Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1472 - Cyanoacrylate embolisation for the treatment of varicose veins due to chronic venous insufficiency

Applicant: **Medtronic Australasia Pty Ltd**

Date of MSAC consideration: **MSAC 70th Meeting, 27 July 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 Medicare Benefit Schedule (MBS) listing of cyanoacrylate embolisation (CAE) for the treatment of varicose veins due to chronic venous insufficiency (CVI) was received by the Department of Health from Medtronic Australasia Pty Ltd.

2. MSAC's advice to the Minister

After considering the evidence presented in relation to the safety, clinical effectiveness and cost-effectiveness MSAC supported MBS listing of cyanoacrylate embolisation for the treatment of varicose veins due to chronic venous insufficiency of the great and small saphenous veins. MSAC considered the service provides an acceptable alternative to other current non-surgical methods (radiofrequency ablation or endovenous laser therapy) at approximately the same cost, with minimal budgetary impact on the MBS.

MSAC queried the proposed fee for CAE being equivalent to its comparators, given that the proposed service required less time and equipment, and may result in wider utilisation than its comparators. MSAC advised the department to seek clarification from the applicant regarding the relevant inputs for the fee, including in relation to technique and operating costs. This information could then be considered by the MSAC Executive.

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

CAE is a minimally invasive, non-thermal, non-tumescent treatment for varicose veins. CAE is delivered as a single course of treatment to each affected leg to block the great saphenous vein (GSV) or small saphenous vein (SSV) by means of a medical adhesive (cyanoacrylate adhesive). MSAC noted that there are currently two other minimally invasive, thermal ablative treatments for varicose veins listed on the MBS: radiofrequency ablation (RFA) and endovenous laser therapy (ELT). These treatments are the main comparators for CAE. MSAC noted that the proposed population and item descriptor is identical to those of the comparators.

MSAC noted that the proposed population includes treatment of the SSV in addition to the GSV, consistent with the eligible patients for whom the comparators ELT and RFA are MBS

listed. MSAC acknowledged that inclusion of treatment of the SSV is likely to be appropriate, noting that TGA approval of this indication has not yet been received for the sponsor's CAE system. MSAC noted that there is currently another CAE system listed on the ARTG which includes treatment of the GSV and SSV.

MSAC noted that the evidence for safety and effectiveness of CAE is based on one randomised controlled trial (RCT) versus RFA (n = 222, VeCLOSE trial, Morrison N et al 2015), one non-randomised study versus radiofrequency-induced thermal therapy (RFITT: similar to RFA) (n = 1,395 veins, Zierau UT 2016) and one non-randomised study versus ELT (n = 310, Bozkurt AK & Yilmaz MF 2016), along with 12 supportive single arm observational studies of CAE. MSAC noted that the majority of safety and effectiveness data for CAE was for treatment of the GSV but considered that the representation of SSVs of ~15% in the total body of evidence was reasonable and may reflect clinical practice. MSAC noted ESC's concerns regarding the applicability of the clinical and safety data presented to treatment of the SSV. MSAC considered that safety and effectiveness are unlikely to differ substantially between the GSV and the SSV given that veins are anatomically similar and the mechanism of action is the same.

MSAC noted that comparative safety data for CAE is available up to 24 months with follow-up of the trial to three years (VeCLOSE study 36 month results as provided in the sponsor's pre-MSAC response). MSAC acknowledged that CAE appears to be non-inferior to RFA and ELT in safety and may offer some advantages over these treatments, particularly for treatment of the SSV given the reports of paraesthesia that have been associated with these thermal, tumescent treatments. MSAC noted that while no long-term safety data for CAE is available beyond three years the use of cyanoacrylate adhesive is well established in other applications such as occlusion of arteries, veins or arteriovenous fistulae. MSAC noted that the low rate of reportable events in the post-market surveillance of CAE also reduces the uncertainty regarding its long-term safety.

MSAC noted that although limited to a single sponsor-funded RCT, the evidence for the comparative efficacy was of reasonable quality and supported non-inferiority of CAE versus RFA with respect to complete closure rates. MSAC considered that the non-randomised studies and observational studies also supported non-inferiority of CAE compared with ELT.

MSAC noted that a cost-minimisation approach was taken in the economic evaluation, and that the proposed fees for CAE are identical to the fees for the comparators RFA and ELT. MSAC noted that CAE does not require the use of machinery with high capital costs, tumescent anaesthesia or compression stockings and questioned whether the same fee is appropriate given the reduced requirements for this method of treating chronic venous insufficiency of the GSV and SSV. MSAC were concerned that an equivalent price for CAE may lead to over-servicing of the item given that there are likely to be advantages to using CAE for patients (such as the non-requirement for tumescent anaesthesia) and higher margins for providers due to reduced capital costs. MSAC requested that the department examine the fee requested and determine the most appropriate fee for the proposed service.

MSAC noted the updated financial impact estimates provided in the pre-MSAC response, which used an assumption of 5% growth and applied the weighted distribution of services across settings as suggested in the critique. MSAC considered that overall, though there may be some growth in the market, costs for CAE would largely be offset by reduced services of items for RFA and ELT and the budget impact of listing CAE on the MBS would be relatively minor.

MSAC was concerned about the substantial out-of-pocket costs associated with both CAE and comparators. MSAC agreed that CAE will need the same multiple service rules and extended Medicare safety net caps as are applicable for RFA and ELT. MSAC acknowledged

the sponsor's comments in the pre-MSAC response regarding the need for funding arrangements for implantable medical technology used to deliver an MBS service for private patients treated outside the hospital setting.

Overall, after considering the strength of the available evidence presented in relation to the safety, clinical effectiveness and cost-effectiveness MSAC supported MBS listing of cyanoacrylate embolisation for the treatment of varicose veins due to chronic venous insufficiency of the great and short saphenous veins.

4. Background

MSAC has not previously considered this application.

5. Prerequisites to implementation of any funding advice

Items on the ARTG that are relevant to the proposed application are shown in Table 1.

Table 1 CAEs listed on the ARTG

ARTG no.	Product no.	Product description	Product category	Sponsor
194201	58708	Venous adhesive occlusion system – intended for the permanent, complete, endovascular adhesive closure of the great saphenous vein (GSV) and associated varicosities in the treatment of venous reflux disease	Medical Device Class IIb	Emergo Asia Pacific Pty Ltd T/a Emergo Australia
283020	58708	Venous adhesive occlusion system – intended for the permanent, complete, endovascular adhesive closure of the great saphenous vein (GSV) and associated varicosities in the treatment of venous reflux disease	Medical Device Class IIb	Diverse Devices Pty Ltd

Source: Therapeutic Goods Administration, accessed 15 December 2016 https://www.tga.gov.au/searching-australian-register-therapeutic-goods-artg

6. Proposal for public funding

The proposed MBS item descriptors are shown in Table 2, the proposed fees are identical to those for RFA (32523, 32526 and ELT (32520, 32522) services.

Table 2 Proposed MBS item descriptors for CAE

Category 3– THERAPEUTIC PROCEDURES
Varicose veins, abolition of venous reflux by occlusion of a primary or recurrent great (long) or small (short) saphenous vein of one leg (and major tributaries of saphenous veins as necessary), using cyanoacrylate adhesive , where it is documented by duplex ultrasound that the great or small saphenous vein (whichever is to be treated) demonstrates reflux of 0.5 seconds or longer, including all preparation and immediate clinical aftercare (including excision or injection of either tributaries or incompetent perforating veins, or both) but not including radiofrequency diathermy or radiofrequency ablation, and not provided on the same occasion as a service described in any of items 32500, 32501, 32504 or 32507 Fee: $533.60
Category 3– THERAPEUTIC PROCEDURES
Varicose veins, abolition of venous reflux by occlusion of a primary or recurrent great (long) and small (short) saphenous vein of one leg (and major tributaries of saphenous veins as necessary), using cyanoacrylate adhesive, where it is documented by duplex ultrasound that the great and small saphenous veins demonstrate reflux of 0.5 seconds or longer, including all preparation and immediate clinical aftercare (including excision or injection of either tributaries or incompetent perforating veins, or both) but not including radiofrequency diathermy or radiofrequency ablation, and not provided on the same occasion as a service described in any of items 32500, 32501, 32504 or 32507 Fee: $793.30

The patient considered for CAE, RFA or ELT would under normal conditions be referred by a general practitioner to a vascular/general surgeon or phlebologist. In some instances, the general practitioner will be the service provider and referral is not required. A pre-procedural consultation with the treating physician is required. During the pre-procedural consultation, duplex scanning will be performed to confirm and map all areas of venous reflux to determine the appropriate treatment plan.

7. Summary of Public Consultation Feedback/Consumer Issues

Two responses from peak bodies were received from the public consultation period.

One response believed that there was no evidence to exclude long term complications. The other response advised that this CAE treatment has been scientifically established as very credible and viable alternate treatment for VVs and CVI and strongly support its use in terms of being non-inferior, more comfortable, with shorter treatment times and less pain for the patient during the treatment process, compared to thermal ablation techniques.

8. Proposed intervention's place in clinical management

CAE is a minimally invasive, non-thermal, non-tumescent treatment for varicose veins. CAE is designed as a single use therapeutic intervention, delivered as a single course of treatment per affected leg to embolise the great and/or short saphenous vein(s) (GSV, SSV) and associated varicosities by means of medical adhesive. To achieve vein occlusion, an ultrasound guided disposable catheter is positioned in the area of treatment and a catheter-administered cyanoacrylate adhesive is then injected into the vein to achieve closure.

The procedure involves four phases:
1. Catheter insertion
2. Adhesive injection
3. Compression
4. Occlusion.

The proposed clinical management algorithm has been adapted from the clinical management algorithm proposed in the Decision Analytic Protocol of application 1166 (RFA).

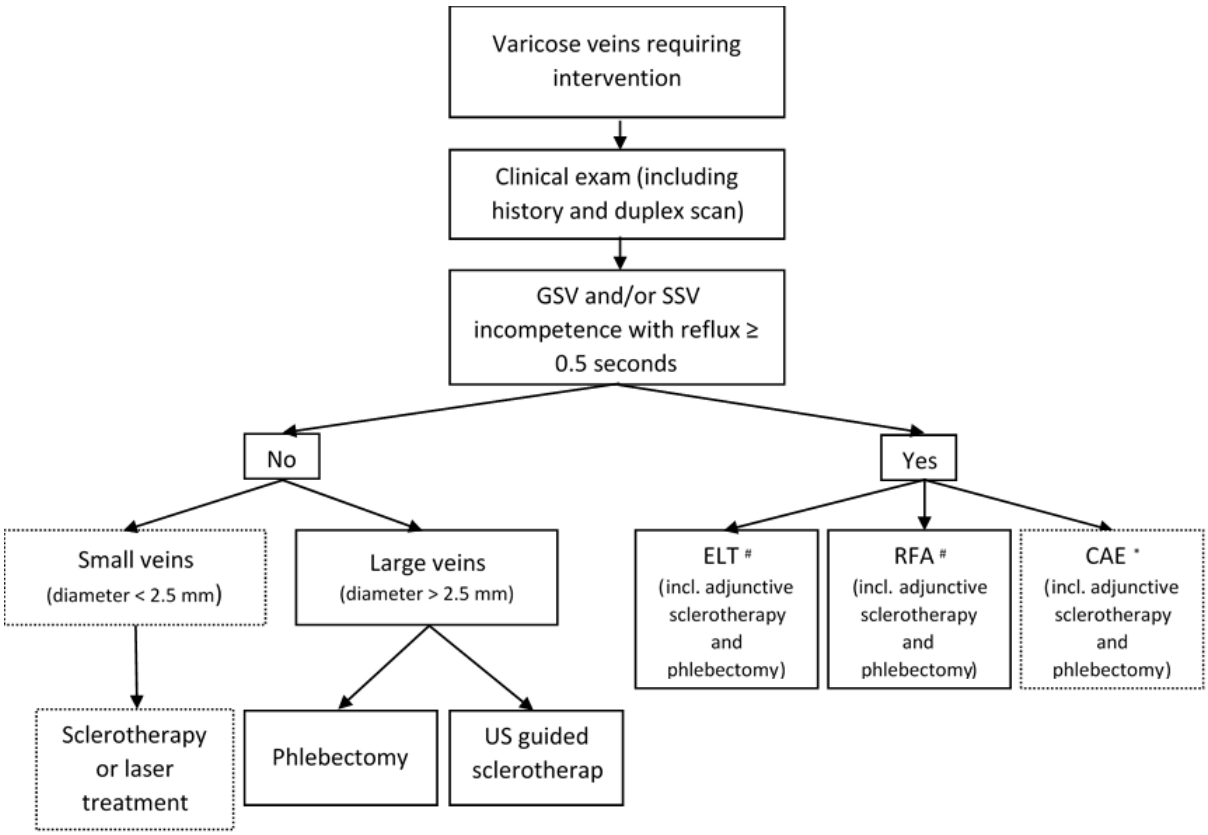

Figure 1 Proposed management algorithm for varicose veins incorporating the proposed CAE service

Source: Application 1166: Final Decision Analytic Protocol (DAP) to guide the assessment of radiofrequency ablation for the treatment of varicose veins due to chronic venous insufficiency.
Abbreviations: CAE, cyanoacrylate embolisation; ELT, endovenous laser therapy; GSV, great saphenous vein; RFA, radiofrequency ablation; SSV, small saphenous vein; US, ultrasound.
NB: Indication for treatment includes exhaustion of conservative treatment measures, significant symptom, and the presence of venous reflux.
NB. Dashed lines represent procedures not currently reimbursed by the Medicare Benefits Schedule.
ELT and RFA require compression therapy for at least one week after the procedure.
* CAE does not require compression therapy post-procedure.

9. Comparator

The nominated comparators to CAE for the proposed patient population are RFA and ELT.

The main difference in the delivery of CAE and the comparators (ELT and RFA) is the means through which occlusion of the vein is achieved: through medical adhesive (CAE), radiofrequency (RFA) or laser (ELT). Only local anaesthesia is needed for CAE, unlike ELT and RFA where tumescent anaesthesia is used. Capital equipment is necessary for ELT and RFA, whereas disposable consumables (the adhesive, dispenser gun, catheter, introducer, dilator, syringe etc.) are used to perform CAE.

10. Comparative safety

The key adverse events (AEs) reported in the SBA were ecchymosis at day 3 and pain. The results of these key comparative safety outcomes have been synthesised across studies and are presented in Table 3 and Table 4.

Ecchymosis at day 3

Table 3 Results of ecchymosis (at day 3) across the studies

Study ID	Risk of bias	CAE n with event / N (%)	RFA n with event / N (%)	ELT n with event / N (%)	Absolute difference RD (95%CI)	Relative difference RR (95%CI)
VeCLOSE (2015)	Serious	35 / 108 (32.4)	59 / 114 (51.8)	NA	0.19 [0.07, 0.32]	1.40 [1.11, 1.76]
Zierau (2016)	Potentially serious	NR	NR	NA	NR	NR
Bozkurt & Yilmaz (2016)*	Not serious	22 / 154 (14.3)	NA	73 / 156 (46.8)	0.33 [0.23, 0.42]	1.61 [1.37, 1.89]

CAE = cyanoacrylate adhesive embolisation; CI = confidence interval; ELT = endovenous laser therapy; NA = not available; NR = not reported; RD = risk difference; RFA = radiofrequency ablation; RR = relative risk
** CAE procedure used in this study is not registered in Australia.*
Table compiled during critique.

Pain

Table 4 Results of pain ratings across the studies

Study ID	Risk of bias	CAE Mean pain rating		Comparator Mean pain rating (range)		P-value
CAE vs RFA						
VeCLOSE (2015)	Serious	During venous access[a] Intra-procedural pain[a] During day 2[a]	1.6 2.2 0.9	During venous access[a] Intra-procedural pain[a] During day 2[a]	2.0 2.4 0.9	0.13 0.11 0.36
Zierau (2016)	Potentially serious	Mean (range) First day after procedure[b] 7 days after procedure[b]	 1.7 (1–3) 1.2 (NR)	Mean (range) First day after procedure[b] 7 days after procedure[b]	 4.1 (3–8) 2.8 (NR)	 NR NR
CAE* vs ELT						
Bozkurt & Yilmaz (2016)*	Not serious	Mean (SD) Procedural pain[b]	 3.1 (1.6)	Mean (SD) Procedural pain[b]	 6.5 (2.3)	 < 0.001

CAE = cyanoacrylate adhesive embolisation; ELT = endovenous laser therapy; NR = not reported; RFA = radiofrequency ablation; SD = standard deviation
[a] Pain was rated on a numeric rating scale of 0 to 10 (0 = no pain; 10 = worst imaginable pain)
[b] Pain was rated on a numeric Visual Analogue Scale (VAS) of 0 to 10 (0 = no pain; 10 = worst imaginable pain)
** CAE procedure used in this study is not registered in Australia.*
Table compiled during critique.

Ecchymosis was more prevalent in the RFA and ELT groups compared to the CAE groups. There was no significant difference in pain between CAE and RFA; however procedural pain was lower in the CAE group compared to the ELT group in the study by Bozkurt & Yilmaz (2016). The most commonly observed adverse event in the VeCLOSE trial was phlebitis, which occurred somewhat more commonly after CAE than RFA (20% versus 14% respectively) although the difference did not reach statistical significance (p=0.21). For all other AEs, the type and rate of expected predefined AEs were similar between treatments. It was not reported whether the reported potential differences in adverse events were also clinically significant.

Twenty-one percent (53/256) of the patients treated by RFITT had neurological sensations lasting longer than 30 days post procedure in the Zierau study, compared to no patients in the CAE group. This was valued as a clinically important difference.

The critique noted that due to the limited comparative evidence available on AEs (with limited study populations), any potential difference in safety (especially rare AEs) between procedures is difficult to determine.

11. Comparative effectiveness

CAE versus RFA
Based on the evidence presented, the SBA stated that it may be concluded that CAE is non-inferior to RFA with respect to effectiveness. The results demonstrated that CAE is statistically non-inferior to RFA with respect to DUS confirmed complete closure at three months (99% versus 96% respectively), with statistical non-inferiority maintained over 24 months (94.3% versus 94% respectively). All pre-specified analyses upon which non-inferiority was defined demonstrated non-inferiority with the lower bound of the CI consistently exceeding -10%. The comparative study of CAE versus RFA included patients with GSV reflux, however, the non-inferior result of CAE and RFA can be extended to include treatment of SSV given the consistency in high closure rates observed across the saphenous veins. The results for all secondary effectiveness endpoints over 24 months, VCSS, AVVQ, EQ-5D and CEAP classification, supported the conclusion of non-inferiority of CAE and RFA.

CAE versus ELT
Based on the evidence presented, the SBA stated that it may be concluded that CAE is non-inferior to ELT with respect to effectiveness. The results demonstrated that CAE is at least non-inferior to ELT with respect to ultrasound (US) confirmed complete closure. At six months, a statistically significantly higher proportion of CAE patients had complete closure (96.6%) compared with ELT patients (91.7%) (RD: 6%, 95% CI: 0%, 11%; p=0.04). Twelve months post-procedure, the difference in treatment effect was numerically in favour of CAE, although the difference was not statistically significant (RD: 4%, 95% CI: -2%, 9%; p=0.20). The lower confidence intervals consistently exceeded -10%, demonstrating non-inferiority of CAE and ELT across all time points. The results from secondary, quality of life outcomes support a conclusion of non-inferiority of CAE and ELT. The quality of life of patients in both treatment groups improved statistically significantly over 12 months relative to baseline.

CAE versus RFITT
Based on the evidence presented, the SBA stated that it may be concluded that CAE is non-inferior to RFITT with respect to effectiveness for the treatment of patients with reflux of the GSV and SSV. Both treatment groups achieved similarly high closure rates over time, with 97.9% and 96.1% of CAE and RFITT veins considered closed at 6 months. Applying the non-inferiority margin from the VeCLOSE study (lower confidence bound exceeding -10%), it may be concluded that CAE is non-inferior to RFITT with respect to closure rate. The overall closure rate in the CAE and RFITT groups over the 46 months' experience was 97.45% (1110/1139) and 95.3% (244/256, numerator calculated). As per personal communication with the author, the average follow-up of the cohorts included in the closure rates at 46 months was 12–24 months, suggesting durability of effectiveness with CAE and RFITT.

Table 5 Balance of clinical benefits and harms of CAE, relative to RFA and ELT, and as measured by the critical patient-relevant outcomes in the key studies

Outcomes (units) Follow-up	Participants (studies)	Quality of evidence (GRADE)[a]	Relative risk (95%CI)	Risk difference (95% CI)	Risk with control n/N (%)	Comments
CAE vs RFA: RCT						
Complete closure, 3 month (LOCF)	n =222 k = 1	⊕⊕⊕⊕ HIGH	1.04 (0.99, 1.08)	0.03 (-0.01, 0.08)	109/114 (96)	Statistically significant non-inferiority demonstrated
Complete closure, 24 month	N = 171 K = 1	⊕⊕⊕⊕ HIGH	1.00 (0.93, 1.08)	0.0 (-0.07, 0.07)	79/84 (94)	Statistically significant non-inferiority demonstrated
CEAP 0/1 at 3 months	n =222 k = 1	⊕⊕⊕⊙ MODERATE	0.78 (0.52, 1.17)	-0.07 (-0.19, 0.05)	38/114 (33)	Result numerically in favour of RFA
Investigator-rated ecchymosis absent at day 3	n =222 k = 1	⊕⊕⊕⊙ MODERATE	1.40 (1.11, 1.76)	0.19 (0.07, 0.32)	55 (48.2)	Result statistically significantly in favour of CAE
Proportion of patients with procedure related AE	n =222 k = 1	⊕⊕⊕⊙ MODERATE	0.92 (0.59, 1.43)	-0.02 (-0.14, 0.09)	31/114 (27)	Result numerically in favour of CAE
CAE vs ELT: non-randomised						
Complete closure at 6 months (%) – OC	n=290 k= 1	⊕⊕⊕⊙ MODERATE	1.06 (1.00, 1.12)	0.06 (0.00, 0.11)	133/145 (91.7)	Result support conclusion of non-inferiority
Complete closure at 12 months (%) – OC	n=283 k= 1	⊕⊕⊕⊙ MODERATE	1.04 (0.98, 1.10)	0.04 (-0.02, 0.09)	130/141 (92.2)	Result support conclusion of non-inferiority
Ecchymosis absent at day 3	n=310 k= 1	LOW[a] ⊕⊕⊙⊙	1.61 (1.37, 1.89)	0.33 (0.23, 0.42)	83 (53.2)	Result statistically significantly in favour of CAE
Procedural pain	n=310 k= 1	LOW[a] ⊕⊕⊙⊙	MD (95% CI): -3.40 (-3.84, -2.96)		Mean (SD): 6.5 (2.3)	Result statistically significantly in favour of CAE; (VAS 0–10)
Paraesthesia	n=310 k= 1	LOW[a] ⊕⊕⊙⊙	0.07 (0.00, 1.17)	-0.04 (-0.08, -0.01)	7 (4.5)	Result statistically significantly in favour of CAE. (CAE = 0%).
CAE vs RFITT: non-randomised						
Complete closure at 3 months (%) – OC	n=480 (veins) k= 1	LOW ⊕⊕⊙⊙	1.01 [0.98, 1.05]	1 [-2, 5]	162/168 (96.6)	Result supports conclusion of non-inferiority
Complete closure at 6 months (%) – OC	n=411 (veins) k= 1	LOW ⊕⊕⊙⊙	1.01 [0.98, 1.06]	1 [-2, 5]	123/128 (96.1)	Result supports conclusion of non-inferiority
Paraesthesia and hypaesthesia (> 30 day duration)	n = 590 (veins) k= 1	VERY LOW[a] ⊕⊙⊙⊙	0.01 [0.00, 0.17]	-0.11 [-0.15, -0.07]	22/202 (11)	Statistically and likely clinically significant difference in favour of CAE

[a] GRADE Working Group grades of evidence (Guyatt et al., 2013)

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

SD=standard deviation; RD=risk difference; RR=relative risk; CAE, cyanoacrylate embolisation; CI, confidence interval; ELT, endovenous laser therapy; MD, mean difference; OC, observed case.

[a]Marked as LOW due to open-label assessment of subjective outcome.

On the basis of the benefits and harms reported in the evidence base (summarised above), the SBA suggested that, relative to RFA and ELT, CAE has non-inferior safety and non-inferior effectiveness.

The critique noted that primary effectiveness outcome listed was the abolition of reflux/complete closure which is a surrogate outcome. Ideally, clinical outcomes (e.g. reduction of symptoms, quality of life) should have been the primary effectiveness outcomes. Non-inferiority was determined if the proportion of subjects with complete closure with CAE was statistically non-inferior to that with RFA, with a 10% non-inferiority margin. Whether 10% was the smallest clinically meaningful difference between treatments was not supported.

The critique noted that it is possible that failure rates may have been significantly underestimated. There were inconsistencies in reported failure rates and in the size of the study population reported over different time points in the key trial (VeCLOSE) which raises questions on the accuracy of the data presented and makes interpretation difficult, and in the study by Bozkurt & Yilmaz, patients with treatment failure appeared more likely to drop out of the study, reducing the calculated failure rate.

The critique noted that a decrease in disease severity and a slight improvement in QoL was observed after treatment. However, whether the slight observed difference in EQ-5D score was also clinically significant was not supported.

Clinical Claim

The SBA stated that, based on direct randomised controlled trial (RCT) evidence, CAE is non-inferior to RFA with respect to effectiveness and safety in patients with GSV and/or SSV reflux. At their August 2012 meeting, MSAC recommended listing of RFA on the MBS for the treatment of GSV and SSV incompetence, based on non-inferior effectiveness and safety versus ELT (Public Summary Document [PSD] for RFA application 1166). It follows that CAE is non-inferior to ELT with respect to effectiveness in the treatment of both GSVs and SSVs.

12. Economic evaluation

The SBA presented a cost minimisation analysis based on a claim of non-inferior effectiveness and non-inferior safety of CAE compared to RFA and ELT. A summary of the cost-minimisation evaluation is presented in Table 6. It was assumed all interventions were performed out of hospital by a non-GP. This assumption dictates the number of GP visits, specialist consults and duplex scanning services associated with the completion of CAE, ELT and RFA procedures.

Table 6 Summary of the economic evaluation presented in the SBA

Perspective	Australian healthcare
Intervention	Cyanoacrylate embolisation
Comparator	Radiofrequency ablation and Endovenous laser therapy
Type of economic evaluation	Cost-minimisation
Outcomes	Cost per procedure
Methods used to generate results	Cost comparison
Software packages used	Microsoft Excel

The overall costs per procedure as calculated for the intervention and comparator, and using the base case assumptions, are shown in Table 7. CAE costs were calculated at $1,929 for GSV or SSV procedures, and $2,189 for GSV and SSV procedures. Comparative RFA costs

were $1,908 (GSV or SSV procedures) and $2,168 (GSV and SSV procedures), and ELT costs were $1,984 (GSV or SSV procedures) and $2,244 (GSV and SSV procedures).

Table 7 Cost-minimisation results for CAE vs RFA and ELT

	CAE	RFA (diff vs CAE)	ELT (diff vs CAE)
GSV or SSV item no.			
MBS resource use[a]	$1,074.90	$1,074.90 ($0)	$1,074.90 ($0)
Other resource use[b]	$854.57	$832.92 (-$21.65)	$909.25 ($54.68)
Total	$1,929.47	$1,907.82 (-$21.65)	$1,984.15 ($54.68)
GSV and SSV item no.			
MBS resource use[a]	$1,334.60	$1,334.60 ($0)	$1,334.60 ($0)
Other resource use[b]	$854.57	$832.92 (-$21.65)	$909.25 ($54.68)
Total	$2,189.17	$2,167.52 (-$21.65)	$2,243.85 ($54.68)

[a] MBS resource use includes: GP referral/s, specialist consult/s, duplex scanning/s and CAE/ELT/RFA procedure/s
[b] Other resource use includes: consumables, equipment costs, compression stockings and tumescent anaesthesia

13. Financial/budgetary impacts

The SBA used a market share approach to estimate the financial implications of listing CAE on the MBS. The estimated service usage increases from 1,185 in year 1 post listing, to 5,363 in year 5 post listing.

The financial implications to the MBS resulting from the proposed listing of CAE estimated by the SBA are summarised in Table 8.

Table 8 Total costs to the MBS associated with CAE (GSV/SSV and GSV and SSV)

	2017-18	2018-19	2019-20	2020–21	2021–22
CAE	-	-	-	-	-
Number of services	1,185	2,435	3,430	4,424	5,363
Sub-total cost	$1,128,548	$2,340,948	$3,315,600	$4,299,176	$5,238,122
ELT and RFA[1]	-	-	-	-	-
Reduction in number of services due to CAE	1,185	2,435	3,430	4,424	5,363
Subtotal cost reductions	$1,128,548	$2,340,948	$3,315,600	$4,299,176	$5,238,122
Net services	**0**	**0**	**0**	**0**	**0**
Net cost to MBS	**$0**	**$0**	**$0**	**$0**	**$0**

CAE = cyanoacrylate emobolisation; ELT = endovenous laser therapy; GSV = great saphenous vein; MBS = Medicare Benefit Schedule; RFA = radiofrequency ablation; SSV = short saphenous vein
[1] MBS items for ELT are 32520 and 32522, and for RFA are 32523 and 32526.

The critique considered that the final estimate of the number of CAE services/year provided in the SBA was uncertain and depends on the uptake of CAE in the clinical practice. Assuming the CAE listing does not impact market growth, the uptake rate of CAE will not have major financial implications for the MBS as CAE will simply substitute for RFA/ELT and the fees are the same. However, if the CAE listing does cause market growth, this will result in additional costs to MBS.

In the pre-MSAC response, the applicant updated the budget impact analysis in addition to changing the base case assumption to 5% market growth. The net financial impact to the MBS of the new base case increases from $651,547 in year 1 to $953,457 in year 5.

14. Key issues from ESC for MSAC

ESC noted that the application requesting MBS listing for cyanoacrylate embolisation (CAE) for the treatment of varicose veins due to chronic venous insufficiency (CVI) was assessed as suitable to progress via the expedited PASC pathway.

The initial application document included treatment of the great saphenous vein (GSV), whereas the proposed population now also includes treatment of the small saphenous vein (SSV). ESC noted that in the pre-ESC response the applicant confirmed their intention to lodge an application with the TGA in September 2017 seeking to expand the indication for their CAE device (VenaSeal) to explicitly include the treatment of SSV. They also noted that an additional ARTG entry has been approved for another CAE device for treatment of both GSV and SSV.

ESC agreed that the comparators, radiofrequency ablation (RFA) and endovenous laser therapy (ELT) are appropriate and that the requested MBS listing for treatment of GSV and SSV is consistent with MBS item descriptors for these comparators. ESC noted the additional comparator, radiofrequency induced thermal therapy (RFITT).

ESC noted that the evidence for CAE is based on one randomised controlled trial versus RFA, and non-randomised studies versus RFITT and ELT. There are 12 single arm studies providing supportive evidence. ESC noted that the majority of data comparing safety and effectiveness of CAE with ELT and RFA were for treatment of the GSV, not the SSV. ESC questioned whether the evidence for the GSV is applicable to the SSV.

ESC noted that CAE appears non-inferior in safety to RFA and ELT in treating the GSV but that no conclusions can be drawn regarding the safety of CAE for treating the SSV. They noted that the vast majority of patients were treated for GSV reflux and no sub-group analysis was performed.

ESC noted anatomical differences are known to increase the adverse event risk for RFA and ELT treatment of the SSV compared with the GSV. It is unknown whether CAE treatment of the SSV would have the same safety concerns. The committee noted that no conclusions can be drawn regarding the long-term safety of CAE as long term data on safety is limited and questions have been raised about the elimination of cyanoacrylate glue from saphenous veins.

ESC noted that the comparative efficacy evidence provided supports non-inferiority of CAE to RFA and ELT and that the technical outcome of complete closure is a surrogate for clinical outcomes such as reduction of symptoms and quality of life, though this was accepted by MSAC in the application for the comparator, RFA.

ESC also noted that failure rates for CAE may have been significantly underestimated in the key trial due to drop-outs, observing the inconsistencies in the size of the study population reported over different time points. They also noted that due to the poor evidence base no conclusions can be drawn regarding the effectiveness of CAE treatment of the SSV; however, the committee acknowledged the clinical need for treatment options for the SSV given the safety concerns with RFA treatment of the SSV.

ESC noted that:

- the cost minimisation approach to the economic evaluation is appropriate if non-inferiority is accepted.
- if a cost-utility analysis were warranted, current data on EQ-5D show a (statistically insignificantly) greater improvement under RFA.

ESC noted:

- the high capital costs associated with the comparators, but acknowledged that the sensitivity analyses provided in the pre-ESC commentary suggest these costs have a negligible effect on the total cost per procedure.
- that the proposed service is assumed to be carried out in an outpatient setting as compared with RFA which is largely carried out in the inpatient setting and ELT which is sometimes carried out in the inpatient setting.

ESC questioned whether the outpatient setting for CAE is realistic, particularly in the short term and that the patient setting is important in considering the cost to the MBS and out of pocket costs for the service that are borne by patients or private health insurers. This is due to the difference in rebates as well as possibilities for funding gaps, (75% in the inpatient setting and 85% in the outpatient setting).

ESC noted that there are differences between the treatments in the non-MBS consumable costs (estimated as ~$**redacted** for the VenaSeal kit, compared with ~$**redacted** for RFA). These costs may also vary depending on the setting and the procedure kits used.

ESC noted the assumption of zero growth in the market associated with MBS listing of CAE and considered that the estimate of 5% growth in the sensitivity analyses is likely to be a more appropriate assumption for the base case, given the argument made for a current unmet need.

The committee also noted the weighted approach to inpatient and outpatient services taken by the critique is more likely to reflect clinical practice. That the current Extended Medicare Safety Net caps for RFA and ELT would also apply to CAE and therefore no impact to the MBS budget is assumed.

ESC noted that the descriptor should be amended to remove SSV if unsupported by the evidence and the wording changes proposed in the critique should be applied.

ESC noted that the out of pocket expenses for CAE are uncertain and differ depending on the patient setting. ESC considered that the high out of pocket costs for both the existing services and the proposed service are important considerations for consumers.

ESC Key ISSUES	ESC ADVICE	Pre-MSAC Applicant response
Evidence	Limited evidence regarding the applicability, safety and effectiveness of CAE for SSV.	The representation of SSV (>15%) is similar to that observed in clinical practice. No evidence of differential results between SSV and GSV exists.
Clinical Effectiveness	Effectiveness outcomes used are technical and do not necessarily represent clinical endpoints. Clinical endpoints are available in the evidence base (the Venous Clinical Severity Score [VCSS], the Aberdeen Varicose Vein Questionnaire [AVVQ] and the EQ-5D). Evaluation based on these outcomes should be presented.	The use of complete closure was accepted by MSAC in the application for RFA. ESC noted that the comparative efficacy evidence provided supports non-inferiority of CAE to RFA and ELT. The assessment of clinical severity (VCSS and CEAP) and quality of life (AVVQ and EQ-5D) support the results from the primary outcome, and demonstrate non-inferiority of CAE versus RFA and versus ELT.
Descriptor	The proposed MBS item descriptor includes treatment of both the GSV and the SSV, which was different to the initial application and ARTG listing (GSV treatment only).	The Applicant included SSV because of advice received from key opinion leaders and the Australian and New Zealand Society of Phlebology

	• The applicants plan an ARTG application in Sept 2017. Descriptor should be amended to follow the evidence (remove SSV if unsupported by evidence) and wording changes proposed in critique added MSAC listing will not specify the brand name; another CAE system includes both GSV & SSV	expressing a high clinical need for an effective, non-thermal treatment for SSV to be reimbursed in Australia. The Applicant believes sufficient evidence of effectiveness and safety of CAE in SSV exists, which was already accepted by the US FDA, Canadian HTA and other health technology assessors, and as such disagrees with the removal of SSV from the MBS item descriptor.
Sensitivity Analyses	5% + growth is more appropriate than 0% growth – given that in the pre-ESC response the applicants also advise that there may be some unmet need	The applicant acknowledges and agrees with ESC advice regarding an assumption of 5% market growth being a more appropriate base case, given the unmet clinical need.
All interventions assumed to be out of hospital by non-GP	Consider that RFA is mainly in hospital (with 75% rebate) compared to ELT and CAE in outpatient setting with 85% rebate. Former is not assumed in the model, therefore the OOP cost is underestimated if replaced by CAE – consider the weighted approach taken by the Assessors – where co-payment will be slightly higher CAE Price in clinical practice not available, important to know for OOP expenses.	The applicant has updated the budget impact analyses using the weighted approach to inpatient and outpatient services presented in the Critique.
Medicare safety net	Net caps of $80.05 for GSV or SSV and $79.35 for GSV and SSV. No impact on MBS budget assumed.	The applicant agrees with ESC that the current Extended Medicare Safety Net caps for RFA and ELT would also apply to CAE and therefore no impact to the MBS budget is assumed
Cost minimisation	Cost minimisation approach is only appropriate if the claim of non-inferior effectiveness and non-inferior safety is upheld. If a CUA is warranted, then current data on EQ5D shows statistically insignificantly higher improvement under RFA (compared to CAE)	The clinical data presented supported a conclusion of non-inferiority of CAE versus RFA and versus ELT, thus cost-minimisation is appropriate.
Capital costs	Larger capital costs in ELT and RFA – but CMA is based on assumption of similar settings so these are not included. Pre-ESC response showed negligible effects of lower capital costs.	The Applicant reiterates that the sensitivity analyses presented in the pre-ESC response showed negligible effects of lower capital costs.

15. Other significant factors

Nil

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

The Applicant thanks MSAC for supporting MBS listing of cyanoacrylate embolisation for the treatment of varicose veins due to chronic venous insufficiency of the great and small saphenous veins, accepting that CAE is non-inferior in terms of safety, effectiveness, and cost-effectiveness. We note ESC accepted the SBA sensitivity analysis that capital costs were a negligible component of costs associated with each comparator procedure. The Sponsor disagrees with MSAC that a comparable MBS fee could lead to over-servicing as the targeted patient population is well defined, and contends that a reduced fee will lead to a disincentive to provide the service. On balance, the overall resources required to deliver the service are comparable taking into account differences in technique and the negligible capital costs per procedure associated with the comparators. We consider this application represents an effective example of efficiency gains made possible by use of the expedited PASC pathway. Targeted clinician feedback made available to the Applicant by the respondent at an

early stage of this evaluation was very useful in enabling the evaluation to also consider SSV treatment. We note MSAC acknowledgement for the need for funding arrangements for implantable medical technology used to deliver an MBS service for private patients treated outside the hospital setting which will help avoid unnecessary expense to patients.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website