Respiratory Subcommittee of PTAC
Meeting held 2 September 2015

(minutes for web publishing)

Respiratory Subcommittee minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2008*.

Note that this document is not necessarily a complete record of the Respiratory Subcommittee meeting; only the relevant portions of the minutes relating to Respiratory Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

The Respiratory Subcommittee may:

a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;
b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or
c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

These Subcommittee minutes were reviewed by PTAC at its meeting held on 11 & 12 February 2016.

Record of the Respiratory Subcommittee of the Pharmacology and Therapeutics Committee (PTAC) meeting held at PHARMAC on 2 September 2015

1 Matters Arising

1.1 The Subcommittee noted that the Anti-Infective Subcommittee reviewed azithromycin for adults with non-cystic fibrosis bronchiectasis in both February and December 2014 and looked upon it unfavourably as it can induce antimicrobial resistance. The Subcommittee believed that this is problematic as it would also be appropriate treatment for adults with non-cystic fibrosis bronchiectasis and is funded for children with bronchiectasis and adults with cystic fibrosis and bronchiectasis. The Subcommittee requested that the evidence on azithromycin received by the Anti-Infective Subcommittee indicating that azithromycin resistance is a greater problem for adults with non-cystic fibrosis bronchiectasis than it is for children or for adults with cystic fibrosis be made available to this Subcommittee.

Modafinil

1.2 The Subcommittee noted that the Special Authority (SA) criteria for modafinil are as follows:

Initial application only from a neurologist or respiratory specialist. Approvals valid for 24 months for applications meeting the following criteria:
All of the following:

1 The patient has a diagnosis of narcolepsy and has excessive daytime sleepiness associated with narcolepsy occurring almost daily for three months or more; and
2 Either:
  - 2.1 The patient has a multiple sleep latency test with a mean sleep latency of less than or equal to 10 minutes and 2 or more sleep onset rapid eye movement periods; or
  - 2.2 The patient has at least one of: cataplexy, sleep paralysis or hypnagogic hallucinations; and

3 Either:
  - 3.1 An effective dose of a subsidised formulation of methylphenidate or dexamphetamine has been trialled and discontinued because of intolerable side effects; or
  - 3.2 Methylphenidate and dexamphetamine are contraindicated.

Note: Modafinil will not be subsidised for hypersomnia associated with any condition other than narcolepsy.
Renewal application only from a neurologist or respiratory specialist. Approvals valid for 24 months where the treatment remains appropriate and the patient is benefiting from treatment.

1.3 The Subcommittee considered that the SA criteria are appropriate, however, access to multiple sleep latency tests (MSLT) is not uniform throughout the country. The Subcommittee considered that approximately 30% of adults and 50% of children at diagnosis of narcolepsy would not demonstrate at least one of the following symptoms: cataplexy, sleep paralysis or hypnagogic hallucinations. As a result, if access to MSLT was not available the patient may not be able to access funded treatment with modafinil, despite a diagnosis of excessive daytime sleepiness associated with narcolepsy.

1.4 The Subcommittee noted that the Australian PBS criteria for modafinil include the option of an electroencephalographic (EEG) recording showing the pathological rapid development of rapid eye movement (REM) sleep to demonstrate the patient meets the diagnosis of narcolepsy. Members considered that this could potentially be obtained during a standard diagnostic polysomnography or as a short daytime EEG.

1.5 The Subcommittee considered that that they were not aware of any access issues to EEG testing. The Subcommittee considered that if the SA criteria were modified to allow use of EEG to demonstrate narcolepsy that there would be a very small number of additional patients able to access treatment.

1.6 The Subcommittee **recommended** PHARMAC seek the advice of the Neurological Subcommittee on the sensitivity and specificity of EEG testing for diagnosis of narcolepsy and if EEG testing would be an appropriate alternative to 2.1 and 2.2 of the current SA criteria.

Omalizumab

1.7 The Subcommittee noted that omalizumab was funded for the treatment of patients with severe persistent allergic asthma from 1 November 2014 with a predicted patient base of ~100 per year. The Subcommittee noted that in the 10 months since being listed only four patients are are being dispensed omalizumab.

1.8 The Subcommittee noted that the small number of patients may be due to the high number of hospitalisations stipulated in the criteria (four admissions to hospital over the previous 24 months with one of those being in the previous 12 months). With the use of oral corticosteroids and improved patient care at Medical Centres and Emergency Departments many of these patients do not get admitted to hospital. The Subcommittee noted that the difficulty of administration may be another barrier to treatment. It is recommended that patients receive the sub-cutaneous injection at an appropriate medical facility due to a possible risk of anaphylaxis.

1.9 The Subcommittee **recommended** making the following changes to the Special Authority criteria (additions are in bold, deletions are in strike through), these include the changes previously recommended at the 30 April 2015 meeting

Special Authority for Subsidy
Initial application only from a respiratory physician. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1. Patient is **six years of age and over** ~~over the age of 6~~; and
2. Patient has a diagnosis of severe, life threatening asthma; and
3. Past or current evidence of atopy, documented by skin prick testing or RAST; and
4. Total serum human immunoglobulin E (IgE) between 76 IU/mL and 1300 IU/ml at baseline; and
5. ~~Proven compliance~~ **Adherence** with optimal inhaled therapy including high dose inhaled corticosteroid (budesonide 1600 micrograms per day or fluticasone propionate 1000 micrograms per day or equivalent (**and budesonide 800 micrograms per day or fluticasone propionate 500 mcg per day for children**), plus long-acting beta-2 agonist therapy (at least salmeterol 50 micrograms bd or eformoterol 12 micrograms bd, **salmeterol 25 micrograms bd or eformoterol 6**

micrograms bd for children) for at least 12 months, unless contraindicated or not tolerated; and

6. Patient has received courses of systemic corticosteroids equivalent to at least 28 days treatment in the past 12 months, unless contraindicated or not tolerated; and
7. At least **two** ~~four~~ admissions to hospital for a severe asthma exacerbation over the previous 24 months with at least one of those being in the previous 12 months; and
8. An Asthma Control **Test** ~~Questionnaire~~ (**ACT** ~~ACQ-5~~) score of ~~at least~~ **no more than** 15 as assessed in the previous month

Renewal only from a respiratory physician. Approvals valid for 2 years for applications meeting the following criteria:

At least 2 of the following ~~All of the following~~:

1. **The number of** hospital admissions have been reduced as a result of treatment; and
2. ~~A decrease~~ **An increase** in the Asthma Control **Test** ~~Questionnaire~~ (~~ACQ-5~~ **ACT**) score of at least 3 from baseline; and
3. A reduction in the maintenance oral corticosteroid dose of at least 50% from baseline.

2 Symbicort SMART program

Application

2.1 The Subcommittee reviewed an application from AstraZeneca requesting the removal of the Special Authority applying to Symbicort and Vannair.

Recommendation

2.2 The Subcommittee **recommended** the removal of the Special Authority on Vannair only if cost neutral to the cost of fluticasone with salmeterol with a high priority.

2.3 The Subcommittee **recommended** declining the submission to remove the Special Authority from all presentations of Symbicort.

2.4 The Subcommittee **recommended** removing the Special Authority from all presentations of Symbicort if the products are cost neutral to the cost of fluticasone with salmeterol.

T*he Decision Criteria particularly relevant to these recommendations are: (i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Maori and Pacific peoples; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

2.5 The Subcommittee noted AstraZeneca had submitted an application requesting the removal of the Special Authority applying to Symbicort and Vannair. The proposal included price reductions for the two presentations of Vannair and the 400mcg with 12 mcg Symbicort Turbuhaler and a continuation of the current pricing differential for the 100 mcg with 6 mcg and 200 mcg with 6 mcg presentations of Symbicort Turbuhaler. The submission also has an objective of

receiving formal acknowledgement of the clinical benefits associated with Symbicort SMART.

2.6 The Subcommittee noted that PTAC and the Respiratory subcommittee had reviewed the use of Symbicort under the SMART program in 2007, 2009 and 2010. The Subcommittee noted that prior to 1 January 2014, Seretide and Symbicort had been listed under the same Special Authority criteria at the similar net prices. The Subcommittee noted that the Special Authority had been removed from Seretide following a price decrease effective from 1 January 2014. The Special Authority remained on Symbicort and Vannair as the prices for these products were not decreased to the same level. The Subcommittee noted that subsidy protection for Symbicort and Vannair ended ion 1 July 2014.

2.7 The Subcommittee noted there have been over 30 randomised clinical trials on the SMART regimen conducted since 2009. Members noted this evidence has resulted in the incorporation of the SMART regimen into a series of treatment guidelines including the Global Initiative for Asthma (GINA) and the Australian Guidelines.

2.8 The Subcommittee noted two open-label trials conducted in New Zealand (Patel et al *Lancet Respir Med 2013;1:32-42* and Pilcher et al *Respirology (2014) 19,842-851).* The Subcommittee noted the Patel study compared two dosing regimens – two actuations of budesonide 200 mcg with eformoterol 6 mcg twice daily plus salbutamol 100 mcg as required vs two actuations budesonide 200 mcg with eformoterol 6 mcg twice daily plus one actuation as required (the single inhaler therapy (SIT) regimen). The Subcommittee noted that the metered dose inhaler (MDI), Vannair, was the branded product used in both arms of the study.

2.9 The Subcommittee noted that the study was for a period of 24 weeks, undertaken at four primary health-care practices and enrolled 303 patients aged between 16-65 years with a physician's diagnosis of asthma, a current prescription for inhaled corticosteroid and at least one asthma exacerbation in the preceding year. The primary outcome was the proportion of participants with at least one high use episode (defined as >8 actuations of Vannair or >16 actuations of salbutamol). Although the outcome difference was not significant (56% vs 46% p=0.058) there was a trend to high use episodes in those patients not using the SIT regimen.

2.10 The Subcommittee noted that in those patients who did have high-use episodes, there were significantly fewer high-use days in the SIT regimen arm (mean 5.1 days versus 8.9 days). The Subcommittee noted that the SIT regimen resulted in higher inhaled corticosteroid exposure but reduced oral corticosteroid exposure with no significant difference in composite systemic corticosteroid exposure.

2.11 The Subcommittee noted the Pilcher et al article which reported on the treatment outcomes of the 44 Maori patients included in the Patel study. As with the Patel study, Pilcher et al found that the magnitude of the benefit from the SMART regimen was similar between Maori and non-Maori.

2.12 The Subcommittee considered that there is evidence in New Zealand of patients using single inhaler therapies with good results. These regimens may have the greatest benefit in the patient group that are at high risk of an exacerbation

and/or admissions to hospital. The Committee considered that it would not be appropriate to extend single inhaler therapy to those patients who have mild to moderate asthma and are doing well on their medication as there would be no reason to change their therapy.

2.13 The Subcommittee noted that the Patel study used MDIs instead of the Turbuhaler as reliable, validated electronic monitors were not available for the Turbuhaler. The MDI is not registered for use in the SMART regimen but the authors considered that since clinical comparability has been shown for budesonide-eformoterol through MDI and Turbuhaler devices, the results would be generalizable to the Turbuhaler. The Subcommittee noted New Zealand evidence and clinical experience has established that Vannair SIT is non-inferior to the SMART regimen, and that both products could be used as single inhalers and should be priced the same.

2.14 The Subcommittee noted that the supplier stated the SMART dosing regimen for Symbicort is one actuation twice daily plus one actuation as required. The Subcommittee considered this regimen was unlikely to be the most commonly prescribed regimen and that the two actuations twice daily plus one as required as used in the Patel study was the most commonly prescribed regimen.

2.15 The Subcommittee noted dispensing data showed that there was no difference between the dispensing of Symbicort Turbuhaler, Seretide and Vannair and the mean number of doses used per day for each of these inhalers. The Subcommittee considered that the dispensing data supported the assumption that the prescribed regimen was most likely two actuations twice daily plus one as required.

2.16 The Subcommittee also considered that starting a patient on the Symbicort SMART regimen can at times take a considerable amount of time with a respiratory nurse explaining the regimen. The Subcommittee noted from dispensing data, that the majority of patients being dispensed Symbicort were also dispensed at least one other inhaler. The Subcommittee considered that, at least in the short term, this may be due to the reticence of patients to be without salbutamol.

2.17 The Subcommittee considered there were benefits in the SIT programmes for some patients and that there may be some savings to the broader health sector if patients adhered to the regimen. The Subcommittee considered that in primary care the SIT/SMART program may be prescribed second line if their asthma was not controlled under standard treatment. The Subcommittee commented that the majority of patients even when using Symbicort would be prescribed medication in the standard manner and only a small percentage of patient would be prescribed the SMART regimen.

2.18 The Subcommittee considered these products are the same or similar to Seretide and **recommended**, with a high priority, removing the Special Authority from Vannair if it were supplied at the same price as the cost of fluticasone with salmeterol – as per the Company's submission.

2.19 The Subcommittee considered there is not sufficient reason for Symbicort to maintain a significant price differential over Seretide and Vannair. The Subcommittee **recommended** removing the Special Authority of Symbicort, but only if cost neutral to the cost of fluticasone with salmeterol.

2.20 The Subcommittee considered that Symbicort and Vannair have the same clinical effect, contain the same pharmaceuticals, have the same or similar effect as Seretide and should be priced the same as the cost of fluticasone with salmeterol. The Subcommittee considered that the price of manufacturing the delivery system should not be a factor.

2.21 The Subcommittee noted the removal of special authority criteria would benefit high risk patients, and particularly Maori and Pacific people.

2.22 The Subcommittee noted Single Inhaler Therapy could result in healthcare savings from reduced exacerbations and hospitalisations.

3 myAIRVO Home Humidification Therapy

Application

3.1 The Subcommittee reviewed a re-submission from Fisher & Paykel for myAIRVO respiratory device for providing domiciliary long term humidification of inspired air in patients with moderate to severe COPD or bronchiectasis.

Recommendation

3.2 The Subcommittee deferred making a recommendation until further evidence is available.

Discussion

3.3 The Subcommittee noted that MyAirvo is a device that can provide humidified high airflow for hypoxic patients. Members considered that although the current evidence was relatively weak, there appears to be benefit related to the washout of the nasopharyngeal dead space, and reduction of inspiratory resistance. The increase in mucocilliary clearance of pathogens also seemed physiologically plausible.

3.4 The Subcommittee noted that PTAC had reviewed a submission for listing myAIRVO in August 2014 and that PTAC had recommended the application be declined. The Subcommittee noted that Fisher and Paykell had responded to the issues raised by PTAC and supplied further information which the Chairman of PTAC had asked to be reviewed by the Respiratory Subcommittee.

3.5 The Subcommittee noted a study by Rea et al (Respir Med 104.4 (2010):525-533) which enrolled 108 patients diagnosed with COPD or bronchiectasis, comparing humidification therapy (with Airvo) against usual standard of care for 12 months (control). Members noted that while the recommendation was to use

myAIRVO for two hours per day, the mean use was for 1.6 hours. Members noted the primary outcome, showed the number of exacerbations over the 12 month period were 2.97/patient per year in the treatment group compared to 3.63 per patient per year in the control group (p=0.067) which is not statistically significant. Members noted secondary outcomes showed less annual exacerbation days in the treatment group versus control (18.2 days versus 33.5 days (p=0.045)) and a longer median time to first exacerbation in the treatment group versus the control group (52 days compared to 27 days (p=0.0495)); Members considered other secondary outcomes showed improved changes in lung function and SGRQ scores in the treatment group from baseline, however members were uncertain of the average response if extrapolated to a wide-spread clinical setting. Members also noted that there was no statistical difference in changes of exercise capacity between treatment and control group, shown by the mean walking distance.

3.6 The Subcommittee noted the study by Rea et al 2010 was underpowered to show statistical significance and lacked subgroup analysis. Members considered that humidification therapy is theoretically tolerable and non-irritating, however stated the study lacked safety data to make any conclusions about safety. Members noted that the majority of patients in the Rea study would be classified as GOLD group D patients.

3.7 The Subcommittee noted a poster by Stoggard et al 2014 (Poster was presented at the ERS conference in September 2014) which showed interim results for a study on severe COPD patients (GOLD D) who were all on oxygen, with patients in the treatment arm to receiving humidified oxygen therapy via myAirvo for a median of 7.7 hours per day. Members considered preliminary results seemed promising with the treatment arm showing significantly fewer exacerbations and hospital admissions compared to control after six months, however Quality of Life measures were not statistically improved.

3.8 The Subcommittee considered the supplier's proposed entry and exit criteria for myAirvo appeared reasonable, but the benefit from the proposed criteria is unclear. Members noted the criteria should include a more robust indicator of symptoms such as the number of exacerbations in the past year and not FEV_1,

3.9 The Subcommittee noted that there are currently no listed alternative treatments similar to this device on the Pharmaceutical Schedule. Members considered if myAirvo were to be listed, it would not cause any change to bronchodilators or inhaled corticosteroids usage, but would be used as an adjunct therapy, and potentially reduce use of prednisone and antibiotics by a small margin as shown in the Stoggard et al 2014 study

3.10 The Subcommittee noted that in addition to the above indications, the device could have a role in multiple patient groups including CF patients and patients with tracheotomies.

3.11 The Subcommittee considered that humidification therapy is most likely a safe treatment and the myAIRVO is a promising device, however further evidence of benefit is needed. The Subcommittee considered that using the device in

conjunction with long term oxygen therapy is less irritating and allows for higher concentrations of oxygen to be given than without the humidifying device.

3.12 The Subcommittee noted device trials were constrained by the difficulty in having an appropriate comparison group and a need for more evidence for patients with moderate disease. Members considered that there were a series of international studies coming through, and the interim results look positive for a specific subgroup, namely those patients with severe COPD and possibly some children with severe bronchiectasis or cystic fibrosis.

3.13 The Subcommittee noted there was insufficient evidence at the current time to suggest myArvo would prevent exacerbations and reduced hospital admissions at a clinically significant level. Members also noted that there was no evidence to support daily 2 hour therapy as used in the Rea et al paper as the optimum dose.

3.14 The Subcommittee considered healthcare costs associated that myAirvo would primarily be direct treatment costs, nursing or support costs, but unlikely increase the need for diagnostic tests. Members also noted that although there are no products funded in New Zealand, there various other products with similar if not the same function available on the market.

3.15 While the Subcommittee considered devices such as myAirvo could play a positive role in the treatment of COPD patients and in particular those with severe disease, the Subcommittee deferred making a recommendation until further evidence is available.

3.16 The Subcommittee would like to review a further submission with a higher level of evidence. In particular the Subcommittee would like to see the completion of the Stoggard trial, a second trial with a similar patient group to the Stoggard trial, studies to compare high flow nasal cannulae to home NIV treatment and studies comparing myAirvo to other devices.

4 COPD – new pharmaceuticals

Applications

4.1 The Subcommittee collectively reviewed 6 separate applications for treatments of COPD. The applications reviewed were: umeclidinium (LAMA), aclidinium (LAMA), umeclidinium with vilanterol (LAMA/LABA combination), tiotropium with olodaterol (LAMA/LABA combination), glycopyrronium with indacaterol (LAMA/LABA combination), and fluticasone furoate with vilanterol (ICS/LABA combination).

Recommendation

4.2 The Subcommittee **recommended** listing the LAMA monotherapies without a Special Authority provided they were cost neutral to indacaterol or listing with the current Special Authority criteria cost neutral to glycopyrronium.

4.3 The Subcommittee **recommended** the listing the LAMA/LABA combinations provided they were cost neutral to combined pharmaceutical budget.

4.4 The Subcommittee **recommended** listing the 100 mcg fluticasone furoate with 25 mcg vilanterol cost neutral to the equivalent the cost of fluticasone with salmeterol inhaler with a low priority.

4.5 The Subcommittee **recommended** declining the high strength 200 mcg fluticasone furoate with 25 mcg vilanterol.

4.6 *The Decision Criteria particularly relevant to these recommendations are: (i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Maori and Pacific peoples; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

4.7 The Subcommittee reviewed applications for the listing of two long–acting muscarinic (LAMA) agents, three long–acting muscarinic/long-acting beta-adrenoceptor agonist (LAMA/LABA) combinations and one inhaled corticosteroid/long-acting beta-adrenoceptor agonist (ISC/LABA) combination.

4.8 The Subcommittee noted that PTAC had reviewed applications for the ICS/LABA combination and two of the LAMA/LABA combinations and had recommended that the Respiratory Subcommittee review all applications for the treatment of chronic obstructive pulmonary disease (COPD).

4.9 The Subcommittee noted that tiotropium was listed on the Pharmaceutical schedule in February 2005 and was the only LAMA listed on the Schedule until November 2014 when glycopyrronium was listed as part of the Novartis bundle deal. The Subcommittee noted that expenditure in this market is high and growing at ~8% per annum.

4.10 The Subcommittee noted that key clinical trials were submitted with each application. The Subcommittee noted that all trials were industry supported and were of reasonably good quality. The Subcommittee noted that there was some variation between the trials in terms of severity of disease, concomitant medicines, treatment duration and choice of outcome variable but considered these variations did not affect the main conclusions.

4.11 The Subcommittee noted there were no new classes or breakthroughs in therapy and that all treatments showed efficacy with no treatment clearly showing superiority within a class. The Subcommittee considered the only clinically important difference between the products within each class was the dosing frequency and the delivery devices.

4.12 The Subcommittee noted that COPD treatments had been discussed at the previous Subcommittee meeting in February 2015 with particular reference to

where glycopyrronium and indacaterol could fit into the treatment regimen. The Subcommittee noted that at that time the Subcommittee had considered there was an unmet need in patients in Group B of the GOLD patient classification who had increased symptoms of COPD and/or exacerbations but maintained good lung function.

Umeclidinium

4.13 The Subcommittee noted that umeclidinium was administered with the Ellipta device which is easy to use and the majority of patients required no instructions to use it. The Subcommittee noted the device had a dose counter, was pre-loaded and 80-90% of patients prefer the Ellipta device. The Subcommittee noted that umeclidinium had some high quality trials and was recommended at an appropriate dose of 62.5 mcg once daily. The Subcommittee noted the trials submitted with the application (Trivedi R. et al Eur Respir J 2014;43:72-81; and Donohue J. et al Resp Med 2013;107:1538-1546) showed it to be effective versus placebo. The Subcommittee noted that preliminary results from a head to head study of umeclidinium versus tiotropium and glycopyrronium (Study 201316) found umeclidinium to be non-inferior compared to glycopyrronium 44 mcg and tiotropium 18 mcg and superior to tiotropium in lung function (FEV_1 59mL (95% CI 29mL to 88mL).

Aclidinium

4.14 The Subcommittee noted that aclidinium was administered with the Genuair device which is easy to use with 80% of patients preferring the device to the Handihaler. The Subcommittee noted the device had a dose counter and was pre-loaded. The Subcommittee noted that aclidinium was a twice daily dose which some patients may find less convenient than therapies with a once daily dose. The Subcommittee noted the pivotal trial (Beier et al COPD, 10:511-52 2013) and a study by Vestbo et al (COPD 2010;7:331-336). The Subcommittee noted that in indirect comparisons, aclidinium showed a similar magnitude of benefit compared to tiotropium. The Subcommittee noted that some clinical trials showed a modest benefit over other LAMAs in morning symptoms but considered that these may not be great enough to be clinically important.

4.15 The Subcommittee considered that while the device may be easier for the elderly, and they are generally good at taking medications in the morning, adherence in the evening is not as good in general as the morning. The Subcommittee considered that the aclidinium would offer benefits for some people as they prefer twice daily dosing and considered it should be listed cost neutral to the other LABAs.

Umeclidinium with vilanterol

4.16 The Subcommittee noted that umeclidinium plus vilanterol was administered with the Ellipta device. The Subcommittee noted that umeclidinium may show minor superiority over tiotropium in lung function but there was no data on vilanterol alone. The Subcommittee noted that umeclidinium with vilanterol (UMEC/VI) combination therapy had high quality trials which showed modest superiority over mono-components and tiotropium. The Subcommittee noted that Donohue et al (Respir Med. 2013;107(10):1538-46) found improvements in trough FEV_1 at week 24 greater with UMEC/VI than with monotherapies (52-95 mL; all $p \leq 0.004$) and a

2.0 increase in the St George's Respiratory Questionnaire (SGRQ). The Subcommittee noted that these improvements were below clinical significance but do not rule out the possibility that there may be responders and non-responders.

4.17 The Subcommittee noted that, very rarely, there may be an increase in the incidence of supraventricular tachycardia with the COPD treatment with LABAs. The increased incidence with UMEC/VI was lower than that seem with LABAs alone.

4.18 The Subcommittee noted that PTAC had considered that the individual components of combination therapies should be available so that treatment can be titrated up and down using the mono-components. The Subcommittee agreed that would be an advantage but does not preclude listing UMEC/VI as UMEC may also be listed and, if not, there are other LAMA monotherapies listed and the 24 hour LABA, indacaterol, could also be used.

Tiotropium with olodaterol

4.19 The Subcommittee noted that tiotropium plus olodaterol was administered with the Respimat Soft Mist Inhaler which 60-70% of patients preferred to a turbuhaler, diskus or MDI and, once primed, was easy to use. The Subcommittee noted that tiotropium plus olodaterol had high quality trials which demonstrated some improvement in FEV_1 compared to olodaterol or tiotropium on their own.

4.20 The Subcommittee noted that in an earlier analysis of pooled phase III data, concern had been raised regarding increased death rates with the use of the tiotropium Respimat compared to the HandiHaler. The Subcommittee considered that this was thought to be due to paradoxical bronchoconstriction possibly due to the presence of ethylene diamine tetra-acetic acid and benzalkonium chloride in the Respimat inhalers. Both products are broncho-constrictors. The Subcommittee considered that the 2013 trial involving 17,135 patients that found Respimat was noninferior to HandiHaler with respect of the risk of death (Wise et al N Engl J Med 369;16:1492-1501), had dispelled the concern regarding the safety of Respimat.

4.21 The Subcommittee noted that high quality clinical trials showed some superiority of the tiotropium/olodaterol combination compared to the individual components. The Subcommittee noted that there trials showed a trend towards fewer exacerbations than tiotropium on its own and considered this may be due to the emerging evidence that LABAs also play a role in reducing the frequency of exacerbations.

Indacaterol with glycopyrronium

4.22 The Subcommittee noted that indacaterol plus glycopyrronium was administered with the Breezhaler which is preferred by some patients to the Handihaler. The Subcommittee noted that it is possible to use the Handihaler with the indacaterol plus glycopyrronium capsules. The Subcommittee noted that this LAMA/LABA combination therapy had undergone an extensive clinical trial programme with some high quality trials which showed modest superiority over the mono-components and tiotropium. The Subcommittee noted that efficacy of the mono-components had already been proven and both glycopyrronium and indacaterol

are listed on the Pharmaceutical Schedule. The Subcommittee noted that the indacaterol/glycopyrronium combination was non-inferior to indacaterol plus tiotropium as concomitant therapies or tiotropium plus a ICS/LABA combination.

4.23 The subcommittee noted that the indacaterol with glycopyrronium was included in the multiproduct agreement with Novartis in 2014 with an agreement that it would be listed following registration.

Fluticasone furoate with vilanterol

4.24 The Subcommittee reviewed an application for listing two strengths of fluticasone furoate (FF) with vilanterol Vi) (100 FF / 25 Vi and 200 FF / 25 Vi). The Subcommittee noted that submission was for the 100 FF / 25 Vi presentation to be listed as a once daily treatment for COPD and asthma, the 200 FF / 25 Vi presentation as a once daily treatment of asthma only. The Subcommittee noted the application had been reviewed by PTAC at its November 2014 meeting where the Committee recommended the 100 FF / 25 Vi strength be listed cost neutral to Seretide with a low priority and recommended the submission to list the high strength 200 FF / 25 Vi be declined.

4.25 The subcommittee noted that fluticasone furoate was more potent than fluticasone propionate and considered a 50 FF / 25 Vi dose may be more appropriate as there may be safety concerns with doses above 100 FF daily.

4.26 The Subcommittee noted there had been an extensive clinical trial programme and the clinical trials were of high quality. The Subcommittee noted that FF/Vi showed non-inferiority to fluticasone propionate with salmeterol in terms of lung function and a modest superiority in terms of quality of life in an indirect comparison. The Subcommittee noted that this ICS/LABA combination therapy had high quality trials which showed reduced exacerbations by 27% in COPD patients (not on LAMAs) compared to baseline or vilanterol monotherapy. The Subcommittee noted that fluticasone furoate plus vilanterol trials had a 3% rate of pneumonia requiring hospitalisation, and a correlation between the strength of the dose of fluticasone furoate and increased rates of pneumonia. The Subcommittee noted that there may be an increased risk of death from pneumonia with increasing strength of fluticasone furoate.

4.27 The Subcommittee noted that the onset of action of vilanterol is 15 to 60 minutes making it unsuitable for single inhaler therapy. The Subcommittee noted that fluticasone furoate plus vilanterol was administered with the Ellipta device and came in two presentations; 100 mcg fluticasone furoate with 25 mcg vilanterol (Breo Ellipta 100/25) and 200 mcg fluticasone furoate with 25 mcg vilanterol (Breo Ellipta 200/25).

Summary

4.28 Overall the Subcommittee considered the strength and quality of the evidence for all products was high although most of the studies were done versus placebo and therefore most comparisons between products were indirect. The Subcommittee considered the evidence showed no clinically meaningful superiority of new agents over existing agents. The Subcommittee considered there were increased risks of pneumonia with the higher dose of fluticasone furoate with vilanterol combination (>100 mcg fluticasone furoate per day).

4.29 The Subcommittee considered there was an unmet need for the group of patients who have symptomatic COPD but preserved lung function as these patients currently do not have access to a LAMA but are able to be dispensed a LABA or an ICS/LABA. The Subcommittee considered there was also an unmet need for the group of patients who have frequent COPD exacerbations and either preserved lung function or fewer symptoms when well. These patients also currently do not have access to a LAMA for exacerbation prevention but are able to be dispensed an ICS or an ICS/LABA. The Subcommittee considered that there are also a few people who are unable to use the HandiHaler or Breezhaler who would find some or all of the submitted inhalers easier to use.

4.30 In summary, the Subcommittee considered that all the products were efficacious in the treatment of COPD, that there is a modest benefit in combination treatment versus single medication but that overall there was little or no difference between these treatments. The Subcommittee considered none of these treatments or the currently listed treatments is clearly superior within a class and no combination inhaler is clearly superior to concomitant mono-component therapy. The Subcommittee considered the main differences were in the dosing frequency and the delivery devices.