PUBLIC SUMMARY DOCUMENT
Product: SALBUTAMOL SULFATE, oral pressurised inhalation, 100 micrograms (base) per dose (200 doses), CFC-free formulation with spacer, VentSpacer®
Sponsor: Medical Developments International Ltd
Date of PBAC Consideration: March 2010

1. Purpose of Application

To request PBS listing for salbutamol sulfate pressurised metered dose inhaler (pMDI) (Ventolin®) with an asthma spacer (Space Chamber®), packaged together in an "Asthma Procedure Pack" (VentSpacer®) as a Restricted Benefit for patients who are unable to achieve coordinated use of other metered dose inhalers containing salbutamol or patients at risk of an acute asthma episode.

2. Background

Ventolin brand of salbutamol sulfate pMDI 100 micrograms per dose has been available on the PBS since 1972. An application for listing of an asthma spacer device has not previously been considered by the PBAC.

3. Registration Status

Ventolin Inhaler CFC-Free (salbutamol 100 microgram (as sulfate) pMDI) was TGA registered on 30 June 1998 for the relief of bronchospasm in patients with asthma or chronic obstructive pulmonary disease, and for acute prophylaxis against exercised-induced asthma and other stimuli known to induce bronchospasm.

The Space Chamber asthma spacer was TGA registered as a Medical Device Included Class 1 on 18 July 2007 with the following intended purpose:

> "a hand-held, portable device used to deliver aerosolized medication directly into the mouth of the user for delivery to the lungs".

The VentSpacer Asthma Procedure Pack was TGA registered as a Medical Device Included Class 1 on 8 December 2009 with the following intended purpose:

> "This pack contains an Aerosol Chamber to enhance the delivery of aerosolised medication from the included pressurised metered dose inhaler for enhanced delivery to the lungs".

4. Listing Requested and PBAC's View

Restricted Benefit

Patients who are:

- unable to achieve coordinated use of other metered dose inhalers containing salbutamol; or
- at risk of an acute asthma episode.

NOTE:

Patients should be restricted to one VentSpacer script per annum. Should they lose or damage their spacer then another script for VentSpacer may be provided. All other scripts of SALBUTAMOL SULFATE oral pressurised inhalation 100 microgram (base) per dose (200 doses), CFC-free formulation should be delivered through a pack not containing an asthma spacer.

The PBAC considered that the requested restriction for patients at risk of an acute asthma episode would in practice include all patients with asthma. The PBAC considered that the note associated with the requested listing restricting to one VentSpacer per annum per patient via a restricted benefit listing was unrealistic and may be clinically inappropriate.

The PBAC's view was that the submission raised a number of policy issues, including whether the PBS was the most appropriate mechanism for the subsidy of spacer devices. The PBAC also noted that the submission requested the listing of one brand of spacer with one brand of salbutamol inhaler.

5. Clinical Place for the Proposed Therapy

Australian clinical guidelines recommend the use of spacers by adults with poor coordination when using a pMDI, by children of all ages, and during an acute asthma attack. Spacer devices hold the aerosol cloud produced from pMDIs in a confined space, and allow subsequent inhalation. They have a valve system, which can assist drug delivery in patients who have problems coordinating actuation of the pMDI and inhalation. They are effective in decreasing the oropharyngeal deposition of medication and increasing the relative dose delivered to the lungs. The submission stated that listing of salbutamol delivered via a spacer on the PBS would reduce the price to the consumer, and with the delivery of a quality use of medicine (QUM) program, would improve awareness and clinical use of asthma spacers.

6. Comparator

The submission nominated salbutamol sulfate pressurised inhalation in breath actuated device (Airomir Autohaler®) as the comparator for patients unable to achieve coordinated use of other metered dose inhalers containing salbutamol. The submission nominated salbutamol nebules or nebuliser solution administered via nebuliser as the comparator for patients at risk of an acute asthma episode. The PBAC noted that the appropriate comparator was not clear but did not consider delivery of salbutamol using alternate delivery systems was appropriate.

7. Clinical Trials

One randomised, placebo-controlled, cross-over trial (Giannini 2000) which compared pMDI, pMDI plus spacer (Volumatic) and breath-activated Autohaler in stable moderate asthma; and one Cochrane review (Cates 2006, updated in 2008) which compared beta-2 agonists delivered by MDI plus spacer (any type) versus delivery by a nebuliser in acute asthma were presented by the submission. None of the studies included the Space Chamber used in the VentSpacer Procedure Pack.

Trial ID / First author	Protocol title / Publication title	Publication citation
Giannini D, et al. (2000)	The protective effect of salbutamol inhaled using different devices on metacholine bronchoconstriction.	Chest 2000; 117:1319-1323.
Cates CJ, et al. (2006)	Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma.	Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD000052. DOI:10.1002/14651858.CD000052.pub2.

8. Results of Trials

In the Giannini (2000) study there was no statistically significant difference in provocative dose of methacholine inducing a 20% fall in the forced expiratory volume in one second ($FEV_{1)}$ or change in FEV_1 between pMDI plus Volumatic spacer and Autohaler. The PBAC noted that Giannini (2000) was a small study and was not powered to demonstrate non-inferiority. The clinical relevance of the outcome from this study was considered uncertain by the PBAC.

In the Cates (2006) review, there were no statistically significant differences between delivery via pMDI plus spacer versus nebuliser in acute asthma in a range of outcomes including hospital admissions, duration in Emergency Departments (ED) (adults only), final rise in FEV_1, 30 minutes rise in FEV_1, final FEV_1 rise in severe asthmatics and final risk in peak flow. The only statistically significant difference was observed for duration in ED in children, favouring pMDI plus spacer. The Cochrane review concluded that MDIs with spacer were at least equivalent to nebuliser therapy. The Cochrane review presented relates to the treatment of acute asthma attack not for the treatment of chronic asthma which is the population primarily targeted with the requested listing. The PBAC noted that the Space Chamber was not used in any of these studies. No clear evidence was available which showed that the treatment effect was improved by one particular kind of spacer.

The submission did not present any safety information specific to the use of the Space Chamber or the proposed combination product.

9. Clinical Claim

The submission described the proposed product as non-inferior in terms of comparative effectiveness and safety over Airomir Autohaler and nebuliser. The Space Chamber was not used in any of the studies presented. The submission's claims rest on inferences that all spacer devices are equally effective.

10. Economic Analysis

The submission presented three cost comparison analyses and reported that there were cost-savings in all three cases. The comparison with Airomir Autohaler relied on the assumption that only one VentSpacer pack was prescribed per year.

The PBAC considered that the cost saving approach presented in the submission is highly unlikely to eventuate in practice as patients who currently achieve the desired health outcome using the autohaler are unlikely to switch to the pMDI with spacer if it were to be listed.

11. Estimated PBS Usage and Financial Implications

The likely number of patients treated with VentSpacer per year were estimated to be between 10,000 and 50,000 in Year 1 of listing, rising to between 100,000 and 200,000 in Year 5 of listing and the net financial cost per year (less patient co-payments) to the PBS was < $10 million in Year 5.

12. Recommendation and Reasons

The PBAC considered that the requested restriction for patients at risk of an acute asthma episode would in practice include all patients with asthma. The PBAC considered that the note associated with the requested listing restricting to one VentSpacer per annum per patient via a restricted benefit listing was unrealistic and may be clinically inappropriate.

There is no mechanism available to restrict prescribing of an item on the PBS to once per year via a restricted benefit listing. Additionally, the PBAC noted that the Asthma Management Handbook 2006 recommends that spacers be replaced at least every 12 months, and that additional spacers could appropriately be prescribed should the patient lose their spacer. The PBAC also noted that prescribers and patients may wish to obtain more than one spacer to use in various locations, such as at home and at school. Further, the PBAC noted that should an authority required listing be considered, the volume of authority requests would be high and would result in a substantial increase in authority applications to Medicare Australia.

In relation to the other part of the requested restriction for patients unable to achieve coordinated use of other metered dose inhalers containing salbutamol, the PBAC noted that the VentSpacer product contains Ventolin brand salbutamol inhaler only, rather than the spacer component of VentSpacer being available with any PBS listed salbutamol inhaler.

In relation to the patient population for which listing was requested, the PBAC noted that the Cochrane review (Cates et. al. 2006) which compared beta-2 agonists delivered by metered dose inhaler (MDI) plus a spacer (various types) versus delivery by a nebuliser in acute asthma was not representative of the target patient population requested, as the Cochrane review relates to the treatment of acute asthma attack, rather than the treatment of chronic asthma (patients at risk of an asthma attack) which was the population primarily intended with the requested listing.

The submission nominated salbutamol sulfate pressurised inhalation in breath actuated device (Airomir Autohaler) as the comparator for patients unable to achieve coordinated use of other metered dose inhalers containing salbutamol and salbutamol nebules or nebuliser solution administered via nebuliser as the comparator for patients at risk of an acute asthma episode. The PBAC agreed with ESC that the appropriate comparator is not clear but did not consider delivery of salbutamol using alternate delivery systems was appropriate.

The PBAC noted the submission presented one randomised, placebo-controlled, cross-over trial (Giannini 2000) which compared pressurised metered dose inhaler (pMDI) (Ventolin brand), pMDI plus spacer (Volumatic brand) and breath-activated pMDI (Autohaler brand) in stable moderate asthma. The results of the study showed no statistically significant difference in a provocative dose of methacholine inducing a 20 % fall in forced expiratory volume in one second (FEV_1) or change in FEV_1 between the pMDI plus Volumatic spacer and the Autohaler. The PBAC noted that Giannini was a very small trial with only 18 subjects and that the study was not powered to demonstrate non-inferiority. Importantly the PBAC noted that the Space Chamber spacer contained in VentSpacer was not used in the Giannini study. For these reasons the PBAC considered that the clinical relevance of the outcome of Giannini was uncertain.

The PBAC noted the Cochrane review (Cates 2006) also did not use the Space Chamber spacer and that the Cochrane review did not provide evidence that the treatment effect is improved by any one particular kind of spacer. The Cochrane review found that in treatment of acute asthma attack there was no statistically significant differences observed between delivery via pMDI plus spacer versus nebuliser in acute asthma measured by a range of outcomes.

The PBAC noted the submission did not present any safety information specific to the use of the Space Chamber or VentSpacer.

The PBAC noted that the submission presented three cost comparison analyses based on the assumption of VentSpacer being of equivalent clinical effectiveness and safety to the nominated comparators. The PBAC noted that the cost comparison analysis to Airomir Autohaler relied on the assumption that only one VentSpacer pack would be prescribed per year. The PBAC considered this to be uncertain considering the restriction issues noted above (inability in the requested restriction to limit prescribing to one VentSpacer per year and the appropriateness of limiting to one per year) and that the cost saving claim is unlikely to eventuate in practice as patients who currently achieve the desired health outcome using an autohaler are unlikely to switch to the pMDI with spacer if it were to be listed.

The PBAC noted the submission reported that the requested price of $38.60 for VentSpacer is slightly lower than the cost of purchasing the components separately ($41.82). However, the PBAC noted that there are other spacers available that are less expensive than the price of $26.60 used for the Space Chamber in the submission and that other brands of salbutamol MDIs are also available at a lower price than the price of $15.22 used in the submission. The PBAC considered that no evidence was presented in the submission to substantiate the significant price premium requested for the Space Chamber spacer component of VentSpacer over other spacers currently available on the market.

The PBAC considered that the utilisation of VentSpacer was uncertain. The PBAC noted that there would be the potential for use beyond the proposed restriction such as prescribing for patients with other respiratory conditions, for example chronic obstructive pulmonary disease. The PBAC also noted that it is likely that in some instances more than one spacer would be prescribed in a period of 12 months. The PBAC also considered that there is the possibility that spacers currently provided in other places, such as emergency departments of public hospitals, and bought over the counter at pharmacies would be switched to provision through the PBS.

The PBAC recognised that spacers have an important place in the treatment of asthma and that the use of spacers is supported by Australian practice guidelines. However the PBAC considered that the submission failed to present sufficient evidence to show that a health benefit to patients or society would result from subsidising VentSpacer via the PBS, or that an improvement in the quality use of medicines in asthma would result from the listing. The PBAC considered that there are some barriers to affordable access to asthma spacers in the Australian community; however the submission did not present any information on potential gaps in access to spacer devices to provide evidence of a clinical need for the PBS subsidy of spacers in Australia. The PBAC was uncertain if providing PBS subsidised spacers would assist with acknowledged gaps in quality use of medicine in asthma such as the lack of use of spacers even in those patients who currently own a spacer.

The PBAC noted that the submission raised a number of policy issues, including whether the PBS was the most appropriate mechanism for the subsidy of spacer devices. The PBAC also noted that the submission requested the listing of one brand of spacer with

one brand of salbutamol inhaler. The PBAC noted that spacers are also used with other medications besides salbutamol in the treatment of asthma, such as with inhaled corticosteroids. Should a spacer device be recommended for listing on the PBS it was uncertain if it was appropriate to restrict supply to the combination with one drug and/ or brand of inhaler.

Therefore the PBAC recommended rejection of the submission on the basis of uncertain clinical and uncertain cost effectiveness.

The PBAC noted that the submission meets criteria for independent review.

Recommendation:
Reject

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor would like to continue to work with the PBAC to determine the best pathway for this important product to be made available to asthma patients through the Pharmaceutical Benefits Scheme.