



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1361 – Transcatheter Aortic Valve Implantation (TAVI)

Applicant: Edwards Lifesciences Pty Ltd

Date of MSAC consideration: MSAC 64th Meeting, 30-31 July 2015

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, see at www.msac.gov.au

1. Purpose of application and links to other applications

An application requesting MBS listing of transcatheter aortic valve implantation (TAVI) for use in patients who are symptomatic with severe aortic stenosis and who have been determined to be either a) at high risk for surgical aortic valve replacement or b) are non-operable was received from Edwards Lifesciences Pty Ltd.

MSAC deferred the application in April 2015 and requested that a number of areas of uncertainty in the economic model be addressed. The evidence for assessment of the original application was submitted in October 2014. An updated economic model was submitted on 29 January 2015 and on 15 May 2015. A further revised model was presented with the pre-ESC response on 29 May 2015.

2. MSAC's advice to the Minister

After considering the strength of the available evidence presented in relation to safety, clinical effectiveness and cost-effectiveness of transcatheter aortic valve implantation (TAVI) via transfemoral delivery for patients with symptomatic severe aortic stenosis who are determined to be at high risk for surgical aortic valve replacement (SAVR) or who are inoperable, MSAC again deferred the application to allow the applicant to address the following economic concerns:

- to allow independent evaluation of the multivariate sensitivity analyses to examine the consequences of the various assumptions
- include balloon aortic valvuloplasty, temporary pacing and left/right heart catheterisation in the costings
- consider lower MBS reimbursement for the TAVI procedure and examine its effect on the model outputs
- to allow independent examination of the consequences of varying the cost of the prosthesis in the sensitivity analyses
- provide a cost-minimisation analysis of TAVI (Edwards Sapien) vs. SAVR.

Other concerns raised by MSAC in relation to the proposed clinical setting, and thus might be addressed at a stakeholder meeting, include:

- incorporating a cardiac surgeon in the associated case conferencing service
- avoiding leakage to lower surgical risk patients and to patients where further management is futile
- clearly defining the referral process and appropriate facility for the service.

MSAC considered that the updated information should be provided via ESC.

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

Clinical considerations

MSAC recalled that, at its April 2015 meeting consideration of this application, the clinical effectiveness and safety of TAVI had been accepted, including being similar across different TAVI prostheses, however the cost-effectiveness of TAVI was uncertain. The application was deferred to allow a modified economic model to be re-presented.

MSAC reaffirmed that TAVI is at least non-inferior with a different safety profile compared with SAVR and more effective but less safe in the short-term compared with medical management. MSAC acknowledged that TAVI is a less traumatic intervention when compared with SAVR, is potentially a less resource intensive procedure, and may reduce hospital length of stay.

For these reasons, MSAC sought to encourage further consideration of the application, separating the outstanding matters into those relating to the economic modelling from the other matters which might be facilitated through a stakeholder meeting.

Economic considerations

MSAC noted the following process led up to its re-consideration of the application to address the matters raised in the context of its April 2015 deferral. The re-application provided updated economic models, which had been subjected to a formal assessment with a critique document. The applicant then supplanted the main updated models with another set of revised models with its pre-ESC response. These were not formally critiqued before consideration by ESC or MSAC. In its pre-MSAC response, the applicant expressed its concerns with the re-application process, and asserted its view that many of the issues raised by MSAC for its reconsideration had been resolved or were considered minor by the critique. MSAC did not review each of these issues individually, but instead considered as a whole the complete set of documents generated since its April 2015 consideration.

MSAC agreed that the revised economic models provided with the pre-ESC response addressed some, but not all, of the issues raised in April 2015. The results from the revised model for high surgical risk patients suggested that TAVI was dominant over SAVR, similar to the results from the version of the model considered in April 2015. When survival derived from the 5-year results for the PARTNER cohort B are used, the ICER/QALY compared to medical management for inoperable patients also became dominant, from \$60,584 in the version of the model considered in April 2015.

Figures 1 and 2 below compared the incremental 5-year survival gain between the revised economic models provided with the pre-ESC response (which were not verified independently) and actual 5-year data from the PARTNER trial. MSAC noted that:

- incremental survival from actual data from the PARTNER cohort B and from the model now appeared to be similar when TAVI is compared to medical management for inoperable patients
- both the initially resubmitted and the revised economic models predicted a numerical survival gain in favour of TAVI when compared to SAVR for high surgical risk patients (however actual data from the PARTNER cohort A showed no statistically significant increase in survival after TAVI compared to SAVR, and the Kaplan-Meier curves in Figure 1 appear further apart than the corresponding curves in Figure 1A of Mack et al. Lancet 2015).

However, MSAC remained concerned that the revised economic models were sensitive to some important assumptions, including:

- same ‘other complication’ costs for TAVI and SAVR, noting that the structure of the model does not appear to treat this health state as transitory despite the arguments of the applicant
- cost of TAVI index hospitalisation, noting that ratio of this cost to that of the SAVR index hospitalisation is more favourable to TAVI when using the small but more recent and more current Western Australia dataset than when using the PARTNER trial basis.

MSAC further considered that the inclusion of balloon aortic valvuloplasty, temporary pacing and left/right heart catheterisation as part of the costs of TAVI would also be appropriate.

Other issues which were not addressed or were expected to have consequences for the results of the analysis, and generally tended to bias the results in favour of TAVI were:

- the revised models were not limited to the 5-year PARTNER data, as previously advised by MSAC (noting that sensitivity analyses extrapolating these 5-year models to a 10-year horizon were also still requested as they would be informative, despite some uncertainty regarding the long-term durability of clinical effectiveness)
- stronger justification of assumptions relating to utilities was not provided
- death following stroke or heart failure was modelled with a ‘death inflation factor’ in each case, which had no epidemiological basis
- the single survival probability based on the 5-year PARTNER trial data was applied equally to “no complications” and “other complications” health states.

MSAC considered now resolved the following other issues previously raised:

- the limitation of the Edwards “Sapien” models to the transfemoral route only
- permanent pacemakers were appropriately included in the revised models
- the inflated probability of SAVR complications provided in the initially updated models and removed from the revised models provided with the pre-ESC response.

MSAC noted that the critique had declared some issues “minor”, and the pre-MSAC response had declared some issues resolved, but noted that the critique was in relation to the previous version of the model and that new matters raised in the pre-ESC response and the pre-MSAC had not been independently assessed. MSAC remained concerned about the cumulative effect of favouring TAVI across multiple issues, including minor issues, because this reduces confidence in being able to rely on the results of the models.

Recalling its clinical conclusions relating to each of the modelled comparisons from the PARTNER trial cohorts, MSAC considered the main residual issue was to be able to assess confidently the consequences for the results of both models when all the other modelling assumptions favouring TAVI to a lesser or greater extent are adjusted to remove the biases.

MSAC therefore advised that any future resubmission should present:

- a cost-minimisation analysis for TAVI compared with SAVR reflecting the conclusions of PARTNER cohort A in relation to overall survival, and removing, or more strongly justifying, assumptions previously identified as favouring TAVI for this comparison
- a revised cost-utility analysis comparison of TAVI compared with medical management for inoperable patients, similarly removing, or more strongly justifying, assumptions previously identified as favouring TAVI for this comparison, and also providing a wider set of multivariate analyses of these assumptions
- consider lower MBS reimbursement for the TAVI procedure and examine its effect on the models
- examine the consequences of varying the cost of the prosthesis in the sensitivity analyses
- fully executable economic models to allow further multivariate sensitivity analyses.

MSAC noted the concern expressed by the Health Economic Subcommittee of PLAC about the high cost of the TAVI prostheses compared to benchmark valves already included in the Prostheses List. MSAC also considered that, given that the procedure time of TAVI is approximately half the time of SAVR, the MBS cost of the service to implant the TAVI prosthesis should be negotiated.

Other considerations

MSAC noted that, although more appropriately generated ICERs would likely be different across the two populations with their different comparators, it would not be possible to support the funding of one population but not the other, because it would not be possible to define the two populations in such a way as to avoid leakage of TAVI from one population to the other.

Similarly, MSAC expressed concern that the funded use of TAVI may extend beyond the proposed populations, to include both patients undergoing lower-risk surgery (rather than the intended limitation to high-risk surgery) and patients for whom further intervention might be futile (rather than the intended limitation to inoperable patients still likely to benefit). Again, it would be difficult to define the two populations in such a way as to avoid leakage of TAVI to these other patient groups.

In this regard, MSAC noted that comments were provided by cardiac surgeons with respect to changes in the descriptor and referral process. The comments highlighted the high risk of leakage and potential implementation issues, particularly the risk of uptake by poorly credentialed providers and/or centres leading to adverse patient outcomes. MSAC was concerned that attempting to address this gatekeeper issue through specifications in item descriptors is likely to be less influential on patient selection than the setting and composition of clinician teams. MSAC considered this gatekeeper role applied particularly in selecting between referred patients, but also deciding which patients to refer, noting several views provided to the Committee that referrals for TAVI consideration should be restricted to written referrals from cardiac surgeons. There could be greater confidence in appropriate patient selection if use of TAVI in Australia was to be through a relatively small number of centres with appropriate expertise and experience rather than if it were to disseminate more widely where important checks and balances may not be so well maintained.

MSAC therefore advised that any future resubmission should present:

- a proposal to avoid leakage of TAVI to low surgical risk patients or to patients for whom further intervention would be futile
- consideration of including a cardiac surgeon in the associated case conferencing service.

MSAC also advised that a possible way forward to deal with these other matters would be to meet with relevant stakeholders. A stakeholder meeting could assist to:

- refine the patient selection criteria
- clearly define the two patient populations, i.e. the high surgical risk group and the inoperable group
- clearly define the referral process for TAVI
- clearly identify the composition of the case conferencing team which would determine which of the referred patients would be suitable for TAVI according to the patient selection criteria
- identify the type of institution and operators (the 'Heart Team') who would be able to perform TAVI
- identify any possible post-implementation issues
- craft a proposed MBS item descriptor reflecting the outcomes of the stakeholder meeting.

4. Background

In April 2015, MSAC noted that, overall, most of the assumptions in the economic model presented were biased in favour of TAVI. MSAC deferred the application to allow the applicant to re-present its economic model. The updated economic model would need to address the concerns raised by the critique and ESC, and would also need particular emphasis on the following:

- incorporate the recently published 5-year PARTNER trial data
- incorporate rehospitalisation appropriately in the estimate of costs in the economic model
- decrease the initial hospitalisation cost difference (compared with SAVR) in the economic model to reflect the current length of stays for TAVI and SAVR
- provide stronger justification for assumptions relating to utilities
- perform multivariate sensitivity analyses as well as univariate sensitivity analyses
- consider using the most recently updated data from the Medtronic CoreValve trial to also inform the economic evaluation, at least in a sensitivity analysis
- the economic model should examine transfemoral delivery only (not transapical) with a separate ICER comparing TAVI to only SAVR or only medical management.

MSAC considered that the updated economic model should be made via ESC, accompanied by a contracted critique of the resubmission.

The applicant provided an updated economic model which was critiqued as part of the resubmission process.

5. Comparative safety

The applicant was not asked to address any specific concerns regarding the safety of TAVI compared to either SAVR or medical management. However, in its April 2015 advice on this application, MSAC considered that the 5-year results for the PARTNER trial did not identify any new safety concerns, and suggested that some early safety concerns, such as stroke, did not increase over time.

The critique of the resubmission indicated that published results of the 5-year follow up of the PARTNER (Cohort A) trial confirmed the differences in the safety profile against SAVR.

6. Comparative effectiveness

The applicant was not asked to address any specific concerns regarding the clinical effectiveness of TAVI compared to either SAVR or medical management.

7. Economic evaluation

The resubmission provided an updated model based on that used for the original submission. The results presented appropriately only considered the transfemoral (TF) approach for TAVI.

For high surgical risk patients, the resubmission claimed that, compared with SAVR, TAVI-TF is cost saving and overall survival at 5 years is approximately equivalent.

For inoperable patients, the resubmission claimed that, compared with medical management, TAVI-TF is associated with significant increases in overall survival at 5 years and an acceptable ICER.

To address issues raised in the critique, the results of a further revised model were presented in the pre-ESC response using the 5-year mortality rates from the PARTNER long-term follow-up (Mack et al. 2015) and updated complication rates. The modelled results were over a 10-year horizon. There was no formal independent critique of this further revised model.

Results of the further revised modelled economic evaluation

| | TAVI | Comparator | Increment |
|---|----------|------------|----------------------|
| High surgical risk patients: TAVI-TF vs. SAVR | | | |
| Costs | \$87,071 | \$88,804 | -\$1,733 |
| QALYs | 3.04 | 2.87 | 0.17 |
| Incremental cost/extra QALY gained | | | TAVI dominant |
| | TAVI | Comparator | Increment |
| Inoperable patients: TAVI-TF vs. medical management | | | |
| Costs | \$87,708 | \$94,262 | -\$6,553 |
| QALYs | 2.46 | 1.12 | 1.34 |
| Incremental cost/extra QALY gained | | | TAVI dominant |
| High surgical risk patients: TAVI-TF (Medtronic CoreValve) vs. SAVR* | | | |
| Costs | \$89,241 | \$93,757 | -\$4,516 |
| QALYs | 1.426 | 1.18 | 0.23 |
| Incremental cost/extra QALY gained | | | TAVI dominant |

* This model for this analysis was not further revised for the pre-ESC response.

The applicant's pre-ESC response also provided mortality outcomes from the model at five years in line with the request to allow validation against results of the 5-year follow up of the PARTNER trial. Figure 1 below presents the derived Markov traces for TAVI-TF vs. SAVR superimposed on the Kaplan-Meier plots from PARTNER cohort A. Figure 2 below presents the derived Markov traces for TAVI-TF vs. medical management superimposed on the Kaplan-Meier plots from PARTNER cohort B. The applicant noted that Australian mortality rates would better represent the current outcomes for the proposed patient populations.

Figure 1: Modelled mortality TAVI-TF vs. SAVR in high surgical risk patients

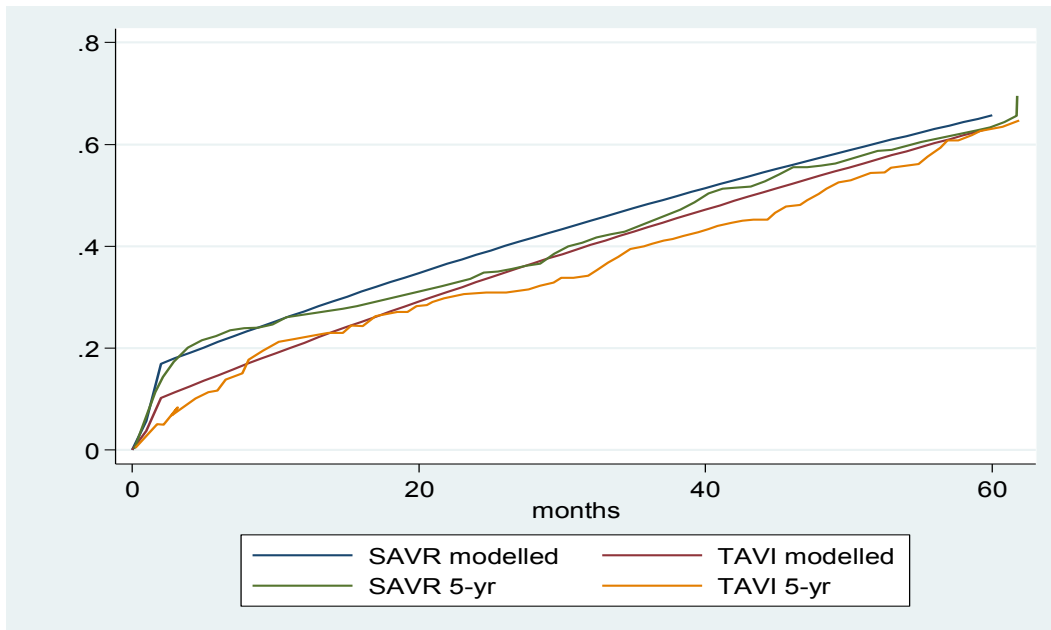
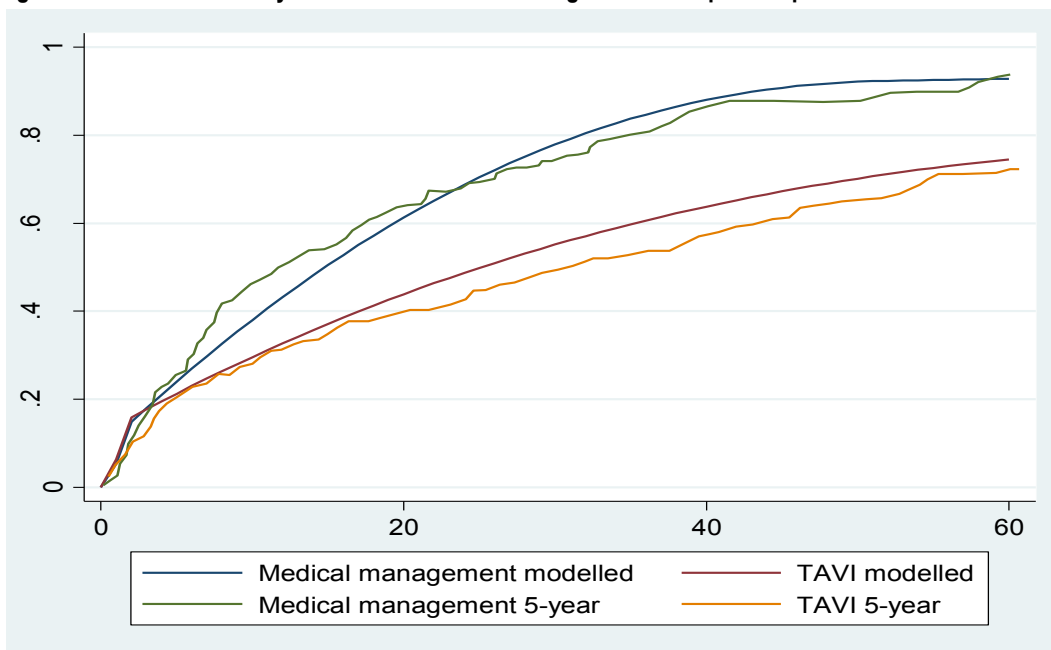


Figure 2: Modelled mortality TAVI-TF vs. medical management in inoperable patients



8. Financial/budgetary impacts

The resubmission did not provide updated costs or net financial implications to the MBS that aligned with related changes to the economic model.

9. Key issues from ESC for MSAC

ESC noted that the application had been deferred by MSAC with a request for the applicant to address a range of specific issues, ahead of consideration by ESC. ESC noted that neither MSAC nor the department had imposed a deadline on the revised analysis.

ESC noted that the model structure remained unchanged and may be inappropriate. ESC considered that MSAC's requests regarding the economic analysis had not been addressed adequately and that the projected numbers of hospitalisations were likely an underestimate.

10. Other significant factors

Nil.

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

The applicant appreciates the further consideration by MSAC of the proposed listing of transcatheter aortic valve implantation (TAVI) on the MBS. Edwards Lifesciences has concerns that some of the information that was provided previously on multiple occasions, does not appear to have been considered. Information which appears to be overlooked includes: 1) the joint position statement from the Cardiac Society of Australia and New Zealand and the Australian & New Zealand Society of Cardiac & Thoracic Surgeons which provides clear guidance on "operator and institutional requirements", and 2) the detailed economic analysis provided with the model. The applicant emphasizes that based on the clinical evidence and economic evaluation, TAVI via transfemoral approach was shown to improve health outcomes and result in cost-savings compared with SAVR, even over the requested shorter 5-year period. Reducing the proposed MBS item fee and/or the price of the device will lead to further cost-savings compared with both SAVR and medical management. The request for a cost-minimisation analysis against SAVR is poorly understood as this information can be read directly from the cost-utility analysis. The applicant acknowledges that the costs for balloon valvuloplasty and temporary pacing should be included in the cost of the TAVI procedure and anticipates these costs will have a relatively small effect on the results. These requests for the provision of relatively minor amendments may severely delay the introduction of TAVI. Finally, the applicant is highly supportive of the stakeholder meeting planned for 30/10/2015 and looks forward to the outcome.

12. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website at: www.msac.gov.au.