



**Australian Government**  

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**Medical Services Advisory Committee**

## **Public Summary Document**

### ***Application No. 1483 - Micro-bypass stenting for open-angle glaucoma (in trabecular meshwork)***

**Applicant:** Glaukos Australia Pty Ltd

**Date of MSAC consideration:** MSAC 71<sup>st</sup> Meeting, 23 November 2017

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

#### **1. Purpose of application**

An application requesting a new Medical Benefits Schedule (MBS) item for expanded access by ophthalmologists to MBS listings of trabecular bypass micro-invasive glaucoma surgery (TB MIGS) stent implantation for open-angle glaucoma (OAG) was received from Glaukos Australia.

#### **2. MSAC's advice to the Minister**

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost effectiveness, MSAC supported the inclusion in the MBS of TB-MIGS stent implantation for patients with OAG who are also undergoing cataract surgery. MSAC accepted that TB-MIGS stent implantation was similar to suprachoroidal micro-invasive glaucoma surgery (SC-MIGS) stent implantation in this population and suggested both services be covered by a single generic MBS item at a fee of \$911.10.

MSAC did not support listing of TB-MIGS as a stand-alone procedure due to insufficient evidence of effectiveness and because the population who would be eligible for the service could not be adequately defined.

For cases where there is failure of the original stent placement, MSAC suggested a single MBS item with a fee of \$300.75 for stent removal regardless of whether it is undertaken with or without stent replacement.

MSAC recommended that usage of MIGS be revisited in 12 months to assess whether it is being used as intended.

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

MSAC noted that there are three different TB-MIGS devices being considered: the iStent, the iStent Inject and the Hydrus Microstent. The iStent Inject system implants two stents in the one eye as part of the same procedure. The iStent system implants one stent per procedure but

may be used once or twice per eye. The Hydrus Microstent implants one stent per eye. The stents are implanted from inside the eye via a corneal incision using an inserter specific to each device.

MSAC noted that a similar application using a stent implanted with one end in the anterior chamber of the eye and the other in the suprachoroidal space (SC-MIGS) - [Application 1496: Micro-bypass stenting for open angle glaucoma \(external to Schlemm's canal\)](#) - is also under consideration at the November 2017 MSAC meeting.

MSAC noted that despite never having been assessed for safety, clinical effectiveness and cost effectiveness, TB-MIGS had been performed under MBS item 42758 (goniotomy) until this use was explicitly prohibited in May 2017. MSAC noted that since then, implantation of MIGS stents has been allowed to continue under an interim MBS item (42705).

MSAC noted that there are two patient populations being considered:

- patients with diagnosed OAG undergoing TB-MIGS stent implantation in conjunction with cataract surgery (population 1). The comparators for this population are cataract surgery alone and cataract surgery in conjunction with SC-MIGS; and
- patients with diagnosed OAG undergoing TB-MIGS stent implantation as a standalone procedure (population 2). These patients may have had no history of cataracts and still have their natural lens or have previously had cataract surgery and have an artificial lens. The comparators for this population are standard of care, laser trabeculoplasty, trabeculectomy and implantation of SC-MIGS stents.

MSAC noted that the evidence for population 1 relied upon four randomised controlled trials considered to be at moderate to high risk of bias (Craven ER et al 2012; Fea AM et al 2010/2015; Fernandez-Barrientos Y et al 2010; Pfeiffer N et al 2015).

MSAC noted that TB-MIGS stent implantation in population 1 had a similar safety profile to cataract surgery alone. MSAC noted that, where reported, there was a similar number of intra-operative or post-operative complications in the TB-MIGS and cataract surgery arm (16.7–40.0%) and in the cataract surgery only arm (0–47.9%). MSAC noted there were also similar numbers of secondary surgical interventions: 2.1–4.3% for TB-MIGS and cataract surgery vs 4.4–5.9% for cataract surgery alone.

MSAC noted that in the pooled analysis of studies which employed a glaucoma medicines wash-out period, the mean reduction in IOP was 0.68 mmHg greater (95% confidence interval [CI] -1.34, -0.02) in the TB-MIGS arm than in the cataract surgery alone arm at 12 months. MSAC also noted that the TB-MIGS and cataract surgery patients were using an average of 0.44 fewer glaucoma medicines (95% CI: -0.62, -0.26) after 12 months than those receiving cataract surgery alone. MSAC noted that queries about whether such changes constituted a minimal clinically important difference (MCID) had been raised in the critique.

MSAC noted that because the longest period of follow-up in the population 1 studies was 48 months, the long-term effectiveness of the procedure, including its impact upon disease progression and avoidance of laser trabeculoplasty or trabeculectomy, remained uncertain. Despite these reservations, MSAC agreed that there was fair evidence that TB-MIGS stent implantation in conjunction with cataract surgery was safe and effective when compared to cataract surgery alone.

MSAC accepted that outcomes using TB-MIGS or SC-MIGS in population 1 were likely to be similar. MSAC noted that when TB-MIGS was indirectly compared with SC-MIGS using cataract surgery alone as the common comparator, there were no significant differences in adverse events, mean change in IOP, reduction in medicine use from baseline and proportion of patients no longer requiring medicines.

MSAC noted that there was no evidence that using two stents instead of one in population 1 improved outcomes. MSAC noted that no study had randomised patients to implantation of either one or two stents in population 1. The only study which compared the impact of one stent against two stents was conducted in the standalone population (population 2; Katz LJ et al 2015). MSAC considered that it was not reasonable to assume that evidence from the standalone population could be applied to implantation of TB-MIGS stents in conjunction with cataract surgery.

MSAC noted that the economic modelling comparing TB-MIGS stent implantation plus cataract surgery with cataract surgery alone (population 1) resulted in a base case ICER of approximately \$redacted per QALY. However, MSAC queried the robustness of this finding given that reducing the time horizon from 15 years in the base case to 5 years increased the ICER to approximately \$redacted. MSAC conceded that some increase in the ICER would be expected with a reduced time horizon given the costs of the surgery are all up front, but the magnitude of the increase raised doubts regarding the strength of the model assumptions.

MSAC noted that there was considerable uncertainty with regards to the financial estimates of the introduction of TB-MIGS. MSAC noted the use of TB-MIGS in population 1 had the potential to be cost saving to the MBS if it reduces or delays surgery (laser trabeculoplasty or trabeculectomy). MSAC noted that it may also reduce PBS expenditure on medicines to treat raised IOP. MSAC noted that the various stent devices are already listed on the Prostheses List.

MSAC did not support the use of TB-MIGS in population 2 due to insufficient evidence of effectiveness against the various comparators and because the population which would be eligible for the service could not be adequately defined. MSAC noted that there was no evidence to compare standalone TB-MIGS implantation to trabeculectomy. MSAC noted that while there was some evidence comparing TB-MIGS with standard of care (continued use of glaucoma medicines) and indirect evidence to compare TB-MIGS with laser trabeculoplasty, it relied upon two randomised trials considered to be at high risk of bias. MSAC also noted that one of these studies was conducted in treatment-naïve patients and such a use was inconsistent with the proposed use of TB-MIGS in the Australian setting.

MSAC considered that insertion of a TB-MIGS stent or a SC-MIGS stent in conjunction with cataract surgery should be covered by a single generic MBS item. MSAC agreed that a fee of \$911.10 was reasonable - this was arrived at by bundling the fee for the interim MBS item 42705 (\$760.65) with 50% of the fee for in-hospital MBS eye injections (to account for the multiple services rule; MBS items 42738–40 \$300.75). MSAC noted a single MBS item for MIGS implantation and cataract surgery would prevent the use of the item for standalone MIGS implantation and limit MBS reimbursement of the procedure to once per eye per lifetime.

MSAC noted MIGS stents were not expected to be used as first-line treatment of glaucoma but that it would be difficult to tighten the wording of the item descriptor to preclude this use. MSAC noted that there is no agreed IOP threshold for undertaking treatment and many patients fail to fully adhere to topical anti-glaucoma medicines making it difficult to define what constitutes non-response to, or intolerance of, these medicines. MSAC noted that clinicians are likely to make treatment decisions based upon individual patient characteristics and the presence or absence of visual deterioration. MSAC noted that restricting use of MIGS to people undergoing cataract surgery would limit first-line use to some extent.

MSAC suggested a single MBS item for stent removal with an associated fee of \$300.75 regardless of whether it is undertaken with or without stent replacement. MSAC noted that this fee is equivalent to the fee for in-hospital eye injections (MBS items 42738–40).

MSAC acknowledged that while there may still be out-of-pocket costs for consumers using the service, this was largely outside the Committee’s control.

MSAC noted that the various stent devices were already listed on the Prostheses List. MSAC noted that given the lack of evidence that using two stents rather than one provides any additional benefit with regards to reducing IOP or medicines use, the Prostheses List Advisory Committee (PLAC) should be advised that the price of each stent device should be similar.

MSAC recommended that usage of MIGS be revisited in 12 months, under the Predicted vs Actual monitoring process, to assess whether it is being used as intended.

#### 4. Background

MSAC has not previously considered this application.

Trabecular bypass MIGS stent implantation has been performed in Australia for the last 3–4 years, and billed under MBS item 42758 (goniotomy). MBS item 42758 was not intended to cover implantation of MIGS stents, and the procedure had not been assessed for safety, clinical effectiveness and cost effectiveness. An amendment explicitly excluding implantation of MIGS drainage devices under MBS item 42758 (goniotomy) took effect on 1 May 2017.

A new interim MBS item 42705 was listed for the insertion of MIGS devices when performed in conjunction with cataract surgery, sunsetting on 31 December 2018.

#### 5. Prerequisites to implementation of any funding advice

The devices are all ARTG listed and on the Prostheses List for the proposed purpose.

#### 6. Proposal for public funding

In the pre-ESC response, the applicant proposed an updated MBS item descriptor which removes the distinction between the cataract and stand-alone procedures and positions any TB MIGS procedure as second-line to topical hypotensive treatment, regardless of whether cataract (or other intraocular) surgery is to be performed (changes are marked in Table 1).

**Table 1 Applicant proposed changes to the MBS item descriptor to remove the distinction between the cataract and standalone settings**

Category 3 – THERAPEUTIC PROCEDURES	
<p>MBS item number            GLAUCOMA, implantation of, a micro-invasive glaucoma surgery stent system into the trabecular meshwork, in patients diagnosed with open-angle glaucoma. <del>Can be delivered as a stand alone procedure or in combination with cataract surgery</del>  <del>When delivered in conjunction with cataract surgery or other intraocular surgery, †</del>The patient must be currently treated with ocular hypotensive medication, have previously been treated with ocular hypotensive medication, or be contraindicated to ocular hypotensive medication  <del>When delivered as a stand alone procedure, other therapies must have failed, be likely to fail, or be contraindicated.</del>            (Anaes)            Multiple Services Rule  <b>Fee:</b> \$699.45     <b>Benefit:</b> 75% = \$524.60</p>	
<p>MBS item number            GLAUCOMA, removal or replacement of, a micro-invasive glaucoma surgery stent system from the trabecular meshwork.            Multiple Services Rule  <b>Fee:</b> \$699.45     <b>Benefit:</b> 75% = \$524.60</p>	

Includes the addition of Anaes as recommended in the critique (page 33)

## **7. Summary of Public Consultation Feedback/Consumer Issues**

The department received four responses from public consultation from Professional Bodies.

All stakeholders who provided feedback saw micro-invasive glaucoma surgery (MIGS) devices as a quick, safe and effective way of managing glaucoma, and all were confident about the cost-effectiveness of the procedure. They believe these devices may reduce the need for more expensive and potentially higher-risk surgical approaches for lowering intraocular pressure (e.g. trabeculectomy, laser trabeculoplasty, filtering surgeries), as well as reducing the need for (and expense of) ongoing topical hypotensive medication.

However, several points arose from consultation in regard to the proposed fee. One ophthalmologist was of the view that the proposed MBS fee, which is identical to the Medicare Benefits Schedule (MBS) fee for goniotomy item 42758 (\$699.45), is possibly higher than this procedure might justify. They did not agree with the proposed time estimate of 30-60 minutes for the procedure, and estimated that it could take less than 15 minutes of the surgeon's time in the operating theatre (even less if combined with cataract surgery).

Two Professional bodies agreed with the proposed fee, stating that it is reasonable, although the fee is considerably lower than in other developed countries.

One professional body advised that *“the time requirement for insertion of MIGS devices is approximately 15-20 minutes in total, and that it is a simple procedure, when performed within the same operation as cataract surgery. The applicant is also of the view that the procedure requires at least 15 minutes of operating time when performed in conjunction with cataract surgery”*.

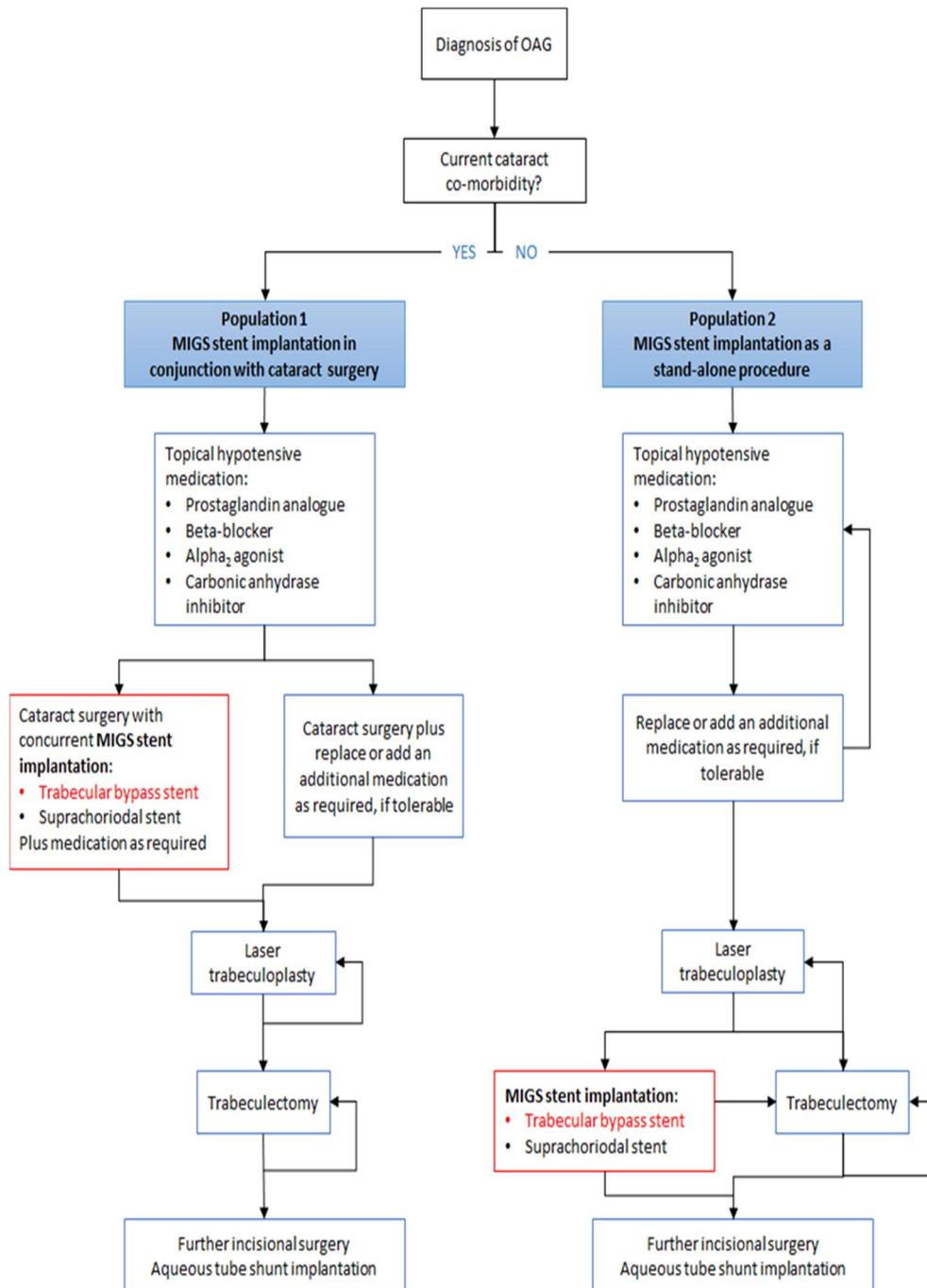
## **8. Proposed intervention's place in clinical management**

Glaucoma is a chronic degenerative optic neuropathy in which the neuro-retinal rim of the optic nerve becomes progressively thinner, caused by an acquired loss of retinal ganglion cell axons and atrophy of the optic nerve. In open-angle glaucoma aqueous outflow is diminished, leading to an elevation of IOP. Patients with glaucoma typically lose peripheral vision, and may suffer complete vision loss if not treated.

A trabecular micro-bypass stent is a micro-invasive glaucoma surgery device used to treat patients with mild-to-moderate primary open-angle glaucoma (POAG). The device improves aqueous outflow through the natural physiologic pathway, the trabecular meshwork, thereby lowering intra-ocular pressure (IOP) and dependence on pressure-lowering topical medication. The procedure is generally performed as a day-stay procedure in an ophthalmology surgical setting, as a stand-alone treatment or in conjunction with cataract surgery.

The clinical management algorithm depicting the intended use of TB MIGS stent implantation in each of the requested patient populations is provided in Figure 1.

**Figure 1 Clinical management algorithm for trabecular bypass MIGS stent implantation in each requested patient population, as it fits into the current treatment algorithm**



The application stated that the clinical management algorithm presented in the PICO Confirmation positions the stand-alone use of TB MIGS after conservative therapies have failed. However, that it is not necessarily the case that TB MIGS as a standalone procedure could not be positioned earlier in the algorithm (as per the positioning when conducted alongside cataract surgery).

The application claimed that as a standalone procedure, the incremental costs (and potentially incremental safety concerns) will be greater than when conducted in the cataract setting. Equally, the incremental effectiveness of MIGS may be improved in the standalone setting because patients are receiving the intervention at a point in their glaucoma treatment history when it is more likely to be clinically indicated (and the effect of the cataract surgery itself on IOP is not applicable).

## **9. Comparator**

### **MIGS stent implantation in combination with cataract surgery**

The comparator to MIGS stent implantation for patients with OAG undergoing concurrent cataract surgery is cataract surgery with medical management of IOP with ocular hypotensive drugs (standard of care, SOC).

The ratified PICO Confirmation also nominates a secondary comparator for this patient population: MIGS stent implantation with a suprachoroidal stent device (also being assessed by MSAC, Application 1496). An indirect comparison is provided to inform this comparison.

There are three TB MIGS stent devices relevant to the current application. Where available, evidence for the safety and effectiveness of each device individually, with concurrent cataract surgery, versus cataract surgery alone, is also presented.

### **MIGS stent implantation as a stand-alone procedure**

Two comparators are presented for this patient population:

- TB MIGS stent implantation as a stand-alone procedure versus continued standard of care (i.e. topical hypotensive medication); and
- TB MIGS stent implantation as a stand-alone procedure versus trabeculectomy.

As with population 1, the ratified PICO Confirmation also nominated MIGS stent implantation with a suprachoroidal stent device as a relevant comparator in this population. No data are available to inform this comparison. The relative effectiveness of these procedures is established via the indirect comparison presented for Population 1.

## **10. Comparative safety**

### **TB MIGS stent implantation with concurrent cataract surgery**

The application stated that the safety outcomes reported, suggest a lower but comparable rate of intraoperative and post-operative complications, and secondary surgical events, associated with TB MIGS stent implantation with concurrent cataract surgery, compared to cataract surgery alone. The nature of the adverse events reported were consistent with ocular surgery, were generally transient in nature, and did not result in any long-term visual defects. These results are consistent with safety outcomes reported in clinical practice, where implantation of TB MIGS stent devices is associated with a very low incidence of intra- and post-operative adverse events.

An indirect comparison between TB MIGS stent implantation and SC MIGS stent implantation, each in combination with cataract surgery (via cataract surgery alone) was presented. There are key differences in design and enrolment criteria of the study informing the safety and effectiveness of SC MIGS stent implantation in conjunction with cataract surgery, which limits comparability with TB MIGS stent trials. The incidence of intraoperative and post-operative complications, and secondary surgical interventions, were numerically lower for patients implanted with a TB MIGS stent device compared to a SC MIGS stent device. Neither result was statistically significant.

Data reported in nine non-randomised studies supported the trend observed, towards a lower incidence of intra-/post-operative complications and secondary surgical interventions in patients implanted with a TB MIGS stent device.

## **TB MIGS stent implantation as a stand-alone procedure**

The application stated that the data showed the safety profile for TB MIGS stent implantation when implanted as a stand-alone procedure to be mild and generally consistent with ocular surgery. No secondary surgical interventions for glaucoma treatment were observed in either included trial. In comparison to topical hypotensive medication, subjects undergoing TB MIGS stent implantation experience a different adverse event profile, but the overall rate of surgical complications is low.

Compared to medical therapy, trabeculectomy is associated with a higher rate of surgical complications requiring additional treatment – including shallow/flat anterior chamber and hyphaema.

The application claimed that on the basis of the data presented, TB MIGS stent implantation is likely to be superior to trabeculectomy in terms of relative safety.

In its pre-MSAC response, the applicant stated that the proportion of MIGS devices that would require removal or replacement is considered minimal. Based on data from two years of follow-up (Craven et al, 2012; Table 1), the proportion of patients requiring stent removal/replacement and re-positioning was low (0.9% and 2.6%, respectively). Patients experiencing stent malposition and obstruction over 24 months of follow-up was <5%, all of which (except for one) occurred within 30 days postoperatively and resolved after paracentesis, neodymium: YAG laser, stent repositioning, or stent replacement. In one eye, the stent obstruction was deemed mild and did not require intervention.

## **11. Comparative effectiveness**

### **TB MIGS stent implantation in conjunction with cataract surgery**

Patients assigned TB MIGS stent implantation in conjunction with cataract surgery experienced a greater mean reduction in IOP (mmHg) from a medicated baseline to 12 and 24 months, compared to patients assigned cataract surgery alone. The weighted mean difference between treatment groups at both the 12 and 24 months' time points was statistically significant ( $p=0.04$ , and  $p=0.008$ , respectively). Patients in the combined TB MIGS stent/cataract surgery group were also more likely to achieve a IOP reduction of  $\geq 20\%$  from baseline at 12 months follow-up ( $p=0.003$ ). The mean difference in the number of ocular medications was significantly greater for subjects who underwent TB MIGS stent implantation in conjunction with cataract surgery at 12 and 24 months follow-up ( $p < 0.00001$  and  $p=0.03$ , respectively).

An indirect comparison of two MIGS stent devices, TB and SC stents, when implanted in combination with cataract surgery was also presented. There are key differences in design and enrolment criteria of the study informing the safety and effectiveness of SC MIGS stent implantation, which limits comparability of the trials. However, based on the evidence available, no significant difference between TB MIGS stent implantation and SC MIGS stent implantation, when performed in combination with cataract surgery, was found for the efficacy outcomes presented.

### **TB MIGS stent implantation as a stand-alone procedure**

TB MIGS stents implantation as a stand-alone procedure is associated with a significant reduction in IOP from baseline, which is maintained through 36 months of follow-up. Further, the vast majority of subjects (~90%) required no further glaucoma treatment to control IOP over this period. Subjects assigned to topical hypotensive medication alone achieve a lesser but comparable mean reduction in IOP from baseline through 36 months

follow-up. However, a greater proportion of these patients require additional medical therapy to maintain IOP at or below target. These data suggest TB MIGS stent implantation as a stand-alone procedure is at least as effective as topical hypotensive medication in reducing IOP from baseline in patients who are inadequately controlled on one hypotensive medication.

For many patients, implantation of a TB MIGS stent device as a stand-alone procedure will delay or avoid the need for filtering surgery, such as trabeculectomy. An incomparable evidence base precludes any formal comparison of efficacy outcomes for TB MIGS stent implantation versus trabeculectomy. Efficacy outcomes for trabeculectomy versus medical therapy show trabeculectomy to be associated with a significantly greater mean reduction in IOP from baseline compared to medical therapy. On the basis of this single outcome, trabeculectomy is likely to be superior to both topical medication and TB MIGS stent implantation in terms of comparative effectiveness. However, it should be noted that the clinical benefit of TB MIGS stent devices may not be limited to their effect on IOP.

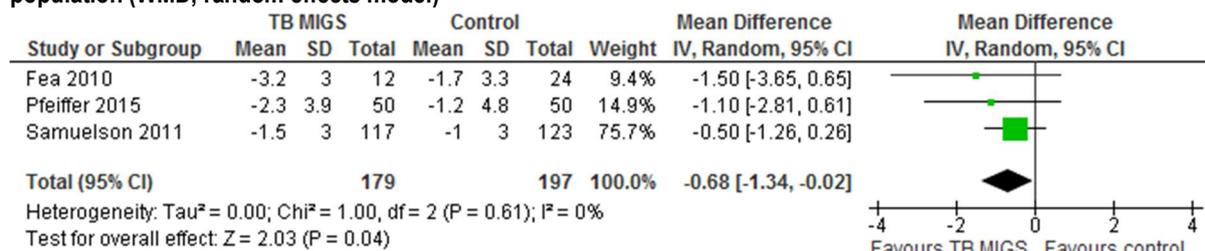
Meta-analyses of key safety and efficacy outcomes for each of the patient populations expected to access TB MIGS stent implantation in practice are shown in Table 2, Figures 2 and 3 (Population 1), and Table 3, Figure 4 (Population 2).

**Table 2 Balance of clinical benefits and harms of TB MIGS stent implantation with concurrent cataract surgery, relative to cataract surgery alone**

Outcomes (units) Follow-up	Participants (studies)	Quality of evidence (GRADE) a	Relative effect OR (95%CI)	Risk or risk difference RD (95%CI), or WMD (95%CI)	Comments
Mean change in IOP from medicated pre-washout baseline 12 months	3 RCTs N=376	Moderate	-	WMD: -0.68 [-1.34, -0.02] p=0.04	Result significantly favours TB MIGS arm. Supports efficacy of TB MIGS + CS is superior to CS alone
Mean change in ocular medication from baseline 12 months	4 studies N=375	Moderate	-	WMD: -0.44 [-0.62, -0.26] p < 0.00001	Result significantly favours TB MIGS arm. Supports efficacy of TB MIGS + CS is superior to CS alone
Proportion of patients with an IOP reduction $\geq$ 20% from baseline 12 months	2 RCTs N=340	Moderate	2.04 [1.27, 3.26] p=0.003	RD: 0.14 [0.04, 0.23] p=0.007	Result significantly favours TB MIGS arm. Supports efficacy of TB MIGS + CS is superior to CS alone
Proportion of subjects with any intraoperative or post-operative complication 15/24 months	3 RCTs N=369	Moderate	0.94 [0.48, 1.81] p=0.84	RD: -0.00 [-0.14, 0.13] p=0.97	Numerically favours TB MIGS Supports safety of TB MIGS + CS is non-inferior to CS alone
Proportion of subjects with secondary surgical intervention 24 months	2 RCTs N=330	Moderate	0.77 [0.46, 1.29] p=0.33	RD: -0.03 [-0.09, 0.03] p=0.35	Numerically favours TB MIGS Supports safety of TB MIGS + CS is non-inferior to CS alone

Abbreviations: RD, risk difference; OR, odds ratio; TB MIGS, trabecular bypass micro-invasive glaucoma surgery; WMD, weighted mean difference

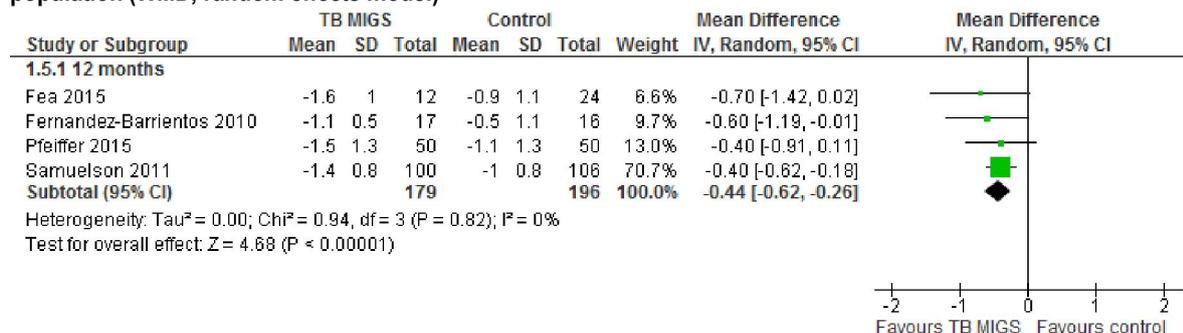
**Figure 2 Forest plot: Mean change in IOP (mmHg) from baseline (medicated pre-washout) to 12 months – Cataract population (WMD, random effects model)**



Source: RevMan v5.0 <Analysis of Outcomes\_TB MIGS.rm5>

Abbreviations: CI, confidence interval; IOP, intraocular pressure; SD, standard deviation; TB MIGS, trabecular bypass micro-invasive glaucoma surgery; WMD, weighted mean difference

**Figure 3 Forest plot: Mean change in ocular hypotensive medication from baseline to 12 months – Cataract population (WMD, random effects model)**



Abbreviations: CI, confidence interval; IOP, intraocular pressure; SD, standard deviation; TB MIGS, trabecular bypass micro-invasive glaucoma surgery; WMD, weighted mean difference

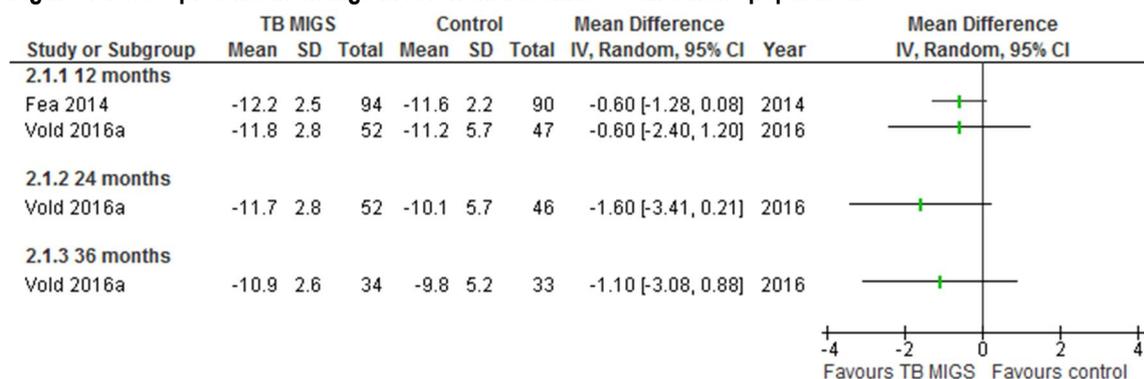
**Table 3 Balance of clinical benefits and harms of TB MIGS stent implantation as a stand-alone procedure, relative to additional topical medication in patients inadequately controlled on one medication**

Outcomes (units) Follow-up	Participants (studies)	Quality of evidence (GRADE) a	Relative effect OR (95%CI)	Risk or risk difference RD (95%CI), or WMD (95%CI)	Comments
Mean change in IOP from unmedicated post-washout baseline 12 months	1 RCT N=192	Moderate	-	WMD: -0.60 [-1.28, 0.08] p=0.08	Result numerically favours TB MIGS arm. Supports efficacy of TB MIGS is non-inferior to topical medication
Proportion of patients with an IOP reduction ≥ 20% from baseline 12 months	1 RCT N=192	Moderate	2.02 [0.66, 6.16] p=0.21	RD 0.05 [-0.03, 0.12] p=0.20	Result numerically favours TB MIGS arm. Supports efficacy of TB MIGS is non-inferior to topical medication
Proportion of subjects with any intraoperative or post-operative complication 15/24 months	1 RCT N=192	Moderate	1.58 [0.26, 9.96] p=0.62	RD: 0.01 [-0.03, 0.06] p=0.62	Numerically favours topical medication Supports safety of TB MIGS is non-inferior to topical medication

Abbreviations: RD, risk difference; OR, odds ratio; TB MIGS, trabecular bypass micro-invasive glaucoma surgery; WMD, weighted mean difference

Note: Results for the study Vold 2016a are not included in this summary table, as the patient population was naïve to glaucoma treatment at the time of enrolment, and is therefore not directly applicable to population 2

**Figure 4 Forest plot: Mean change in IOP from baseline – Stand-alone population**



## Clinical Claim

### Population 1 – Trabecular bypass MIGS stent implantation in conjunction with cataract surgery

#### TB MIGS with concurrent cataract surgery vs cataract surgery only

The application clinical claim for TB MIGS stent implantation in conjunction with cataract surgery is superior comparative effectiveness and non-inferior comparative safety versus cataract surgery alone.

#### TB MIGS with concurrent cataract surgery vs SC MIGS with concurrent cataract surgery

The application stated that due to key differences in the evidence base, no formal clinical conclusions could be drawn regarding the comparative safety and effectiveness of TB MIGS stent implantation, and SC MIGS stent implantation, when performed in conjunction with cataract surgery. With this in mind, relative to SC MIGS, TB MIGS stent implantation is likely to be non-inferior in terms of safety with a trend towards lower intraoperative and post-operative complications, and secondary glaucoma surgical interventions, and non-inferior in terms of relative effectiveness.

#### Comparison of alternative TB MIGS stents

The application clinical claim for each available TB MIGS stent device, implanted in conjunction with cataract surgery is one of non-inferior comparative effectiveness and non-inferior comparative safety. The application clinical claim for patients implanted with two TB MIGS stent devices is one of superior efficacy and non-inferior safety over patients implanted with one TB MIGS stent device.

### Population 2 – Trabecular bypass MIGS stent implantation as a stand-alone procedure

#### TB MIGS stent implantation as a stand-alone procedure vs standard of care (continued use of topical hypotensive medications)

The application clinical claim for TB MIGS stent implantation as a stand-alone procedure, it is considered at least non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety versus topical hypotensive medication in patients where additional control of IOP is required

#### TB MIGS stent implantation as a stand-alone procedure vs trabeculectomy

The application stated that based on the evidence presented, TB MIGS stent implantation is likely to be inferior to trabeculectomy in terms of comparative effectiveness, but superior in terms of comparative safety. However, due to an incompatible body of evidence, a definitive conclusion regarding the relative safety and effectiveness of these interventions cannot be made.

With this in mind, it is anticipated the superior safety of MIGS would position MIGS ahead of trabeculectomy in the treatment algorithm and potentially delay or prevent trabeculectomy. The impact of MIGS in delaying/preventing surgery is captured within the economic model for the first comparison. Therefore, if MIGS is considered cost-effective early in the treatment algorithm then it will be at least as cost-effective later in the algorithm.

TB MIGS stent implantation as a stand-alone procedure vs SC MIGS stent implantation as a stand-alone procedure

The application stated that no clinical claim is made for the comparative effectiveness or safety of TB MIGS stent implantation versus SC MIGS stent implantation as stand-alone procedures, due to a lack of published evidence of SC MIGS stent implantation in this setting. The relative effectiveness of these procedures is established via the indirect comparison presented for Population 1.

## 12. Economic evaluation

Based on the evidence presented, a cost-utility analysis was conducted for MIGS versus standard of care (SOC) in conjunction with cataract surgery for the treatment of glaucoma.

The economic model measured the incremental cost per QALY gained of adding MIGS to the treatment algorithm. A summary of the economic evaluation is presented in Table 4.

**Table 4 Summary of the economic evaluation**

<b>Perspective</b>	Health care system
<b>Comparator</b>	Standard of Care (i.e. treatment algorithm without MIGS)
<b>Type of economic evaluation</b>	Cost-utility analysis
<b>Sources of evidence</b>	Key clinical evidence for the economic model is a meta-analysis of four randomised controlled trials
<b>Time horizon</b>	15 years
<b>Outcomes</b>	QALYs
<b>Methods used to generate results</b>	Individual patient microsimulation
<b>Health states</b>	Mild, Moderate, Advanced, Severe, End stage (defined by visual field Humphrey scores)
<b>&lt;Cycle length&gt;</b>	3 months
<b>Discount rate</b>	5% per annum
<b>Software package used</b>	TreeAge

Over the model duration, MIGS therapy is associated with increased healthcare costs of \$redacted per patient. In decreasing order of magnitude, the cost of MIGS is offset by lower surgery (\$619 per patient), medication (-\$406 per patient) and laser therapy costs (-\$359 per patient). The overall costs and outcomes, and incremental costs and outcomes as calculated for MIGS+SOC and SOC in the model, and using the base case assumptions, are shown in Table 5. For MIGS+SOC versus SOC the incremental cost is calculated to be \$ with an incremental effectiveness of redacted, resulting in an ICER of \$redacted.

**Table 5 Incremental cost-effectiveness of MIGS to standard of care**

<b>Outcome</b>	<b>MIGS+SOC</b>	<b>SOC</b>	<b>Incremental</b>
MIGS and/or cataract surgery	\$redacted	\$redacted	\$redacted
Medications costs	\$redacted	\$redacted	\$redacted
SLT costs	\$redacted	\$redacted	\$redacted
Filtering surgery	\$redacted	\$redacted	\$redacted
Health state costs	\$redacted	\$redacted	\$redacted
Total costs	\$redacted	\$redacted	\$redacted
Total QALYs	redacted	redacted	redacted
Incremental cost per QALY gained			\$redacted

Abbreviations: ICER, Incremental Cost Effectiveness Ratio

In its pre-MSAC response, the applicant stated that allowing for the cost of stent removal or replacement would add an additional **\$redacted** to the total cost of treatment for patients in the TB MIGS+CS treatment arm. Noting that this approach conservatively assumed that stent repositioning would incur the same cost as stent removal or replacement. As a result, the ICER in population 1 increases from **\$redacted** to **\$redacted**), whereas the ICER in population 2 increases from **\$redacted** to **\$redacted**).

### 13. Financial/budgetary impacts

A market share approach was used to estimate the financial implication of the listing of TB MIGS on the MBS. The expected size of the MIGS market was based on projections of MBS data from MBS item 42758 (goniometry) to estimate uptake of MIGS stent implantation when MIGS were used in clinical practice (2014 to 2017).

The financial implications to the MBS resulting from the proposed listing of MIGS are summarised in Table 6. Through reductions in the number of SLT procedures the listing of MIGS is estimated to result in a yearly net savings of between \$530,000 and \$440,000 from 2018 to 2022.

**Table 6 Total costs to the MBS associated with TB MIGS**

Service/Budget	2018	2019	2020	2021	2022
Services delivered	redacted	redacted	redacted	redacted	redacted
Cost of the service to the MBS	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Laser trabeculoplasty (savings of \$371.92 per MIGS service)	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Total MBS	-\$526,801	-\$582,796	-\$563,823	-\$517,861	-\$435,738

Table 7 outlines the broader budget impact of the MBS listing of TB MIGS. TB MIGS listing is estimated to save the PBS between **\$redacted** and **\$redacted** million a year over the next five years. A net cost to private health funds of between **\$redacted** million and **\$redacted** million is expected due to the additional costs incurred for TB MIGS devices despite cost savings through the reduction of trabeculectomy procedures.

**Table 7 Broader budget impact of TB MIGS listing on public and private healthcare**

Service/Budget	2018	2019	2020	2021	2022
PBS perspective					
Hypotensive medication	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Private health funds perspective					
SC MIGS device	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Stand-alone hospitalisations	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Trabeculectomy	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Total Private Health	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted

The total impact to the healthcare system, public and private, is estimated to be between **\$redacted** million and **\$redacted** million per year, as seen in Table 8.

**Table 8 Total net budget impact of TB MIGS listing on public and private healthcare**

Service/Budget	2018	2019	2020	2021	2022
Government health budgets	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Private health funds	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Total all health care	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted

## 14. Key issues from ESC for MSAC

ESC noted that the application is for trabecular bypass micro-invasive glaucoma surgery (TB-MIGS) stent implantation for patients with open-angle glaucoma (OAG). The proposed service involves the insertion of a trabecular bypass stent into the trabecular meshwork of the eye. This augments the drainage of aqueous humour through the trabecular meshwork, reducing pressure within the eye (intraocular pressure [IOP]) and slowing the progression of glaucoma. There are three different stent devices that can be implanted into the trabecular meshwork — the iStent, the iStent inject and the Hydrus Microstent. All three are implanted from inside the eye via a corneal incision using an inserter specific to the device. Two stents per eye are implanted if the iStent inject system is used; one or two stents can be implanted per eye if the iStent system is used, and only one Hydrus Micro stent is implanted per eye.

ESC noted that a similar application — [Application 1496: Suprachoroidal micro-invasive glaucoma surgery \(SC-MIGS\) stent implantation for open-angle glaucoma](#) — is also currently under consideration. ESC noted that many of the concerns raised were relevant to both applications. Given this, information that is common to both summaries is italicised to assist the reader.

ESC noted that TB-MIGS had previously been performed under MBS item 42758 (goniotomy) despite never having been assessed for safety, clinical effectiveness and cost effectiveness. ESC noted that MBS item 42758 was never intended to cover implantation of MIGS stents and in May 2017 use of this item to do so was explicitly prohibited. ESC noted that since then, implantation of MIGS stents has been allowed to continue under an interim MBS item (42705) which will lapse on 31 December 2018. ESC noted that the various TB-MIGS stents are already listed on the Prostheses List but it was likely that they would be removed if this application is unsuccessful.

ESC noted that it was originally proposed that the service be restricted to primary open-angle glaucoma (POAG) but that the patient population has been expanded to OAG. ESC noted arguments that restricting the service to people with POAG would disadvantage patients with rare types of glaucoma (e.g. pseudoexfoliation glaucoma, pigmentary glaucoma) who are treated in the same manner. ESC noted that other changes to the item descriptor introduced since the PICO Confirmation had the potential to result in leakage.

ESC noted that there were two patient populations considered in this application. The populations are:

- patients with diagnosed OAG undergoing TB-MIGS stent implantation in conjunction with cataract surgery (population 1); and
- patients with diagnosed OAG undergoing TB-MIGS stent implantation as a standalone procedure (population 2); such patients may have previously undergone cataract extraction and intraocular lens (IOL) implantation (pseudophakic) or may have never undergone cataract surgery (phakic).

ESC noted that there were significant limitations in the evidence base for both populations with all included studies at moderate to high risk of bias. In addition, ESC noted that while the critique argued that an appropriate minimal clinically important difference (MCID) is a 1.5 mmHg decrease in IOP since this value is accepted by the PBAC for new glaucoma medicines, the applicant argued that every 1 mmHg reduction in IOP is associated with a 10% reduction in glaucoma progression.

ESC noted that TB-MIGS stent implantation was reasonably safe with a low risk of usually minor adverse events reported in both populations.

ESC noted that the submission and the critique had reached different conclusions regarding the effectiveness of TB-MIGS stent implantation in population 1 and this largely came down to the way that the data had been pooled. The submission pooled efficacy data from all three types of TB-MIGS stents — the critique argued this was inappropriate because it pooled results from studies using one stent per eye with those that used two stents per eye. The critique also questioned the appropriateness of pooling data from studies in which patients were assessed while using hypotensive medicines while in other studies patients were assessed after a medication washout period.

In population 1, ESC noted that the submission argued that cataract surgery plus TB-MIGS stent implantation was more effective than cataract surgery alone as it reduced IOP further, reduced use of hypotensive medicines and increased the proportion of patients achieving an IOP reduction of 20% or more. In contrast, ESC noted that the critique argued that cataract surgery plus TB-MIGS stent implantation was non-inferior to cataract surgery alone because:

- in patients who received one stent per eye and were using hypotensive medicines:
  - there was no significant difference in IOP at 12 months (Samuelson TW et al 2011; Fea AM 2010) or 48 months (Fea AM et al 2015);
  - there was a significant difference in IOP of 1.4 mmHg at 24 months (Samuelson TW et al 2011) but this difference was lower than the 1.5 mmHg MCID;
  - at 12 months the TB-MIGS group were taking 0.42 fewer hypotensive medicines (Samuelson TW et al 2011; Fea AM 2010; Pfeiffer N et al 2015) but the MCID for this outcome was not defined making it impossible to establish whether this was clinically significant;
  - there was no significant reduction in the number of medicines taken at 24 months (Samuelson TW et al 2011; Pfeiffer N et al 2015);
  - a significantly larger proportion of patients achieved a greater than 20% reduction in IOP from baseline at 12 months (Samuelson TW et al 2011; Pfeiffer N et al 2015) but the MCID for this outcome was not defined; and
  - there was a significantly higher proportion of patients who no longer required hypotensive medicines at 12 and 24 months (Samuelson TW et al 2011; Pfeiffer N et al 2015) but the MCID for this outcome was not defined.
- there was no information provided on outcomes in patients who received two stents per eye and were using hypotensive medicines.
- in patients who received two stents per eye and were not using hypotensive medicines at randomisation:
  - one study reported a 2.8 mmHg difference in IOP at 12 months (Fernandez-Barrientos Y et al 2010) but the study was not powered to detect the 1.5 mmHg MCID;
  - there was no significant reduction at 12 months in the number of medicines taken or significant increase in the proportion of patients who no longer required hypotensive medicines (Fernandez-Barrientos Y et al 2010); and
  - there was no information on the proportion of patients who achieved a greater than 20% reduction in IOP from baseline.

ESC noted that there was no evidence in population 1 that using two TB-MIGS stents per eye gives any better outcome than using one TB-MIGS stent per eye. ESC noted the critique did not find any difference in IOP or hypotensive medicines use when patients who had one TB-MIGS stent per eye were compared with patients who had two TB-MIGS stents per eye implanted.

In population 2 (standalone TB-MIGS stent implantation), only two studies were identified - both used two TB-MIGS stents per eye (Fea AM et al 2014; Vold SD et al 2016). ESC noted that one study (Vold SD et al 2016) was conducted in patients who had not been previously treated with hypotensive medicines and noted that this kind of first-line use was inconsistent with the proposed use of TB-MIGS stent implantation in Australia. ESC also noted that:

- both the submission and the critique suggested that standalone TB-MIGS stent implantation was non-inferior in terms of safety and effectiveness to continued use of hypotensive medicines (standard of care);
- the submission did not attempt to compare standalone TB-MIGS stent implantation to laser trabeculoplasty (SLT). The critique suggested that standalone TB-MIGS stent implantation was non-inferior to SLT on the basis of an indirect comparison using hypotensive medicines use as the common comparator; and
- standalone TB-MIGS stent implantation was not formally compared with trabeculectomy. ESC accepted that this was appropriate given trabeculectomy is usually reserved for patients with more advanced disease than the proposed population 2 patients.

ESC noted that when TB-MIGS stent implantation was compared to the alternative procedure, SC-MIGS stent implantation, there was:

- no significant difference in safety or efficacy outcomes in population 1 (using cataract surgery alone to indirectly compare TB-MIGS and SC-MIGS) regardless of whether one or two TB-MIGS stents were used; and
- no direct or indirect evidence to inform safety and effectiveness in population 2.

ESC noted that there was very limited information to compare the different types of TB-MIGS stents and none were compared to another in a head-to-head trial. In the four studies conducted in population 1 (one Hydrus Microstent and three iStent studies), a naïve comparison of adverse events and effectiveness outcomes reported in the intervention arms suggested these two types of TB-MIGS stent are similar. In the two studies conducted in population 2 (one iStent and one iStent inject study), a naïve comparison of reported adverse events and effectiveness outcomes in the intervention arms of each study suggested these two types of TB-MIGS stents are similar.

ESC noted the proposed fee for implantation of TB-MIGS stents in conjunction with cataract surgery, the proposed fee for implantation as a standalone procedure and the current fee for goniotomy were all the same. ESC requested further justification for the proposed fees and also noted that the time and resources needed to implant in conjunction with cataract surgery would be different to a standalone procedure. ESC noted that when MBS item 42758 was being used 97.5% of MIGS stents appear to be implanted in conjunction with cataract surgery and as such the benefit paid would be lower than the proposed MBS fee under the multiple services rule. However, ESC noted the application estimated 20% of MIGS implantations would be standalone procedures by 2022. ESC noted that this 20% figure had not been justified.

ESC noted that the fees requested for implantation of a MIGS stent and replacement or removal of a MIGS stent are the same. ESC queried whether the time and resources required to replace or remove a MIGS stent justified paying the same amount for both procedures. In addition, ESC requested information on the proportion of MIGS stents that would require removal or replacement and requested that the associated costs be included in the economic and financial models.

ESC clarified that the \$1,600 cost for the iStent inject device was for implantation of two stents concurrently, not one stent, and as such the costs used in the economic modelling did not need to be increased to reflect use of two stents.

ESC noted the economic modelling was undertaken per eye, not per patient.

ESC noted that the economic modelling for population 1 assumed that changes in the use of medicines and improvements in IOP will change the rate at which patients move through the glaucoma treatment algorithm, slow OAG progression and improve quality of life. ESC noted the ICER was ~\$redacted in the base case.

ESC requested a probabilistic sensitivity analysis of the modelling be undertaken. In the meantime, ESC noted that the economic model was largely driven by time to addition of another hypotensive medicine, time to first use of a laser to treat OAG and time to trabeculectomy. ESC noted that the trial evidence did not extend beyond four years. ESC noted that if the time horizon were reduced from 15 years in the base case to 5 years, the ICER would increase to ~\$redacted.

ESC also noted that the model included an additional 1.9 mmHg reduction in IOP for use of two stents per eye, despite no clear evidence that outcomes in people who received two stents per eye were any better than implantation of one stent. ESC noted that if this benefit were removed from the base case, the ICER would rise to ~\$redacted.

ESC noted that information on adherence to hypotensive medicines and treatment failure or revision should be included in the model.

ESC noted that no economic evaluation for population 2 was undertaken. Instead, a sensitivity analysis was undertaken using the population 1 model in which cataract surgery costs were removed from the model and it was assumed that the effectiveness of TB-MIGS stent implantation as a standalone procedure was the same as TB-MIGS stent implantation in conjunction with cataract surgery. ESC queried whether this was a reasonable assumption.

ESC noted that no economic evaluation comparing TB-MIGS stent implantation with SC-MIGS stent implantation was undertaken.

ESC noted that both application 1483 and application 1496 extrapolated data from MBS item 42758 (goniometry) to estimate uptake of MIGS stent implantation. ESC noted that the methods and assumptions used in the extrapolation of this data had not been provided. ESC also noted that as it was not possible to separate the numbers of MBS item 42758 services carried out using TB-MIGS stents from those using SC-MIGS stents, application 1483 assumed that 100% of these services used TB-MIGS stents while application 1496 assumed 100% of these services used SC-MIGS stents. ESC noted that this makes it appear that, should both TB-MIGS stent implantation and SC-MIGS stent implantation be listed, the uptake would be double that expected in reality.

ESC suggested that the Prostheses List Advisory Committee (PLAC) may be able to provide figures on the relative numbers of each type of MIGS stent used in Australian practice which could be used to better model the expected uptake of either or both of these services on the MBS.

ESC noted that a lack of information about how many procedures would be undertaken per year and what proportion of services would be undertaken in private or public hospitals added uncertainty to the financial costs.

ESC expressed concerns that there may be out-of-pocket expenses for consumers. ESC suggested that information from the Department on the fees being charged for MBS items

42758 (goniotomy) prior to the exclusion of MIGS stent implantation, interim MBS item 42705 and MBS item 42702 (cataract surgery) could provide some guidance on potential out-of-pocket expenses.

ESC also noted that if TB-MIGS stent implantation were recommended as a standalone procedure (population 2) there was a risk that some patients could undergo cataract surgery and then undergo a separate procedure to implant a TB-MIGS stent at some later stage in order to maximise the benefits paid. ESC noted that the items should be structured and priced to encourage the most appropriate use of the items for the patient.

ESC noted consumer concerns that TB-MIGS stent implantation had been inappropriately subsidised on the MBS without an assessment of its safety, effectiveness and cost-effectiveness. ESC noted that should it be shown to be safe and effective, consumers are likely to welcome a procedure which may slow down progression of OAG.

ESC suggested that the item descriptor:

- restrict use to patients with mild to moderate disease;
- specify use of the item to once per lifetime per eye;
- specify the co-administered interventions used to deliver the service (i.e. cataract surgery and gonioscopy);
- define what constitutes an adequate trial of hypotensive medicines;
- more tightly define what is considered to be failure of, or contraindications to, hypotensive medicines and other treatments to prevent first-line use of TB-MIGS stent implantation, particularly in the standalone population;
- specify whether the service attracts an anaesthetic or an assistant benefit; and
- note any training and/or accreditation requirements.

ESC agreed that using the generic term ‘glaucoma drainage device’ in the item descriptor to describe MIGS stents was probably not appropriate.

## **15. Other significant factors**

Nil

## **16. Applicant’s comments on MSAC’s Public Summary Document**

Glaukos welcomes the recommendation from MSAC for inclusion on the MBS of T.B-MIGS in conjunction with cataract. We look forward to working with the Department of Health to implement this advice as soon as possible. Whilst disappointed with the decision for the standalone population we will continue to advocate and work for MBS reimbursement for this group of patients with high clinical need.

The Australian and New Zealand Glaucoma Society (ANZGS) provides justification for the proposed indication, stating that “the indications for cataract surgery and iStent implantation are completely different. Forcing the procedures to be done in combination is likely to create decision biases either for or against surgery”. ANZGS are concerned this is biased against a proportion of glaucoma patients for a reason unrelated to their glaucoma.

The Australia Society of Ophthalmologists (ASO) welcomes MSAC’s recommendation to include TB-MIGS on the MBS. They are, however, concerned about the proposed MBS fee and the rationale for it. There is not any reason why the fee for MIGS implantation should be considered similar to an eye injection. The skills, qualifications and resources required for

stent implantation are different to those of eye injections. Stent implantation is most similar to a goniotomy and they believe this is an appropriate basis for determining the fee.

Glaukos would like to re-iterate and clarify that the evidence for improved outcomes with two stents over a single stent is sound. So much so, that the two stent iStent inject system is recommended in treatment practice and used in over 95% of cases in Australia.

#### **17. Further information on MSAC**

MSAC Terms of Reference and other information are available on the MSAC Website:  
[visit the MSAC website](#)