the applicant and economic model used to prepare the comparative effectiveness assessment should be provided to MSAC.

Other important clinical issues and areas of clinical uncertainty?

ESC noted inconsistencies between the assessment of comparative effectiveness and the economic evaluation. ESC was concerned this arose from a range of factors including:

- The raw data and the economic model used to prepare the assessment were not provided;
- The model was based on UK figures and updated for the Australian situation;
- It was not clear whether medical management was included in the model; and
- The basis for the QALY gains was not apparent.

Main economic issues and areas of uncertainty?

The total cost of the proposed intervention to the health care system in Year 5 is estimated at $451m. Therefore, the budget impact is likely to be substantial. However, ESC noted that $303.5m of this came from patients who would otherwise receive medical management. ESC was concerned that should the MitraClip fail there may be limited options for these patients as full mitral valve replacement surgery may be required.

ESC queried:

- Why a 40 year time horizon was used in the decision analytic model for fee cost utility analysis; and
- The basis for the modelled QALY gains against each comparator when the EVEREST trial shows similar safety and effectiveness to surgery.

Any other important areas of uncertainty (e.g. budget impact, translation of clinical evidence into the economic evaluation, linkage between an investigative intervention and a subsequent therapeutic intervention and outcomes?

ESC noted the need for a separate item descriptor for the removal of the MitraClip in the event of failure.

14. Other significant factors

Not applicable.

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

MSAC agreed that there was no evidence of MitraClip's safety over surgery. MSAC noted that complications of the MitraClip procedure include leaflet tear.

MSAC agreed that MitraClip is inferior to surgery in terms of effectiveness. Evidence did not demonstrate that MitraClip is as good as surgery for all candidates. However, MitraClip may be beneficial for interventional cardiologists to treat high risk patients.

MSAC agreed that although there is now 3 years of data showing that the trend is maintained in regard to efficacy as MitraClip has been targeted at the same patient group as for surgery and that there needed to be a longer comparison time (5 years +) to demonstrate durability of the procedure.

MSAC discussed where this technology fits in for high risk patients and whether MitraClip treats the underlying cause. It was noted that improvement in a patient's condition following MitraClip insertion can be due to medication and other therapy. Patients with functional

mitral regurgitation can be treated medically, have fluid removed, receive pacing therapy or mitral valve surgery. However, it is uncertain whether mitral valve surgery for functional mitral regurgitation improves patient survival.

MSAC noted that there is not much data for the failure rate of MitraClip. If MitraClip fails or the patient requires further surgery, only 50 to 60 per cent of these patients have mitral valve repair. In comparison, normally 90 per cent of patients requiring surgery for mitral regurgitation would have mitral valve repair.

MSAC noted that MitraClip is very expensive **(redacted)**. Given that it is also inferior to surgery in terms of effectiveness, it is not a cost-effective alternative. This is compounded by the fact that 20 per cent of patients would need a second MitraClip. The number of services expected to be performed per year were uncertain. This made estimations of total usage and MBS expenses very difficult to ascertain.

MSAC noted that although MitraClip has a place amongst high risk patients, there would need to be a high level study performed to address the lack of data. Until this time, there was no evidence to indicate that MitraClip was safer, more effective and more cost-effective than surgery.

16. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of MitraClip, MSAC did not support public funding for the reduction of mitral regurgitation through tissue approximation using transvenous /trans-septal techniques on the basis that there is no evidence to suggest that the procedure is more effective than surgery.

17. Applicant's comments on MSAC's Public Summary Document

Nil

18. Context for decision

This advice was made in accordance with MSAC Terms of Reference.

MSAC is to:

Advise the Minister for Health and Ageing on medical services 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 Ministers' 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 its Executive sub-committee.

19. Linkages to other documents

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