Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1384.1 – Bronchial Thermoplasty for the treatment of patient with asthma

Applicant: **Boston Scientific Pty Ltd**

Date of MSAC consideration: **MSAC 67th Meeting, 28-29 July 2016**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit MSAC website

1. Purpose of application and links to other applications

A resubmission requesting a new Medicare Benefit Schedule (MBS) listing of bronchial thermoplasty (BT) for severe persistent asthma was received from Boston Scientific by the Department of Health.

This public summary document (PSD) should be reviewed in conjunction with the PSD for Application 1384.

2. MSAC's advice to the Minister

After considering the available evidence presented in relation to safety, clinical effectiveness and cost effectiveness of BT for the treatment of severe persistent asthma, MSAC did not support public funding due to uncertain effectiveness and cost-effectiveness of BT in the target population.

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

MSAC recalled that it had not supported public funding of BT for the treatment of uncontrolled severe asthma at the April 2015 meeting because of uncertainties with the patient population, the place of the proposed treatment in the clinical management of severe persistent asthma, its clinical effectiveness and consequently its cost effectiveness.

The previous application had proposed the use of BT for the treatment of uncontrolled severe asthma despite treatment and adherence with optimised asthma therapy (OAT). OAT was defined as the maximal inhaled therapy including high-dose inhaled corticosteroids (ICS) combined with a long-acting $beta_2$ agonist. BT was proposed as an alternative option to: maintenance treatment with Maintenance Oral Corticosteroids (MOCS); the humanised monoclonal antibody omalizumab (OM); or best supportive care/optimised asthma therapy alone (BSC/OAT) for people with uncontrolled, severe, non-allergic and allergic asthma.

Safety and efficacy comparisons between BT and BSC/OAT in the previous application were based on three randomised controlled trials (RCTs), namely AIR, AIR2 and RISA. MSAC noted the AIR trial was later excluded because the trial population was not representative of the population targeted for BT on the MBS. At the time, limitations in the evidence which compared BT with either MOCS or OM meant that MSAC was uncertain of the clinical safety or efficacy claims made by the applicant.

MSAC noted that the resubmission provided a new positioning of BT therapy as an end of line treatment for patients with uncontrolled severe asthma despite OAT who have received oral corticosteroids (OCS) and who have failed or are ineligible to receive OM. The proposed threshold of exposure to OCS prior to BT would be the same as that currently applied in the Pharmaceutical Benefits Scheme (PBS) restriction for OM. MSAC accepted that this new positioning addressed some of their previous concerns regarding positioning of BT in the management algorithm.

MSAC was concerned that no new RCTs assessing the safety and efficacy of BT were presented in the resubmission. Data from the AIR2 and RISA trials therefore remained the basis of the safety and efficacy claims made by the applicant. MSAC noted that the AIR2 study was a double-blind, sham-controlled trial that randomly assigned 288 participants with symptomatic, severe asthma 2:1 to BT (n=190) or sham treatment (n=98). RISA was a smaller (n=34), open-label RCT that provided supportive information. MSAC recalled that it had expressed a number of concerns regarding the AIR2 trial during consideration of the previous submission and was concerned about the short follow-up of control patients in the RISA study.

MSAC noted the safety data from these trials, which had been considered at its April 2015 meeting, remained unchanged in the current resubmission.

When considering the clinical effectiveness of the proposed therapy, MSAC was concerned that in the AIR2 trial, a statistically significant difference was not observed in patients' Asthma Quality of Life Questionnaire (AQLQ) scores (primary outcome measure) at baseline and following treatment using intention to treat analysis. MSAC noted a statistically significant difference was achieved using the per-protocol analysis when Bayesian methods were used but not when analysed using a Frequentist approach. Improvements in AQLQ scores from baseline were also evident among those who received the sham treatment, providing evidence of a 'sham effect'. MSAC noted that this may have led to a smaller difference between treatment groups which may have biased the results against the intervention. However, as a substantial 'sham effect' was observed for several additional outcomes, MSAC remained concerned about the clinical effectiveness of BT.

MSAC noted that five-year follow-up extension data included in the resubmission provided some indication of long-term outcomes in BT subjects. However, MSAC was concerned that only those patients randomised to BT were followed for this duration and noted that therefore, the outcomes for those who would not have received the intervention were unclear. Supporting this concern, MSAC noted the findings of a study cited by its Evaluation Sub-committee (Chen W et al, 2016) which indicated that the asthma status of patients with severe asthma can improve over time.

MSAC noted that previous use of OCS or OM was not a requirement for entry into the AIR2 or RISA trials. MSAC noted that the patient population in the RCTs was broader and had less severe asthma than the population proposed in the current resubmission. MSAC considered

that this increased the uncertainty regarding the applicability of the findings of these RCTs to the proposed population.

MSAC reviewed the new post hoc subgroup analyses of data from the AIR2 trial undertaken by the applicant to investigate whether the outcomes were applicable to the more targeted proposed population. MSAC was unconvinced by the applicant's claim that the treatment effects in the more severe patient group favoured BT relative to sham treatment. Overall, MSAC concluded there was insufficient high-level comparative evidence of improved health outcomes or changes in management in the target population.

MSAC noted that the two studies (NCT01350336 and NCT01185275) due to report in the near future are open label and observational studies. Thus, no new RCTs were evident.

MSAC considered the updated economic model provided in the resubmission and noted that it addressed previous concerns around analysis of missing utility data and the application of asthma-related mortality data. MSAC was concerned with the number of consultations included for a full course of BT (currently listed as four, although six is more likely) and with the costing of BT procedures as day cases (an overnight stay is current practice). However, MSAC noted that these were not significant drivers of the model. The model was highly sensitive to changes in the time horizon. MSAC noted that resubmission modified the model length from 10 years to 20 years, although no new evidence was provided to support this change. Additionally sensitivity analysis demonstrated that the ICER was highly sensitive to assumptions of treatment effect of BT beyond the controlled period of the trials. MSAC noted that the assumption of treatment effect persistence for the life of the model was not supported by the evidence base. MSAC concluded that the ICER of $14,045 per QALY is therefore likely to represent a scenario that favours BT and cannot be relied upon as a consequence.

MSAC noted the MBS costings based on four uptake scenarios - base, realistic, high and very high. MSAC considered that the estimates for each of these scenarios were uncertain given the concerns raised in relation to the economic model.

4. Background

MSAC considered Application 1384 at its April 2015 meeting. MSAC did not support public funding for BT for the treatment of severe persistent asthma because of uncertainties with the patient population, its place in the clinical management of severe persistent asthma, its clinical effectiveness and resulting uncertain cost-effectiveness. The PSD for this application can be viewed on the MSAC website.

5. Prerequisites to implementation of any funding advice

The applicant is the manufacturer of the Alair® Bronchial Thermoplasty System, which was listed on the Australian Register of Therapeutic Goods (ARTG) in 2012 for the treatment of asthma in patients 18 years and older.

No other BT systems or related interventions are currently listed on the ARTG, considered in the assessment or were identified during the course of the critique.

BT is conducted as an inpatient procedure in Australia, given the equipment and facility requirements, and patients undergoing the treatment would require the services of a medical team (pulmonologist or an experienced bronchoscopist) throughout the treatment period.

6. Proposal for public funding

The proposed population targeted to receive BT on the MBS comprises adults (at least 18 years old) with uncontrolled severe asthma despite optimised asthma therapy (OAT) who have received a stipulated threshold level of exposure to oral corticosteroids (OCS) (i.e., either daily oral corticosteroids for at least 6 weeks, OR a cumulative dose of oral corticosteroids of at least 500 mg prednisolone equivalent in the previous 12 months, unless contraindicated or not tolerated) and have failed or are ineligible to receive a PBS listed biologic asthma maintenance therapy (which currently only includes omalizumab (OM)).

The resubmission states that this patient population represents a patient group with a greater clinical need compared to the patient population targeted in Application 1384 because they have no further effective asthma treatment options available to them.

An additional requirement, not outlined in the descriptor, but stipulated in the manufacturer's directions for use of the BT catheter, is that a patient must have stable asthma symptoms without an increase in rescue inhaler usage and no recent exacerbations or infections in the 4 weeks preceding the procedure. If a patient meets these criteria, he or she should receive prednisone at 50 mg/day for the 3 days before the procedure.

It is proposed the same MBS Item will be claimed for each of the three procedures (whilst each procedure applies the thermoplasty to a different area of the lung, the total time and resources for each procedure is approximately the same).

Table 1 sets out the proposed MBS item descriptor and restrictions on the use of BT.

Table 1 Proposed MBS item descriptor

Category [3] – [Therapeutic Procedures]
BRONCHIAL THERMOPLASTY for delivery of thermal energy to the airway wall as a means of reducing excess airway smooth-muscle in patients with uncontrolled severe asthma (a) the patient to whom the service is provided: (i) must be under the care of the same physician for at least 12 months AND (ii) must have a diagnosis of asthma confirmed and documented by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma AND (iii) must have failed to achieve adequate asthma control with optimised asthma therapy, despite adherence to correct inhaler technique, which has been formally assessed and documented, and adherence to optimised asthma medication, which has been formally monitored AND (iv) has received treatment with oral corticosteroids, either daily oral corticosteroids for at least 6 weeks, OR has received a cumulative dose of oral corticosteroids of at least 500 mg prednisolone equivalent in the previous 12 months, unless contraindicated or not tolerated AND (v) has failed to respond to OR is not eligible to receive OR is contraindicated/intolerant to any monoclonal antibody asthma maintenance therapy available on the PBS (b) The following criteria indicate failure to achieve adequate control: (i) While receiving optimised asthma therapy in the past 12 months, experienced: (1) at least 1 admission to hospital for a severe asthma exacerbation,

OR (2) at least 1 severe asthma exacerbation, requiring documented use of systemic corticosteroids (oral corticosteroids initiated or increased for at least 3 days, or parenteral corticosteroids) prescribed/supervised by a physician. (c) optimised asthma therapy includes: (i) maximal inhaled therapy, including high-dose inhaled corticosteroid (budesonide 1600 micrograms per day or fluticasone propionate 1000 micrograms per day or equivalent), plus long-acting beta-2 agonist therapy (at least salmeterol 50 micrograms bd or eformoterol 12 micrograms bd) for at least 12 months, unless contraindicated or not tolerated, (d) failure to respond to a monoclonal antibody asthma maintenance therapy means the patient did not meet the criteria for continuing treatment on the PBS (e) the service is performed by a specialist or consultant physician with appropriate training in bronchial thermoplasty To be claimed a maximum of three times in the patient's life-time. Multiple services rule (Anaes.)
Fee: [:$770.85 Benefit: 75% = $578.14]

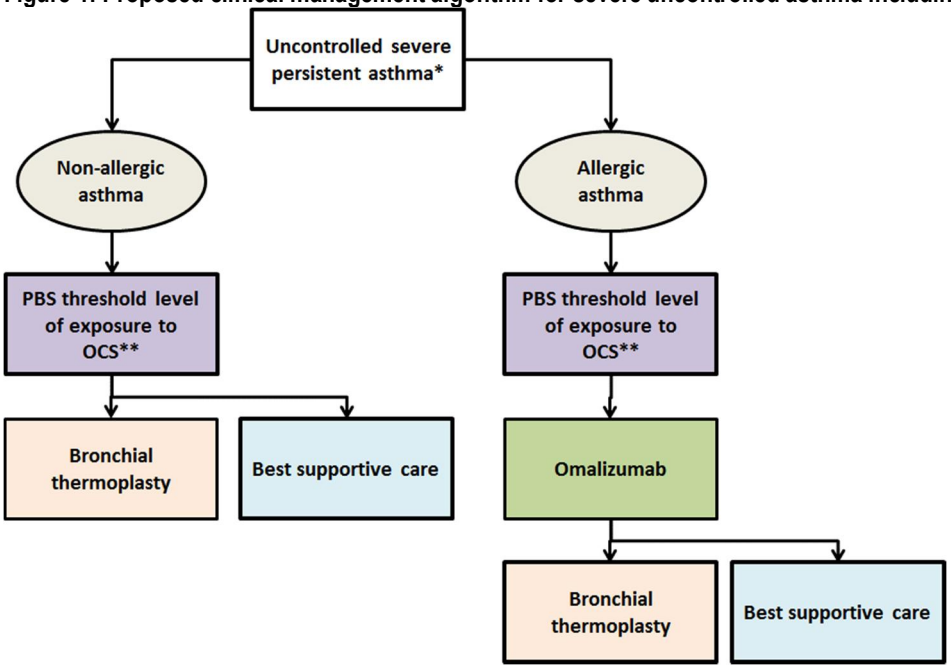
7. Summary of Public Consultation Feedback/Consumer Issues

No consumer issues were raised.

8. Proposed intervention's place in clinical management

The proposed clinical algorithm for the intended use of BT is presented in Figure 1 (extracted from the resubmission). This treatment algorithm assumes the diagnosis of uncontrolled severe asthma consistent with the current clinical management algorithm. BT represents a treatment option after OCS (non-allergic asthma) and after OM (allergic asthma).

Figure 1: Proposed clinical management algorithm for severe uncontrolled asthma including thermoplasty



Abbreviations: OCS, oral corticosteroids

Note:

* The algorithm assumes, prior to BT, for confirmation of uncontrolled severe asthma, patients have undergone extensive assessments either by a respiratory specialist or by a general physician experienced in the management of patients with severe asthma, to exclude the patient's symptoms are due to an underlying non-asthma related cause, to identify and manage or eliminate factors which may aggravate underlying asthma, to optimise the patient's asthma management skills, to assess and document the correct use of inhalers and to monitor and assess the patient's adherence and compliance to their current asthma medication

** Treatment with oral corticosteroids, either daily oral corticosteroids for at least 6 weeks, OR a cumulative dose of oral corticosteroids of at least 500 mg prednisolone equivalent in the previous 12 months, unless contraindicated or not tolerated. Patients contraindicated, intolerant or resistant to oral corticosteroids pass on through to the next line of treatment

[a] Uncontrolled severe asthma is defined as asthma symptoms not well-controlled despite optimised asthma therapy which comprises adherence to maximal inhaled therapy, including ICS (budesonide 1600 µg/day or fluticasone 1000 µg/day or equivalent), plus LABA (at least salmeterol 50 µg bid or eformoterol 12 µg bid or equivalent), unless contraindicated or not tolerated, after ruling out non-asthma related causes, avoidable aggravating factors, poor medication compliance and bad inhaler technique.

[b] The algorithm does not preclude the possibility that patients may recycle back through any of the available therapies except bronchial thermoplasty, which is a once per life-time therapy. However, a patient who fails to respond to a course of PBS-subsidised omalizumab for the treatment of uncontrolled severe allergic asthma will not be eligible to receive further PBS-subsidised treatment with omalizumab for this condition within 6 months of the date on which treatment was ceased.

9. Comparator

The resubmission nominated OAT alone as the appropriate main comparator.

Asthma patients are expected to remain on OAT (i.e. inhaled corticosteroids, long-acting beta agonists, and short-acting beta agonists when needed) throughout the BT treatment period and as required after treatment. In the resubmission, BT is proposed to be eligible to patients with the highest clinical need. Hence in the proposed target patient population, there is no further effective treatment option available and OAT alone remains the only comparator.

10. Comparative safety

No new randomised controlled trials assessing the efficacy and safety of BT were identified in the resubmission. AIR2 and RISA remain the only completed randomised controlled trials of BT conducted in adult subjects with uncontrolled severe asthma.

The resubmission stated that the key safety findings from AIR2 were that BT treatment was associated with a transient increase in respiratory adverse events peri-procedure. Most of these adverse events were mild to moderate in severity, occurred soon after a procedure, were easily managed and resolved with standard therapy. There was no increased risk of adverse events occurring with subsequent procedures in BT-treated subjects. No clinically significant negative radiologic findings were observed related to BT treatment. The resubmission claimed that the overall safety profile of subjects in the AIR2 trial demonstrates the BT procedure is well tolerated by patients with uncontrolled severe asthma.

The extended assessment of harms for BT were presented in Application 1384 based on the long-term (5 year) follow-up data from the AIR2 and RISA trials. The data show the adverse events and safety concerns due to BT are confined to the treatment period.

The critique noted that BT is associated with a transient increase in respiratory adverse events peri-procedure, accompanied by an increased frequency of unscheduled physician office visits and hospitalisations for respiratory adverse events. Overall, most adverse events experienced by subjects receiving BT were mild to moderate in severity. There was no increase in the rate of respiratory adverse events attributed to subsequent BT treatment sessions. In contrast, post-treatment, BT was associated with a lower frequency of respiratory adverse events accompanied by fewer unscheduled physician office visits, emergency visits and hospitalisations.

A meta-analysis study including all three BT Trials (RISA, AIR and AIR2) 429 participants) showed improvement in quality of life at 12 months in participants who received BT that did not reach clinical significance (Torrego A et al 2014).

11. Comparative effectiveness

The clinical efficacy claim and evidence base remain unchanged from Application 1384.

New post hoc subgroup analyses of the AIR2 trial were presented as evidence to support the claim that similar gains from the use of BT are expected in more severe uncontrolled asthmatics. In these subgroup analyses, a list of single variables such as AQLQ, severe exacerbations, FEV1 and use of maintenance asthma medication were used to define alternative severe subgroups. The resubmission claimed that the subgroup analyses results point to a trend towards a greater absolute BT treatment effect in the patient group targeted for MBS reimbursement.

The resubmission claimed that BT plus ongoing OAT, compared to OAT alone, for the treatment of uncontrolled severe asthma is superior in the longer term. The clinical claim is based on the two randomised controlled trials (AIR2 and RISA) of BT in patients with uncontrolled severe asthma, with post-treatment follow-up periods of one year.

Five-year follow-up extension studies provide some suggestion of long-term outcomes and safety in BT subjects. However, the lack of comparison data on sham operated controls beyond 12 months in the AIR2 trial (as sham operated controls exited the study after the 12-month follow-up) makes efficacy data less useful especially because the natural history of severe asthma shows considerable improvement (70%) after the first year, which persists at the 10-year follow-up.

12. Economic evaluation

An updated modelled economic evaluation was presented. The evaluation is in the form of a cost-utility analysis and in addition, a stepped economic evaluation is presented. The model structure was changed to reflect only one comparator (OAT alone). Other changes to the economic modelling inputs included updated utility values, revised cost inputs and a new mortality rate.

The results of the updated economic evaluation are shown in Table 2.

Table 2 Results of the economic evaluation

	BT + OAT	OAT alone	Increment
Costs	$34,350	$26,667	$7,683
QALYs	10.9181 (95% CI)	10.3711 (95% (CI)	0.5470
Incremental cost-effectiveness ratio			$14,045

Abbreviations: BT, bronchial thermoplasty; ICER, incremental cost-effectiveness ratio; OAT, optimal asthma therapy; QALY, quality-adjusted life year
Note: All costs/outcomes discounted at 5% per annum
CI=confidence interval (Note that no 95% CIs are presented by the applicant).

For BT compared to OAT alone, the ICER of $14,045 for the updated economic evaluation compares to an ICER of $28,435 in the original Application 1384. The difference between the previous and current ICER is driven by differences in time horizon (10 years vs 20 years), extrapolation assumptions following Year 5 (decrease in treatment effect to converge with OAT by year 10 vs fully maintained treatment effect 20 years), structural changes to mortality (mortality no longer permitted from ER visits) and the new lower cost for BT procedure ($1,126.60 vs $770.85).

The economic model is most sensitive to the time horizon/extrapolation of treatment effect, exacerbation rates and utility values. The economic model does not appear to be highly sensitive to mortality rate, which was set at 1.8%; other literature supports figures of 0.8-1.1% estimates.

13. Financial/budgetary impacts

The resubmission stated that the actual use of BT will be limited by the caseload capacity to perform the procedure. There are currently only five centres equipped to perform BT in Australia. The resubmission acknowledged that the uptake of BT in Australia has been relatively slow and the proposed patient population is more restrictive

As specified in Application 1384, the base case analysis assumed that the number of public and private centres equipped with the Alair® Bronchial Thermoplasty System would grow to 20 over time and each centre expected to perform up to 48 procedures each year. Of the 20 centres, 8 of them (40%) are expected to be private centres; thus generating cost implications to the MBS.

In the resubmission, the cost of the BT procedure is $770.85 and the cost per catheter is $2,750. The costs of anaesthetist services have also been included in the analysis.

Under this caseload/uptake scenario, the cost of BT procedures to the MBS was estimated to be approximately $86,419 in Year 1, increasing to $265,478 in Year 5. When combined with additional MBS costs due to specialist consultations and anaesthetics, the total MBS cost is estimated to be approximately $123,815 in Year 1, increasing to $462,379 in Year 5.

14. Key issues from ESC for MSAC

ESC's primary concern was that application 1384.1 Bronchial Thermoplasty (BT) for the treatment of uncontrolled severe asthma had been resubmitted with no new randomised controlled trial (RCT) data.

ESC noted that the resubmission provides a new positioning of BT therapy as an end of line treatment for patients with uncontrolled severe asthma despite Optimal Asthma Treatment (OAT) who have received oral corticosteroids (OCS) and who have failed or are ineligible to receive omalizumab (OM). ESC agreed that this new positioning is likely to have addressed most of MSAC's previous concerns regarding positioning of BT in the management algorithm.

However, ESC was concerned that the repositioning of BT therapy, and the lack of new clinical data, meant that the resubmission had no patient data on the actual target population. In particular, ESC questioned whether claims for fewer emergencies are valid for a more severe population.

ESC noted that the patient population in the RCTs was broader and had less severe asthma than the population proposed in the application. This therefore increased the uncertainty that the outcomes of those RCTs could apply to uncontrolled severe asthma patients.

ESC noted that the clinical claim in the resubmission was based on only two RCTs, which varied in the severity of the patients. The RISA trial included 34 participants with symptomatic, severe asthma and the AIR2 trial randomly assigned 288 participants with symptomatic, persistent asthma 2:1 to BT (n=190) vs sham (n=90). Further, these RCT's were funded by the manufacturer and they had potential for conflict of interest. ESC also noted that the studies showed no significant improvements in pulmonary function.

ESC was concerned that only one study (AIR2) was double blinded and, due to ethical reasons, only remained double blinded for one year. ESC also noted that whilst the AIR2 study constituted the pivotal evidence for BT, the reliability of the findings of this trial are questionable as the 12-month follow-up small changes in Asthma Quality of Life Questionnaire (AQLQ) did not reaching the threshold for clinical significance of 0.5. ESC discussed a number of other concerns with the AIR2 trial including the type of statistical analysis used (Bayesian statistics) and that the allocation methods and concealment of the randomisation sequence were inadequately described and therefore the AIR2 trial was at an unknown risk of selection bias. Blinding was imperfect on the AIR2 study beyond the first BT procedure (as BT participants were able to tell that they had received BT). ESC was also concerned that the efficacy of BT was uncertain due to the substantial 'sham effect' observed in many outcomes. Results from the AIR2 suggest a large placebo/Hawthorne effect in the studies without a sham intervention.

ESC noted that the two studies (NCT01350336 and NCT01185275) to be completed in the near future are open label and observational studies; and thus, no new RCT studies will be completed in the near future.

ESC was also concerned that the resubmission demonstrated no large clinical registry data.

ESC also noted that recent data on the natural history of severe asthma showed that a significant proportion (70%) of patients with severe asthma improved to mild or moderate asthma after the first year, perhaps due to patients learning how to better manage themselves after a year or to the natural disease course (Chen W et al Thorax 2016; 71:267-275).

ESC noted that the resubmission had revised utilisation of costs and ESC agreed that, due to this, some errors in the previous application had been corrected

Overall ESC agreed there was large uncertainty in the data and large uncertainty regarding the clinical and cost effectiveness of this application.

ESC noted that the item descriptor had been revised to better reflect the new last line repositioning. ESC queried whether the revised wording should also include an adult only restriction as the studies only included people over 18 years of age and below 65 years of age.

ESC discussed the number of consultations required for a full course of BT. ESC noted that whilst the application allows for four consultations, the policy area maintains that a full course of treatment may require six. ESC was concerned that the fee did not include follow-up visits, that consultations were not included in the fee for each procedure and that the cost estimates presented assumes patients are discharged on the same day of the procedure when the current practice has included an overnight stay. ESC discussed that in practice, most patients remain in hospital overnight for observation and agreed that an 'outpatient setting' may not be appropriate.

ESC noted that because of the repositioning of BT, comparisons between BT and OCS and between BT and OM are no longer applicable. ESC was satisfied with the main comparator being OAT alone in the resubmission, however it was noted that in practise 'best supportive care' is likely to contain combinations of therapy between OAT, MOCS and OM.

ESC hoped to see data that BT could lead to changes in medication usage or in symptomatic control in severe asthma. ESC agreed that the resubmission is missing data demonstrating that the application will reduce the amount of OCS needed in severe patients.

15. Other significant factors

Nil.

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

Boston Scientific are disappointed with MSAC's decision not to recommend bronchial thermoplasty for listing on the Medicare Benefits Schedule at this time. The clinical literature supports BT as a therapeutic consideration for some carefully chosen patients in Australia who, despite optimal medical treatment, have persistent burden of disease, asthma exacerbations, emergency department visits or hospitalisations. The applicant believes that the clinical literature shows a therapeutic benefit to a broad indication of severe, persistent asthma patients in Australia and the positioning of BT within this resubmission as an end-of-line treatment offered hope to patients not responding to other treatments. Finally, evidence published since this submission demonstrates a positive correlation between reduction of anatomical smooth muscle (ASM) and (i) asthma control, (ii) reduced exacerbations, and (iii) reduced frequency of ED visits. (n.b. BT is the only treatment for asthma targeting and reducing ASM) [Pretolani M , Bergqvist A, Thabut G, et al. JACI 2016 Sep 5 pii: S0091-6749(16)30896-X. doi: 10.1016/j.jaci.2016.08.009. [Epub ahead of print]; PUBMED LINK].

17. Further information on MSAC

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