Record of the Respiratory Subcommittee of PTAC Meeting held on 28 October 2020

Respiratory Subcommittee records are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016.

Note that this document is not necessarily a complete record of the Respiratory Subcommittee meeting; only the relevant portions of the meeting record 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.

PTAC Subcommittees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Subcommittee meeting will be reviewed by PTAC at its February 2021 meeting.

PTAC Subcommittees and PTAC may differ in the advice they provide to PHARMAC, including recommendations' priority, due to the committees' different, if complementary, roles, expertise, experience, and perspectives.

PHARMAC is not bound to follow the recommendations made below. Applications are prioritised by PHARMAC against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or PTAC Subcommittees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

Chair

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Present from the Respiratory Subcommittee:
Andrew Corin
David McNamara
Greg Frazer
Ian Shaw
Justin Travers
Matthew Strother (Chair)
Neil Whittaker
Stuart Dalziel *(part of)*
Tim Christmas
Tim Stokes

Present from PHARMAC:
Adam McRae
Beth Caudwell *(part of)*
Eric Matthews *(part of)*
Vivienne Rijnberg *(part of)*
Gina Armstrong *(part of)*
Logan Heyes
Scott Metcalfe
Sonam Naidu

1. Summary of recommendations

1.1. The Subcommittee **recommended** that fluticasone furoate /umeclidinium bromide/vilanterol trifenatate (Trelegy Ellipta) be funded only if it was **cost-neutral** to the pricing of the same components received from multiple inhalers (fluticasone furoate/vilanterol trifenatate 100/25 [Breo Ellipta] in combination with the umeclidinium

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[Incruse Ellipta]), within the context of treatment of respiratory disease, and subject to the following Special Authority criteria:

Initial application — from any relevant practitioner. Approvals valid for 2 years for applications meeting the following criteria:
All of the following
1 Patient has a diagnosis of COPD confirmed by spirometry; and
2 Patient is currently receiving an ICS/LABA or LAMA/LABA treatment; and
3 Any of the following:
3.1 Patient has a COPD Assessment Test (CAT) score greater than 10;
3.2 Patient has had greater than 2 exacerbations in the previous 12 months; or
3.3 Patient has had an eosinophil count greater than or equal to 0.3 x 10^9 cells/L in the previous 12 months

Renewal — from any relevant practitioner. Approvals valid for 2 years for applications meeting the following criteria:
Both:
1 Patient is adherent with medication; and
2 The treatment remains appropriate and patient is benefitting from treatment.

1.2. The Subcommittee **recommended** that budesonide/eformoterol inhalers (100/6 and 200/6; dry powder for inhalation and pressurised metered dose inhalers) be dispensed stat with a **high priority** within the context of treatment for respiratory diseases.

1.3. The Subcommittee **recommended** that budesonide/eformoterol metered dose inhaler (Symbicort Rapihaler 100/3) be listed as **cost-neutral** to the per dose price of Vannair 200/6 metered dose inhaler within the context of treatment for respiratory diseases.

1.4. The Subcommittee **recommended** that fluticasone furoate/vilanterol 200/25 mcg (Breo Ellipta 200) be funded for the treatment of severe asthma with a **medium priority** within the context of respiratory disease, subject to the following Special Authority criteria:

Initial application – (severe asthma) from any relevant practitioner on the recommendation of a paediatrician or respiratory physician. Approvals valid for 12 months for applications meeting the following criteria:
Both:
1. Despite adherence to optimised asthma therapy including inhaled corticosteroids (equivalent to at least 500 mcg per day of fluticasone propionate) plus long acting beta-2 agonist, or budesonide/formoterol as part of the anti-inflammatory reliever plus maintenance regimen including previous trials of appropriate meds, the patient has experienced an asthma exacerbations in the previous 6 months that required oral corticosteroids; and
2. Conditions that mimic asthma (e.g., vocal cord dysfunction, central airway obstruction etc.) have been excluded or managed.

Renewal – (severe asthma) from any relevant practitioner on the recommendation of a paediatrician or respiratory physician. Approvals valid without further renewal where the treatment remains appropriate and the patient continues to benefit from treatment

1.5. The Subcommittee **recommended** that the application for widening access to mepolizumab for the treatment of severe eosinophilic asthma in patients with <u>a blood eosinophil count of greater than 300 cells/µL</u> be funded with a **high priority**, in the context of treatment for respiratory disease, as follows (additions in **bold**, deletions in ~~strikethrough~~ to the current special authority for mepolizumab):

Initial application — (Severe eosinophilic asthma) only from a respiratory physician or clinical immunologist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:
1 Patient must be aged 12 years or older; and
2 Patient must have a diagnosis of severe eosinophilic asthma documented by a respiratory physician or clinical immunologist; and
3 Conditions that mimic asthma e.g. vocal cord dysfunction, central airway obstruction, bronchiolitis etc. have been excluded; and

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4 Patient has a blood eosinophil count of greater than **0.3 × 10^9 cells/L** ~~0.5 × 10^9 cells/L~~ in the last 12 months; and
5 Patient must be adherent to optimised asthma therapy including inhaled corticosteroids (equivalent to at least 1000 mcg per day of fluticasone propionate) plus long acting beta-2 agonist, or budesonide/formoterol as part of the single maintenance and reliever therapy regimen, unless contraindicated or not tolerated; and
6 Either:
6.1 Patient has had at least 4 exacerbations needing systemic corticosteroids in the previous 12 months, where an exacerbation is defined as either documented use of oral corticosteroids for at least 3 days or parenteral corticosteroids; or
6.2 Patient has received continuous oral corticosteroids of at least the equivalent of 10 mg per day over the previous 3 months; and
7 Patient has an Asthma Control Test (ACT) score of 10 or less. Baseline measurements of the patient's asthma control using the ACT and oral corticosteroid dose must be made at the time of application, and again at around 52 weeks after the first dose to assess response to treatment.

Renewal — (Severe eosinophilic asthma) only from a respiratory physician or clinical immunologist. Approvals valid for 2 years for applications meeting the following criteria:
Both:
1 An increase in the Asthma Control Test (ACT) score of at least 5 from baseline; and
2 Either:
2.1 Exacerbations have been reduced from baseline by 50% as a result of treatment with mepolizumab; or
2.2 Reduction in continuous oral corticosteroid use by 50% or by 10 mg/day while maintaining or improving asthma control.

1.6. The Subcommittee **recommended** that the initial and renewal criteria for mepolizumab for the treatment of severe eosinophilic asthma be amended <u>to remove the Asthma Control Test (ACT)</u> with a **medium priority**, in the context of treatment for respiratory disease, as follows (additions in **bold**, deletions in ~~strikethrough~~ to the current special authority for mepolizumab):

Initial application — (Severe eosinophilic asthma) only from a respiratory physician or clinical immunologist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:
1 Patient must be aged 12 years or older; and
2 Patient must have a diagnosis of severe eosinophilic asthma documented by a respiratory physician or clinical immunologist; and
3 Conditions that mimic asthma e.g. vocal cord dysfunction, central airway obstruction, bronchiolitis etc. have been excluded; and
4 Patient has a blood eosinophil count of greater than 0.5 × 10^9 cells/L in the last 12 months; and
5 Patient must be adherent to optimised asthma therapy including inhaled corticosteroids (equivalent to at least 1000 mcg per day of fluticasone propionate) plus long acting beta-2 agonist, or budesonide/formoterol as part of the single maintenance and reliever therapy regimen, unless contraindicated or not tolerated; and
6 Either:
6.1 Patient has had at least 4 exacerbations needing systemic corticosteroids in the previous 12 months, where an exacerbation is defined as either documented use of oral corticosteroids for at least 3 days or parenteral corticosteroids; or
6.2 Patient has received continuous oral corticosteroids of at least the equivalent of 10 mg per day over the previous 3 months**.** ~~; and~~
~~7 Patient has an Asthma Control Test (ACT) score of 10 or less. Baseline measurements of the patient's asthma control using the ACT and oral corticosteroid dose must be made at the time of application, and again at around 52 weeks after the first dose to assess response to treatment.~~

Renewal — (Severe eosinophilic asthma) only from a respiratory physician or clinical immunologist. Approvals valid for 2 years for applications meeting the following criteria:
~~Both:~~
~~1 An increase in the Asthma Control Test (ACT) score of at least 5 from baseline; and~~
~~2~~ Either:
~~2.1~~ **1** Exacerbations have been reduced from baseline by 50% as a result of treatment with mepolizumab; or

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~~2.2~~ **2** Reduction in continuous oral corticosteroid use by 50% or by 10 mg/day while maintaining or improving asthma control.

1.7. The committee **recommended** that benralizumab for the treatment of severe eosinophilic asthma be funded within the context of respiratory disease only if **cost-neutral** to mepolizumab, subject to Special Authority criteria.

BENRALIZUMAB
Initial application — (Severe eosinophilic asthma) only from a respiratory physician or clinical immunologist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:

1. Patient must be aged 12 years or older; and
2. Patient must have a diagnosis of severe eosinophilic asthma documented by a respiratory physician or clinical immunologist; and
3. Conditions that mimic asthma e.g. vocal cord dysfunction, central airway obstruction, bronchiolitis etc. have been excluded; and
4. Patient has a blood eosinophil count of greater than 0.5 × 10ˆ9 cells/L in the last 12 months; and
5. Patient must be adherent to optimised asthma therapy including inhaled corticosteroids (equivalent to at least 1000 mcg per day of fluticasone propionate) plus long acting beta-2 agonist, or budesonide/formoterol as part of the single maintenance and reliever therapy regimen, unless contraindicated or not tolerated; and
6. Either:
   6.1 Patient has had at least 4 exacerbations needing systemic corticosteroids in the previous 12 months, where an exacerbation is defined as either documented use of oral corticosteroids for at least 3 days or parenteral corticosteroids; or
   6.2 Patient has received continuous oral corticosteroids of at least the equivalent of 10 mg per day over the previous 3 months; and
7. Patient has an Asthma Control Test (ACT) score of 10 or less. Baseline measurements of the patient's asthma control using the ACT and oral corticosteroid dose must be made at the time of application, and again at around 52 weeks after the first dose to assess response to treatment.

Renewal — (Severe eosinophilic asthma) only from a respiratory physician or clinical immunologist. Approvals valid for 2 years for applications meeting the following criteria:
Both:

1. An increase in the Asthma Control Test (ACT) score of at least 5 from baseline; and
2. Either:
3. Exacerbations have been reduced from baseline by 50% as a result of treatment with benralizumab; or
4. Reduction in continuous oral corticosteroid use by 50% or by 10 mg/day while maintaining or improving asthma control.

2. The role of PTAC Subcommittees and records of meetings

2.1. This meeting record of the Respiratory Subcommittee of PTAC is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016, available on the PHARMAC website at https://www.pharmac.govt.nz/assets/ptac-terms-of-reference.pdf.

2.2. The Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of PTAC Subcommittees and PTAC.

2.3. Conflicts of Interest are described and managed in accordance with section 7.2 of the PTAC Terms of Reference.

2.4. The Respiratory Subcommittee is a Subcommittee of PTAC. The Respiratory Subcommittee and PTAC and other PTAC Subcommittees have complementary roles, expertise, experience, and perspectives. The Respiratory Subcommittee and other PTAC Subcommittees may therefore, at times, make recommendations for treatments for Respiratory disease that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for treatments for Respiratory disease that differ from the Respiratory Subcommittee's, or PTAC Subcommittees may make recommendations that differ from other PTAC Subcommittees'.

PHARMAC considers the recommendations provided by both the Respiratory Subcommittee and PTAC and any other relevant PTAC Subcommittees when assessing applications for treatments for Respiratory disease.

3. Declared interests

3.1. David McNamara noted that:

- He is a member on the scientific advisory board Asthma and Respiratory Foundation of New Zealand, author on child and adult asthma guidelines.
- He is an advisor for the CARE study examining the use of budesonide/eformoterol as needed compared with salbutamol in children.

Tim Christmas noted that:

- He had an investigator role in an asthma study involving a novel agent. He noted that this did not involve any of the agenda items and he received no personal remuneration for his involvement. The Chair deemed this as no conflict.

Ian Shaw noted that:

- He is on the organising committee of the Respiratory workshop in Rotorua supported by Boehringer Ingelheim. The Chair deemed this as a conflict, but participation permitted under Board Chair's Standing Permission.

Stuart Dalziel noted that:

- He was an investigator on the paediatric studies of budesonide/eformoterol vs. salbutamol (CARE study), was an investigator on the Novel START and PRACTICAL trials (one funded by AZ and the other by HRC) and works closely with investigators of the NOVEL and PRACTICAL trials on a number of additional studies. He was not present for the discussion relating to item 8.

Andrew Corin noted that:

- He was an investigator on the NOVEL AND PRACTICAL trials (one funded by AZ and the other by HRC). He contributed to the design and reporting of the trials. The trial site for which I am a director was paid a fee for conducting the trials. He was also paid a fee as a Names Investigator for PRACTICAL. The Chair deemed this as a conflict, but participation in the discussion was permitted under Board Chair's Standing Permission, however he would abstain from voting.

- He is an advisor for the CARE study examining the use of budesonide/eformoterol as needed compared with salbutamol in children. There has been no payment for this.

- He was an investigator in the TERRANOVA trial for benralizumab. The Chair deemed this as a conflict, but participation permitted under Board Chair's Standing Permission.

Greg Frazer, Tim Stokes, Justin travers and Neil Whittaker declared they had no new actual or potential conflicts of interest.

4. Record of Subcommittee meeting held Friday, August 4, 2017

4.1. The Subcommittee noted and accepted the record of the previous meeting held on 4 August 2017.

5. Terms of reference update

5.1. PHARMAC staff provided an update on the relationship definitions between PTAC and Subcommittees. PHARMAC staff noted the change to the recording of advice specifically within the context of the Subcommittee expertise. The Subcommittee agreed to the proposed wording, in that it provides its recommendations for funding "within the context of respiratory disease".

5.2. The Subcommittee were supportive of a change that would require a meeting every 18 months. The Subcommittee noted that it has been highly engaged with PHARMAC this year for a variety of issues that have come up.

5.3. PHARMAC staff noted that the key change would be to formally change the naming convention to an advisory group rather than a Subcommittee of the Pharmacology and Therapeutics Advisory Committee.

5.4. PHARMAC staff noted that a key change is the importance placed on equity considerations and noted the value of advisors providing the view of equity from clinical practice. The Subcommittee considered that they would be happy to put forward names of representatives that would bring this view to the Subcommittee.

6. Therapeutic Group and NPPA Review

Expenditure Summary and funding decisions

6.1. The Subcommittee noted a summary of community expenditure on pharmaceuticals in the Respiratory System and Allergies therapeutic group. The Subcommittee had no comments regarding the community expenditure in the Respiratory System and Allergies therapeutic group.

6.2. The Subcommittee noted the funding decisions that had occurred since the last meeting.

6.3. The Subcommittee noted the proposal to decline aclidinium bromide for the treatment of COPD. The Subcommittee considered that it was not concerned from a clinical perspective regarding the proposal to decline aclidinium bromide as there were multiple other long-acting muscarinic agonists listed on the Pharmaceutical Schedule.

6.4. The Subcommittee noted the cost-neutral recommendation provided by PTAC for the Tobi Podhaler and considered that this analysis should include the cost of nebulisers and nebuliser bowls, which cost approximately $450 per 5 years and $50 per year, respectively.

6.5. The Subcommittee noted the application status of the adrenaline autoinjector and that for patients living in rural areas it may take one hour or more to be reached by emergency services and that the currently funded option is a vial and injection (drawing up from the vial). The Subcommittee considered that it would appreciate reviewing the clinical and epidemiological assumptions that have gone into the economic modelling for the adrenaline autoinjector.

Antihistamines

6.6. The Subcommittee noted the seasonality of usage of antihistamines.

6.7. The Subcommittee noted that for many antihistamines, there is currently a part charge. The Subcommittee considered that there was no need at this time to remove the part charge for antihistamines that currently have a part charge as there were multiple antihistamines that were fully funded.

6.8. The Subcommittee noted that PHARMAC has received an application for fexofenadine hydrochloride for use in patients 6 months to 2 years of age. The Subcommittee considered that the need for this product was low and that most patients are managed appropriately through the off-label use of other listed antihistamines such as loratadine in this age group without clinical concern and that paediatricians were comfortable with this.

Short-acting bronchodilators and Inhaled corticosteroids/ Long-acting bronchodilators

6.9. The Subcommittee noted the seasonality of usage of short-acting beta agonists (SABAs). The Subcommittee noted that usage of this product has been consistent in recent times. The Subcommittee noted the increase in usage of inhaled corticosteroids/ long-acting beta agonist (ICS/LABA) in recent times. The Subcommittee noted that there was a significant spike in usage of both products in the month of April 2020, preceding the COVID-19 Alert Level 4 lockdown.

6.10. The Subcommittee noted the current NZ adult and adolescent asthma guidelines that now recommend anti-inflammatory reliever (AIR) therapy with or without maintenance treatment. The Subcommittee noted that the use of a SABA only treatment was specifically discouraged and not recommended. The Subcommittee noted that the age group with the highest rate of SABA-only treatment was the preschool age group. In addition, the Subcommittee noted dispensing data that indicated that there were greater proportions of Māori and Pacific people currently receiving salbutamol only treatment for their asthma or COPD. The Subcommittee considered that it would be useful to understand the usage of SABA only treatments if stratified by both age and ethnicity and after excluding those patients of preschool age from the analysis.

6.11. The Subcommittee noted that there was a trial underway (CARE trial) evaluating the effectiveness of budesonide and formoterol in children aged 5 to 15 years old.

6.12. The Subcommittee considered that in patients of preschool age, a LABA was not recommended and that around half of patients of preschool age would not be prescribed an inhaled corticosteroid.

6.13. The Subcommittee considered that the primary drivers that would impact the uptake of AIR therapy would be patient preference and that there are patients seen by primary care with asthma controlled by salbutamol alone. The Subcommittee considered that it would be important for the inhaler to look and perform similarly to currently-funded salbutamol pressurised metered dose inhalers (pMDIs). The Subcommittee considered that education was important, especially for Māori/Pacific patients receiving salbutamol only. In addition, the Subcommittee considered that access to a budesonide/formoterol inhaler in out-of-hours care and for continuity of care with general practitioners would be important. However, the Subcommittee considered that after-hours and emergency settings would continue to require salbutamol and considered that it was important to find ways to engage these patients with their primary care provider after presenting acutely to these settings.

6.14. The Subcommittee considered that the new guidelines may take some time to implement due to the more immediate feedback of the bronchodilatory effect of salbutamol compared with eformoterol.

6.15. The Subcommittee considered that children account for a large proportion of the use of salbutamol only. The Subcommittee considered that in adults, approximately 60% of salbutamol-using patients would have asthma compared to COPD. The Subcommittee considered that the key variables that would help attempt delineate between patients with asthma and COPD were prescription history and age.

6.16. The Subcommittee considered that if the patient was less than 30 years of age and receiving salbutamol, they would likely have asthma and that patients under 40 were unlikely to have COPD. The Subcommittee noted that there are patients between the age of 35 and 60 that have asthma COPD overlap syndrome (ACOS). In addition, the Subcommittee considered that if the patient is not receiving an inhaled corticosteroid, it is less likely that they have a diagnosis of asthma, and if not receiving a long-acting muscarinic agonist (LAMA) it is less likely that the patient has COPD.

6.17. The Subcommittee considered that there would be many patients who would be prescribed an inhaled corticosteroid but would not have it dispensed for them at pharmacy, and that this would likely constitute a significant proportion of patients who would be dispensed salbutamol-only as their inhalers in any given year.

6.18. The Subcommittee noted that the use of salbutamol-only for mild asthma was previously standard of care and considered it would be several years before the updates to the NZ adult and adolescent asthma guidelines were commonplace in clinical practice. The Subcommittee considered that the rate of uptake would be affected by uptake in primary care and emergency care provider prescribers. The Subcommittee considered that the change would constitute a large shift, which would not be linear and that its implementation would occur over a long time.

6.19. The Subcommittee was unable to estimate the numbers of patients currently using salbutamol inappropriately for disordered breathing other than asthma for the short-term relief of symptoms.

6.20. The Subcommittee considered that there may be much wastage of salbutamol currently for patients with true intermittent/mild asthma needing only intermittent use.

Long-acting muscarinic agonists

6.21. The Subcommittee noted that the usage of long-acting muscarinic agonists (LAMAs) has increased consistently since the initial funding of tiotropium bromide. The Subcommittee noted that there was a significant spike in dispensings in the month of April 2020, preceding the national COVID-19 Alert Level 4 lockdown.

6.22. The Subcommittee considered that at least 90% of patients receiving a LAMA currently would have COPD. The Subcommittee noted the removal of the requirement for a diagnosis by spirometry in the endorsement, to both reduce the impact of the initial demands of the COVID-19 epidemic and its health sector response on primary health services and reduce the need for patients to perform aerosol generating procedures (risking COVID-19 transmission).

6.23. The Subcommittee considered that if the endorsement were removed there would be a low risk of adverse events. The Subcommittee considered there to be a risk that the use of LAMAs would creep into asthma and that there would be a risk of overuse of these LAMA products where they have no role so would be of limited benefit. The Subcommittee considered that there was a patient group who were at risk of COPD (e.g. smokers with symptoms), but with insufficient disease to constitute a diagnosis of COPD but would benefit from LAMA treatment as there is less pressure on prescriber to confirm COPD diagnosis via spirometry.

6.24. The Subcommittee considered that if a single LAMA inhaler were open listed on the Pharmaceutical Schedule, most patients would remain on their existing LAMA inhalers, however, that new patients would likely commence treatment with the open listed LAMA inhaler. The Subcommittee considered that the number of patients switching from an inhaled corticosteroid (ICS)/LABA containing inhaler to a LAMA would be low, as these are used to treat different indications within COPD, but that a LAMA inhaler may be used as an add-on therapy to provide triple therapy.

Long-acting muscarinic agonists/Long-acting bronchodilators

6.25. The Subcommittee noted that the usage of LAMA/LABA has increased consistently since the funding of these products in 2016. The Subcommittee noted that there was a significant spike in dispensings in the month of April 2020, preceding the COVID-19 Alert Level 4 lockdown.

6.26. The Subcommittee considered that approximately 95% of patients receiving a LAMA currently would have COPD as a diagnosis, required in order to obtain a LAMA.

6.27. The Subcommittee noted the upcoming update to the New Zealand COPD guidelines (unpublished), which were informed by COPD-X Australian and New Zealand Guidelines 2020 (Yang et al. The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease 2020) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 (Global Initiative For Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2020 Report). The Subcommittee indicated that two thirds of patients would be evenly distributed between GOLD categories A and D, with the remainder of patients representing the other two categories. The Subcommittee considered that there would be few patients with COPD receiving ICS alone, small numbers of patients receiving an ICS/LABA (recommended for patients with COPD and high eosinophil counts [>300 cells/ul]), and that the use of LABA-only treatment is rare.

Inhaled corticosteroids

6.28. The Subcommittee noted that usage of ICS-only products has decreased in recent times. The Subcommittee considered that this was likely due to the advent of combination products that contained an ICS component, and that this increase was particularly marked for budesonide/eformoterol and fluticasone furoate/vilanterol formulations. The Subcommittee noted however that there was a significant spike in dispensings for all formulations in the month of April 2020, preceding the COVID-19 Alert Level 4 lockdown.

6.29. The Subcommittee considered that the majority of the use of ICS was in asthma, however members have observed patients with COPD treated with an ICS product. The Subcommittee considered that it was likely that the proportion of patients receiving an ICS inhaler for asthma would be approximately 70-80%. The Subcommittee considered that when used in combination with a LAMA, this would indicate that the patient likely had COPD.

6.30. The Subcommittee considered that in addition to the transfer of patients receiving ICS monotherapy to other combination products, another reason for the decreased usage observed in recent times was due to the better education regarding the role of ICS treatment and the risk of pneumonia in patients with COPD.

Long-acting bronchodilators

6.31. The Subcommittee noted that usage of LABA-only products has decreased significantly in recent times. The Subcommittee considered that this was likely due to the advent of combination products that contained a LABA component. The Subcommittee noted however that there was a significant spike in dispensings in the month of April 2020, preceding the COVID-19 Alert Level 4 lockdown.

6.32. The Subcommittee considered that most patients receiving LABA monotherapy would have COPD if the guidelines were followed, but that there would be a small proportion of patients who would have asthma, such as severe asthma. Specifically, this would include those patients treated with extra-fine beclomethasone, who may need an additional LABA. The Subcommittee considered that it would be very rare for an asthma patient not to be prescribed a LABA not in combination with an ICS.

Mucolytics

6.33. The Subcommittee noted recent correspondence regarding the transition to Special Authority for dornase alfa, and was supportive of the transition from panel managed access criteria to the proposed Special Authority criteria.

Antiallergy Preparations, anticholinergic agents, antifibrotics, leukotriene receptor agonists, methylxanthines, nasal preparations, respiratory devices, respiratory stimulants

6.34. The Subcommittee noted the usage and expenditure in these therapeutic subgroups. The Subcommittee considered that it had no particular comment or advice on these therapeutic subgroups

PAH Panel transition to Special Authority

6.35. The Subcommittee considered that they were comfortable to defer to the Pulmonary arterial Hypertension (PAH) panel for the transition of these treatments to a Special Authority.

6.36. PHARMAC noted that it was looking into the inclusion of PAH expertise on the Respiratory Subcommittee to facilitate this transition and the ongoing treatment of PAH.

Monoclonal antibodies

6.37. The Subcommittee considered that it was important that the access criteria for biological treatments were aligned, to best enable clinical use of these products.

Named Patient Pharmaceutical Assessment (NPPA)

6.38. The Subcommittee noted the NPPA applications received since 1 January 2019 for pharmaceuticals relevant to the Respiratory System and Allergies Therapeutic Group.

6.39. The Subcommittee considered that it would be appropriate for mepolizumab for eosinophilic granulomatosis and polyangiitis (EGPA) as well as other hyper-eosinophilic diseases be assessed for schedule funding. The Subcommittee considered that there is a need for this, and that the submission of a clinician-led application would be appropriate.

Horizon scanning

6.40. The Subcommittee raised a question regarding the new cystic fibrosis medicines. PHARMAC staff noted that ivacaftor has been funded since March via the exceptional circumstances pathway. PHARMAC staff noted that it is expected that a transition to Special Authority would occur once Medsafe approval had been obtained. It was expected that this transition would occur in the first quarter of 2021.

6.41. PHARMAC staff noted that for elexacaftor/tezacaftor/ivacaftor (Trikafta), the supplier would have to submit an application to Medsafe and receive approval prior to PHARMAC review of a funding application. PHARMAC staff noted that once approval had been obtained in Australia, a submission to Medsafe for expedited approval would likely occur.

6.42. The Subcommittee considered the following medicines to be of interest:

6.42.1. Mepolizumab for eosinophilic granulomatosis with polyangiitis EGPA and other rare eosinophil driven conditions

6.42.2. Expand varenicline access to allow 12 weeks' use and concomitant nicotine replacement therapy

6.42.3. *Pirfenidone and nintedanib for non-idiopathic pulmonary fibrosis interstitial lung disease.* The Subcommittee considered that there is emerging trial evidence for both treatments, including a heterogenous group of patients with non-idiopathic pulmonary fibrosis interstitial lung disease, and that the initial results from these studies is encouraging.

6.42.4. *Tobramycin solution for inhalation for bronchiectasis.* The Subcommittee noted that there are a small number of trials being conducted in inpatients but that there is difficulty discharging these patients and therefore it is prescribed in unusual ways to ensure funding. The Subcommittee considered that the nebulised solution for injection is occasionally not tolerated and as patients have an asthma-like reaction but that the solution for inhalation is more expensive. The Subcommittee considered that there is a need for tobramycin solution for inhalation for bronchiectasis for patients with bronchiectasis, and that the number of patients would be higher than those receiving this for cystic fibrosis. The Subcommittee noted that the prevalence and incidence of bronchiectasis is much greater in Māori and Pacific populations.

6.42.5. *LAMA treatments for severe asthma.* The Subcommittee noted that this is indicated as a potential add-on treatment for patients with severe asthma in the recent update to the NZ adult and adolescent asthma guidelines, however all currently funded LAMA's are only funded for COPD and specifically require a diagnosis of COPD to access treatment.

6.42.6. Infliximab for the treatment of severe sarcoidosis

6.42.7. Sirolimus or everolimus for the treatment of lymphangioleiomyomatosis

6.42.8. Modafinil for the treatment of idiopathic hypersomnia

6.42.9. *Riociguat for chronic thromboembolic pulmonary hypertension (CTEPH).* The Subcommittee noted that CTEPH is a somewhat rare condition and that the evidence base is poor, however overseas expert guidelines recommend its use in a specific subset of patients. The Subcommittee considered that this condition is not exceptional and not rare enough to be referred to the Rare Disorders Subcommittee. The Subcommittee considered there to be a high unmet need for this patient group, and that if inoperable then there are very few treatment options available.

6.42.10. Roflumilast for the treatment of chronic bronchitis

6.42.11. *Alfa-1 antitrypsin replacement for COPD due to alpha-1 antitrypsin deficiency.* The Subcommittee considered there to be an unmet need in this patient group but that the evidence base for this treatment in this indication is poor.

6.42.12. *Formoterol & extra fine ICS for AIR therapy* with or without maintenance. The Subcommittee considered that an extra fine formulation of ICS, which would result in less ICS use during the uptake of AIR therapy, would be beneficial. The Subcommittee considered that an advantage of an extra fine formulation has been observed in clinical trials.

7. Fluticasone furoate with umeclidinium bromide and vilanterol trifenatate

Interests

7.1. The Subcommittee reported no conflicts of interest with regard to this agenda item.

Application

7.2. The Subcommittee reviewed a funding application, and subsequent related correspondence, for the triple therapy fluticasone furoate (FF) /umeclidinium bromide (UMEC) /vilanterol trifenatate (VI) (brand name Trelegy Ellipta) inhaler for the treatment of chronic obstructive pulmonary disease (COPD).

7.3. The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

7.4. The Subcommittee **recommended** that fluticasone furoate /umeclidinium bromide/vilanterol trifenatate (Trelegy Ellipta) be funded only if it was **cost-neutral** to the pricing of the same components received from multiple inhalers (fluticasone furoate/vilanterol trifenatate 100/25 [Breo Ellipta] in combination with umeclidinium [Incruse Ellipta]), within the context of treatment of respiratory disease, and subject to the following Special Authority criteria:

> **Initial application** — from any relevant practitioner. Approvals valid for 2 years for applications meeting the following criteria:
> **All of the following**
> 1 Patient has a diagnosis of COPD confirmed by spirometry; and
> 2 Patient is currently receiving an ICS/LABA or LAMA/LABA treatment; and
> 3 Any of the following:
> 2.1 Patient has a COPD Assessment Test (CAT) score greater than 10; or
> 2.2 Patient has had greater than 2 exacerbations in the previous 12 months; or
> 2.3 Patient has had an eosinophil count greater than or equal to 0.3 x 10^9 cells/L in the previous 12 months
>
> **Renewal** — from any relevant practitioner. Approvals valid for 2 years for applications meeting the following criteria:
> Both:
> 1 Patient is adherent with medication; and
> 2 The treatment remains appropriate and patient is benefitting from treatment.

7.5. The Subcommittee made this recommendation on the basis that the clinical data indicates equivalent benefit from FF/UMEC/VI when compared with multiple inhaler triple therapy, but that the benefit over combination therapies containing two active treatments (LAMA/LABA and ICS/LABA) is not of particular relevance. The Subcommittee however considered that there may be the potential for improved adherence to treatment and decreased patient costs due to only having to use and pay the co-payment for one inhaler instead of two or three inhalers. The Subcommittee therefore considered that the appropriate comparator would be the same components received from multiple inhalers.

Discussion

7.6. The Subcommittee noted that in May 2019, PTAC recommended that fluticasone furoate (FF)/umeclidinium bromide (UMEC)/vilanterol trifenatate (VI) (Trelegy Ellipta) be listed only if it was cost-neutral to the future prices of triple therapy agents that include an inhaled corticosteroid (ICS), long-acting beta agonist (LABA) and long-acting muscarinic antagonist (LAMA) that are listed on the Pharmaceutical Schedule as either individual components or as combination inhalers.

7.7. The Subcommittee noted that there are currently many funded options for triple therapy (ICS/LAMA/LABA) combinations, but no funded single inhaler triple therapy options in New Zealand. The Subcommittee considered that the most appropriate comparator for FF/UMEC/VI is the same components delivered via multiple inhalers

(fluticasone furoate/vilanterol trifenatate 100/25 [Breo Ellipta] in combination with the umeclidinium [Incruse Ellipta]).

7.8. The Subcommittee noted that Māori and Pacific people are evidenced to have a high burden of disease for COPD compared to non-Māori, non-Pacific people. The Subcommittee considered that a single inhaler triple therapy would contribute to reducing the barriers to access for population groups known to be experiencing inequities such as Māori, Pacific and people from more socioeconomically deprived areas (for example by needing to pay a only single co-payment when collecting their prescription). In addition, the Subcommittee considered that the reduction in complexity due to the provision of triple therapy from a single inhaler may provide additional benefit.

7.9. The Subcommittee noted the correspondence provided by the supplier in response to the 2019 PTAC recommendation, presenting updated clinical evidence for FF/UMEC/VI in this patient population.

7.9.1 The Subcommittee noted a Phase III, randomised, double-blind trial (IMPACT trial) of patients aged 40 years or older with symptomatic COPD (n=10,355) who were randomised 2:2:1 to FF/UMEC/VI 100/62.5/25 mg, FF/VI 100/25 mg, or UMEC/VI 62.5/25 mg following a run-in on their COPD therapies over 52 weeks (Lipson et al. N Engl J Med. 2018;378:1671-80), in which the incidence of moderate or severe exacerbations per year was 0.91 with FF/UMEC/VI vs 1.07 with FF/VI ($p<0.001$) vs 1.21 with UMEC/VI ($p<0.001$), and the rate of hospitalisation per year was 0.13 with FF/UMEC/VI vs 0.15 with FF/VI ($p<0.06$) vs 0.19 with UMEC/VI ($p<0.001$).

7.9.2 The Subcommittee noted a post-hoc analysis of the IMPACT trial investigating all-cause mortality (Lipson et al. Am J Resp Crit Care Med 2020;201:1508-16).

7.9.3 The Subcommittee noted the results reported to date of a randomised, open-label, phase IV effectiveness trial (INTREPID) of patients aged 40 years or older with symptomatic COPD (CAT score ≥10 at screening and receiving non-Ellipta maintenance therapy for at least 16 weeks prior to entry) randomised 1:1 to receive FF/UMEC/VI or Non-Ellipta MITT for 24 weeks (Halpin et al. Treatment of Obstructive Lung Disease. Poster. ATS Annual Scientific Meeting 2020 - unpublished).

7.9.4 The Subcommittee noted the results of the study by Bremner et al., which demonstrated non-inferiority of FF/UMEC/VI to FF/VI + UMEC in patients with COPD (Bremner et al. Respiratory Research. 2018;19:19).

7.10. The Subcommittee considered that the clinical data indicated equivalent benefit from FF/UMEC/VI when compared to MITT, but that the benefit over combination therapies containing two active treatments (LAMA/LABA and ICS/LABA) was not of particular relevance as the comparator treatments were not triple therapies.

7.11. The Subcommittee considered that patients' behaviours change when part of a clinical trial and that this would likely improve the adherence of patients while on the trial. The Subcommittee considered that any benefit that could be attributed to improved adherence in a trial is difficult to extrapolate to everyday clinical settings.

7.12. The Subcommittee noted that there is evidence that multiple device types have a negative association with correct handling technique and patient adherence. The Subcommittee noted that, historically, when multi-therapy single inhalers have reached reach cost-neutrality, they have been favoured over regimens including the same components from multiple inhalers. The Subcommittee considered that having more

than one device increases the chance of critical errors, and that different devices, brands, concentrations, and formulations can be confusing for both prescribers and patients which may perpetuate adherence problems. The Subcommittee considered that, if adherence was improved through use of a single inhaler triple therapy regimen, that there is a potential for decrease in cost associated with COPD exacerbations and hospitalisations.

7.13. The Subcommittee considered that most COPD patients currently receiving triple therapy would likely switch to a single-inhaler regimen if available. The Subcommittee considered that a key driver for uptake of FF/UMEC/VI would be if clinicians considered that a single inhaler would help improve control for patients currently symptomatic while receiving an ICS/LABA or LABA/LAMA dual therapy. As a result, the Subcommittee considered that patients numbers may exceed the current estimate of 14-19,000 patients, which is the estimated number of prevalent patients currently receiving a triple therapy regimen.

7.14. The Subcommittee considered that it would be important that the Special Authority criteria for FF/UMEC/VI prevent patients from automatically switching to triple therapy when treatment with an ICS may not be an appropriate treatment option.

8. Budesonide/Formoterol (AIR and AIR plus maintenance therapy)

Interests

David McNamara noted that:

- He is an advisor for the CARE study examining the use of budesonide/eformoterol as needed compared with salbutamol in children.

Stuart Dalziel noted that:

- He was an investigator on the paediatric studies of budesonide/eformoterol vs. salbutamol (CARE study), was an investigator on the Novel START and PRACTICAL trials (one funded by AZ and the other by HRC) and works closely with investigators of the NOVEL and PRACTICAL trials on a number of additional studies. He was not present for the discussion relating to item 8.

Andrew Corin noted that:

- He was an investigator on the Novel START and PRACTICAL trials (one funded by AZ and the other by HRC). He contributed to the design and reporting of the trials. The trial site for which I am a director was paid a fee for conducting the trials. He was also paid a fee as a named investigator for PRACTICAL. The Chair deemed this as a conflict, but participation in the discussion was permitted under Board Chair's Standing Permission, however he would abstain from voting

- He is an advisor for the CARE study examining the use of budesonide/formoterol as needed compared with salbutamol in children.

Application

8.1. The Subcommittee reviewed a PHARMAC initiated proposal regarding the frequency of dispensing for, budesonide/eformoterol dry powder inhalers for the treatment of asthma.

8.2. The Subcommittee also reviewed a supplier application for budesonide/eformoterol pressurised metered dose inhaler (Symbicort Rapihaler) in the treatment of asthma.

8.3. The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

8.4. The Subcommittee **recommended** that budesonide/eformoterol inhalers (100/6 and 200/6; dry powder for inhalation and pressurised metered dose inhalers) be dispensed stat with a **high priority** within the context of treatment for respiratory diseases.

8.4.1. The Subcommittee made this recommendation based on the need to facilitate a transition to and alignment with the 2020 update to the NZ Adult and Adolescent Asthma guidelines relating to the use of anti-inflammatory reliever (AIR) therapy, given the quality of the evidence supporting this.

8.5. The Subcommittee **recommended** that budesonide/eformoterol metered dose inhaler (Symbicort Rapihaler 100/3) be listed as **cost-neutral** to the per dose price of Vannair 200/6 metered dose inhaler within the context of treatment for respiratory diseases.

8.5.1. The Subcommittee made this recommendation based on the considerations that use of Vannair as AIR therapy does not pose a significant clinical risk and that the benefit of the Symbicort Rapihaler would be derived from its similarity in behavioural requirements for patients transitioning from salbutamol, which requires two puffs per use.

Discussion

Background

8.6. The Subcommittee noted that asthma is a common and sometimes severe chronic lung disease characterised by inflammation, subsequent narrowing of the airways and reversible airway obstruction, and that inhaled corticosteroids (ICS) and beta agonist combination treatments have long been indicated for the maintenance treatment of asthma.

8.7. The Subcommittee noted that adult medicated asthma is 1.4 times more common in women than in men, and that Māori adults have an increased prevalence of medicated asthma than non-Māori (Ministry of Health Annual Update of Key Results 2018/2019).The Subcommittee noted that Māori, Pacific people, and people living in the most socioeconomically deprived areas experience the highest rates of hospitalisations due to asthma, and that Māori are 3.3 times and Pacific peoples 3.7 times more likely to be hospitalised than Europeans or other New Zealanders (Asthma and Respiratory Foundation NZ Report 2018).

8.8. The Subcommittee noted that the most recent guidelines for asthma treatment (2020 Update of the NZ Adolescent and Adult Asthma guidelines) indicate that the preferred algorithm for treatment of mild and moderate asthma for adolescent and adult patients is budesonide and eformoterol, denoted as Anti-Inflammatory Reliever (AIR) therapy with or without maintenance. The Subcommittee noted that the main changes to the guidelines relevant to the use of budesonide with eformoterol are:

8.8.1. The recommendation to avoid short-acting beta agonist (SABA)-only treatment;

8.8.2. The use of an ICS/fast-acting beta adrenoceptor agonist such as eformoterol with budesonide as the preferred reliever medication over SABA, across the spectrum of asthma severity;

8.8.3. Introduction of the terminology 'anti-inflammatory reliever (AIR)' therapy to describe the use of budesonide with eformoterol as a reliever medication, with or without budesonide with eformoterol as maintenance therapy. This approach is an extension of the 'Single combination ICS/ long-acting beta agonist (LABA) inhaler Maintenance and Reliever Therapy' (SMART) approach recommended in the previous guideline (2016).

8.9. The Subcommittee noted that at the time of publication of the updated 2020 guidelines, the dry powder inhalers (DPIs) Symbicort Turbuhaler (100/6, 200/6, 400/12) and DuoResp Spiromax (200/6, 400/12) are the only formulations that had regulatory approval in New Zealand for AIR therapy. The Subcommittee noted that there are currently no pressurised metered dose inhalers (pMDIs) that are approved for use as AIR therapy with or without maintenance, but considered that the registration status for these products for use in these particular indications was not a particular concern clinically.

8.10. The Subcommittee noted that asthma exacerbations pose a significant cost to the healthcare system and as well as to patients, family, and whānau. The Subcommittee noted that an urgent GP visit for an adult, depending on location, can cost up to $100 per visit, and that exacerbations that result in hospitalisation can cost the health system upwards of $3,000.

Budesonide/eformoterol dry powder inhaler (DPI)

8.11. The Subcommittee noted a request for information by PHARMAC staff regarding the use of budesonide/eformoterol dry powder inhalers for the treatment of asthma in light of the 2020 Update of the NZ Adolescent and Adult Asthma guidelines.

8.12. The Subcommittee noted that the majority of patients receiving budesonide/eformoterol DPIs suffer from asthma, and only a small proportion of patients receive budesonide/eformoterol DPIs for the relief of chronic obstructive pulmonary disease (COPD).

8.13. The Subcommittee noted that in October 2020, Teva's budesonide with eformoterol inhaler (DuoResp Spiromax) was listed on the Pharmaceutical Schedule alongside the Symbicort Turbuhaler, both of which are approved for use as AIR therapy with or without maintenance (DuoResp Spiromax being only approved as AIR therapy for adults, while Symbicort Turbuhaler is approved in ages 12 years and over for AIR without maintenance and in the 100/6 strength is approved in ages 4 years and over for AIR with maintenance).

8.14. The Subcommittee noted that in practice the 100/6 strength of the Symbicort Turbuhaler is often used to treat children under the age of 12 years. The Subcommittee noted that the 200/6 strength formulation, available in both brands, is also occasionally used in children aged under 12. The Subcommittee noted that DuoResp Spiromax is not currently approved for AIR therapy with or without maintenance for patients under the age of 18, but that a decision by Medsafe whether to approve for adolescent patients is expected in 2021. The Subcommittee considered that the appropriate age cut-off for this inhaler should be 12 years old, as there is no 100/6 strength of DuoResp Spiromax at this time.

8.15. The Subcommittee noted that the currently available strengths of budesonide/eformoterol dry powder inhalers are 200/6 and 400/12 for DuoResp Spiromax, and 100/6, 200/6, and 400/12 for Symbicort Turbuhaler. The Subcommittee noted that the 400/12 strength dose is rarely used in primary care, and considered that there is a risk of it being used for AIR therapy with or without maintenance, which is inappropriate due to the high ICS and LABA dose administered during each actuation. The Subcommittee considered that prescribing lower doses provides more flexibility with dosing without the concern of high doses of steroids being prescribed and taken inappropriately as reliever therapy. The Subcommittee considered that the high dose formulation (400/12) was not required as patients could sufficiently obtain the equivalent dose from two inhalations of the 200/6 strength formulation. The Subcommittee considered that if not available, this would reduce the risk of inappropriate use of the 400/12 strength of budesonide/eformoterol as reliever therapy in primary care.

8.16. The Subcommittee noted that current practice with salbutamol pMDIs is that they are dispensed in large quantities so that patients can receive multiple inhalers per dispensing. The Subcommittee also noted that, in light of the recent updates to the NZ asthma guidelines for mild-moderate asthma, PHARMAC has been requested to makes a change to enable an increase in the dispensing quantities, frequencies and funding of budesonide/eformoterol inhalers to align with this shift in treatment paradigm. The Subcommittee considered that a change to enable stat dispensing would help facilitate this change and align with the new guidelines. The Subcommittee noted that enabling stat dispensing of budesonide/eformoterol would allow patients to have multiple inhalers in different locations, similar to what members considered occurs now with salbutamol pMDIs. The Subcommittee considered that this change could potentially lead to wastage of budesonide/eformoterol inhalers but clinically would reduce the risk of serious exacerbations. In addition, the Subcommittee also considered that enabling primary care providers to provide budesonide/eformoterol on a practitioner's supply order would help facilitate implementation of the update 2020 update to the guidelines.

8.17. The Subcommittee noted that the Symbicort Turbuhaler has a shelf-life of 24 months, and that the supplier had indicated that there is no separate shelf-life once opened. The Subcommittee also noted that the DuoResp Spiromax has a 36-month shelf-life, however the datasheet indicates that the product must be used within 6 months of opening. The Subcommittee noted that patients with mild asthma who do not need to use their inhalers as AIR therapy regularly would likely stockpile these without keeping track of when they were opened or when they expire, resulting in the use of expired inhalers. The Subcommittee considered that there are potential stability issues with DPIs, but there is insufficient data on shelf-life stability of these inhalers to know if their efficacy reduces appreciably once expired. The Subcommittee considered that if an expired inhaler was delivering 80% of the expected dose that this would still be beneficial to patients using AIR therapy, and that patients would likely slightly increase their weekly dose or number of actuations as necessary to compensate.

8.18. The Subcommittee noted 5 trials providing evidence for the use of budesonide/eformoterol DPIs for AIR and AIR plus maintenance therapy:

- Balang et al. Plum Pharmacol Ther. 2006;19:139-47
- Bateman et al. N Eng J Med. 2018;378:1877-87
- O'Byrne et al. N Eng J Med. 2018;378:1865-76
- Beasley et al. N Engl J Med. 2019;380:2020-30
- Hardy et al. Lancet. 2019;94:919-928

8.19. The Subcommittee noted the results of the Beasley et al trial, which was a 52-week, randomised, open-label, parallel-group, controlled trial involving 675 adults with mild asthma; comparing AIR therapy with budesonide plus salbutamol as needed and salbutamol only as needed. The Subcommittee noted that the annualised exacerbation rate was lower for the AIR therapy group than that of the salbutamol group (absolute rate, 0.195 vs. 0.400; relative rate 0.49, 95% confidence interval [CI] 0.33 to 0.72; p<0.001) and that the number of severe exacerbations was reduced in the AIR therapy group compared with the salbutamol only group. The Subcommittee considered that the benefit of AIR therapy was that in mild asthma it would reduce the annualised exacerbation rate and the number of severe exacerbations compared to salbutamol-only therapy. However, the Subcommittee considered that it was important to incorporate baseline exacerbation rates into any analysis of the impact of AIR therapy, as a direct comparison between trial arms could over-estimate true rates due to the variation in exacerbation rates between arms at baseline.

8.20. The Subcommittee considered that if budesonide/eformoterol were to be funded in New Zealand stat for AIR therapy in patients with mild asthma, the most appropriate comparator would be currently funded SABA treatments. The Subcommittee considered that the comparator for dosage and usage calculations when extrapolating the usage from the Beasley et al trial to the New Zealand population would the LABA component in budesonide/formoterol treatment options, as it is the most appropriate surrogate for symptom relief when a SABA is used as the comparator.

8.21. The Subcommittee noted the results of the Hardy et al. trial, which indicated that the annualised rate of exacerbations for AIR therapy was less than that of maintenance budesonide plus terbutaline as needed (0·119 vs 0·172; relative rate 0·69, 95% CI 0·48 to 1·00; p=0·049).

8.22. The Subcommittee noted the results of the O'Byrne et al trial, which indicated that the mean percentage of weeks with well controlled asthma for patients using AIR therapy was superior to terbutaline (SABA) used as needed (34.4% vs. 31.1% of weeks; odds ratio 1.14; 95% CI 1.00 to 1.30; p=0.046).

8.23. The Subcommittee noted the results of the Bateman et al trial, which indicated that annualised rate of severe asthma exacerbations for AIR therapy was non-inferior to budesonide/eformoterol maintenance plus terbutaline as needed.

8.24. The Subcommittee considered that the evidence to support the use of AIR therapy with or without maintenance was strong and of good quality, and was of particular relevance to the New Zealand population, with the recent update to the adult and adolescent asthma guidelines, as many of these trials were performed in New Zealand centres.

Budesonide/eformoterol pressurised metered dose inhaler (pMDI)

8.25. The Subcommittee noted an application from AstraZeneca for the use of budesonide/eformoterol pressurised metered dose inhaler (pMDI) (Symbicort Rapihaler 100/3) for use as AIR therapy with or without maintenance for the treatment of mild and moderate asthma.

8.26. The Subcommittee noted that the equivalent pMDI currently available in New Zealand is AstraZenica's Vannair pMDI. The Subcommittee noted two doses of Symbicort Rapihaler 100/3 is equivalent to one dose of Vannair 200/6, and similar to one dose of the DuoResp Spiromax and Symbicort Turbuhaler 200/6 DPIs. The Subcommittee noted that Vannair does not have approval for use as AIR therapy with or without

maintenance, however considered that there would be a proportion of the population who are receiving Vannair off-label for AIR therapy.

8.27. The Subcommittee considered that, if Symbicort Rapihaler 100/3 were to be funded, it would often be prescribed as it has a low dose of both ICS and LABA as well as a reliable dose counter. The Subcommittee considered that the lack of a dose counter on currently used salbutamol reliever inhalers is a safety issue, as it there is the potential for a patient to unknowingly rely on an inhaler for use in an emergency situation when it is empty. The Subcommittee noted that Symbicort Rapihaler 100/3 is not appropriate for use as AIR therapy with or without maintenance in children under 6 years of age.

8.28. The Subcommittee noted that there is a lack of evidence for efficacy of AIR therapy in children but considered it reasonable to extrapolate from the adult population using the Symbicort Rapihaler 100/3 for AIR therapy. The Subcommittee noted that there is a clinical trial underway for use of AIR in children, which will likely provide results for the use of AIR therapy in this patient group in approximately two years' time (ACTRN12620001091998). The Subcommittee nonetheless considered that budesonide/eformoterol AIR therapy with or without maintenance would be appropriate in children (older than five years of age), regardless of the lack of evidence yet in this age group.

8.29. The Subcommittee noted that the Symbicort Rapihaler 100/3 has a lower dose of LABA and ICS and considered that the risk of adverse events from overdose of these agents is lower than with higher dose formulations. The Subcommittee however considered that there may be possible reduced efficacy for acute symptoms with the lower dose, particularly with patients with poor inhaler technique.

8.30. The Subcommittee noted that, for patients transitioning to AIR from SABA alone, it may be beneficial to transition to a product which requires two actuations to reach the equivalent of a dose of 200 mcg budesonide and 6 mcg of eformoterol, which would require similar handling to that of salbutamol inhalers. Comparatively, the Subcommittee noted that that switching from two actuations of salbutamol to Vannair 100/6 or 200/6, where Vannair 100/6 or 200/6 require one actuation for dose delivery, could lead to increased rates of overdosing adverse events associated with the increased intake of LABA. The Subcommittee considered that similarity in dose and the device itself is an important factor for patients transitioning to AIR. The Subcommittee noted that the Symbicort Rapihaler looks similar to the Vannair inhaler and considered that this may be confusing for some patients and prescribers if both were to be listed together.

8.31. Members noted that by virtue of the Symbicort Rapihaler increased dosing requirement compared to Vannair, this would increase the emissions of hydrofluoroalkane propellant per dose, being a greenhouse gas with implications for climate change.

8.32. The Subcommittee noted the following studies as evidence for use of pMDI budesonide/eformoterol inhalers in the treatment of asthma:

- Unpublished AstraZeneca study D5897C00003 (ClinicalTrials.gov identifier: NCT00536731)
- Morice et al. Int J Clin Pract. 2007;61(11):1874-83
- Morice et al. Plum Pharmacol Ther. 2008;21(1):32-9
- Morice et al. Pulm Pharmacol Ther. 2008;21(1):152-9
- Patel et al. The Lancet Respiratory Medicine. 2013;1(1):32-42

8.33. The Subcommittee noted that none of the above studies included AIR therapy as a treatment arm. The Subcommittee also noted that there were no studies available on the use of budesonide/eformoterol pMDIs as AIR therapy. The Subcommittee noted that the four studies provided evidence for the use of budesonide/eformoterol DPIs as AIR therapy (listed above) used strengths of at least 200/6, and that there was no evidence for a 100/3 strength. However, the Subcommittee considered that the evidence supporting the use of DPIs as AIR therapy was of relevance and could be reasonably extrapolated to budesonide/eformoterol pMDIs.

8.34. The Subcommittee considered that funding Symbicort Rapihaler could impact health sector costs or expenditure, and that the reduction in asthma exacerbations may lead to health sector savings long term. However, the Subcommittee considered this benefit would occur as a result of the uptake of AIR therapy in patients currently receiving salbutamol. The Subcommittee considered that the lack of Medsafe approval for AIR therapy for Vannair was not an important clinical consideration in the recommendation for funding of Symbicort Rapihaler. The Subcommittee considered that off-label use of Vannair as AIR therapy did not pose a risk clinically, and that the benefit of the Symbicort Rapihaler would be derived from its similarity in behavioural requirements for patients transitioning from salbutamol, which requires two puffs per use.

8.35. The Subcommittee considered that the comparator for dosage and usage calculations, when extrapolating the usage from the Beasley et al trial to the New Zealand population, would be the LABA component in budesonide/formoterol treatment options, as the most appropriate proxy for direct symptom relief when a SABA is used as the comparator.

8.36. The Subcommittee noted that the shelf-life for Symbicort Rapihaler 100/3 as packaged for sale is 2 years, however the shelf-life after first opening is 3 months and that this is the same as both strengths of the currently listed Vannair. The Subcommittee considered that the short shelf-life of the Symbicort Rapihaler may increase the financial impact of a change to stat dispensing, in that patients with mild asthma and infrequent use may see their medication deteriorate or be wasted.

Summary

8.37. The Subcommittee noted that there is likely high use of SABA pMDI only in Māori and Pacific populations, who are disproportionately affected by asthma, and that there is a higher need for AIR therapy options for these groups. The Subcommittee considered that availability of AIR therapy could be a driver for transitioning patients from their reliance on SABA inhalers to budesonide/eformoterol, which is safer and more effective at reducing exacerbations. The Subcommittee also considered that funding decisions should minimise barriers for patients and clinicians to adhere to the updated treatment guidelines.

8.38. The Subcommittee considered that budesonide/eformoterol DPIs and pMDIs could replace the use of SABA and ICS inhalers, but that they could potentially be used incorrectly in combination with SABA and other ICS if patients were confused about inhaler use.

8.39. The Subcommittee noted that the paradigm shift from using SABA reliever inhalers alone for the treatment of mild asthma to using budesonide/eformoterol inhalers for symptom relief could see a large proportion of current SABA-only patients shift to budesonide/eformoterol products for symptom relief over 5-years. The Subcommittee considered that the PHARMAC estimate of 8% uptake per annum, which was based on the uptake of SMART therapies earlier, was likely too low, as advocacy and health

sector support for AIR therapy is strong, and AIR is a simpler regimen than SMART. However, the Subcommittee considered that it is unclear how many patients would transition from SABA-only therapy to budesonide/eformoterol based AIR therapy, given previous experience with salbutamol generic transitions. The Subcommittee noted that some patients are loyal to a certain product and in many cases are willing to pay an extra part charge per dispensing to maintain treatment with their current branded therapy, which could mean that some patients will resist switching from SABA-only to budesonide/eformoterol based AIR therapy.

8.40. The Subcommittee considered that there would be cost saving to the health system from reduced exacerbations as a result of AIR vs SABA-only therapy. The Subcommittee noted the absolute reduction in severe exacerbations from the Beasley et al trial.

8.41. The Subcommittee considered it would be important to consider the potential savings from less repeat dispensing of ICS with salbutamol when salbutamol is the only part of the dispensed treatment being used by patients, as this may be very common.

8.42. The Subcommittee noted that SABA-only as a reliever treatment will still be used by emergency services and in hospital ICUs, and that GPs may still prescribe SABA for use as needed. The Subcommittee also considered that, during the phase-out of SABA-only use in favour of AIR, costs to the combined pharmaceutical budget will escalate in the interim due to the higher price of AIR treatment options compared with SABA inhalers.

8.43. The Subcommittee noted that patients are likely to require more than two inhalers per dispensing in order to keep inhalers in more than one location in case exacerbations were acute and severe. The Subcommittee considered that a clinician would typically be comfortable with prescribing 6 months' supply to a patient deemed to be well managed on current therapy, if this meant they would be able to store inhalers at more than one location. The Subcommittee considered however that this would also contribute to greater potential wastage of a product with a shorter shelf-life.

Future procurement process for budesonide/eformoterol

8.44. The Subcommittee noted the record of the Respiratory Procurement Advisory Group meeting (September 2019).

8.45. The Subcommittee considered that it would be important to retain both 100/6 and 200/6 strengths after any commercial process regarding budesonide/eformoterol inhalers. The Subcommittee considered that having both strengths available is important regardless of whether the inhalers are DPIs or pMDIs, and that having multiple strengths makes it easier for prescribers and patients to individualise dosing for their specific needs. The Subcommittee however considered that the inclusion of the high strength (400/12) formulation in a future procurement process was not necessary.

8.46. The Subcommittee noted that some patients may find it difficult to transition to a new or different brand of inhaler, due to confusion about how to use the inhaler, which is especially the case with the elderly and patients currently using multiple inhalers. The Subcommittee considered that similarity between devices and methods of administration of the medicine, as well as the formulation, would be important to consider during any transition to a sole supply arrangement. The Subcommittee considered that a six-month transition period would be an appropriate amount of time

to transition patients from different budesonide/eformoterol formulations to a single budesonide/eformoterol inhaler for AIR with or without maintenance.

8.47. The Subcommittee considered that prescriber and patient education will be important if patients are to be transitioned onto different brands, in order to limit the nocebo effect, and that similarity of use between old and new brands will aid with familiarity and therefore adherence to treatment. The Subcommittee noted the importance of engaging with organisations and key stakeholders, such as GPs, pharmacists, the Pharmaceutical Society of NZ, and asthma nurses, who play a key role in asthma education and dispensing of asthma medication. The Subcommittee considered that if a single generic brand was funded as the result of a commercial process, it would be important for prescribers and pharmacy to provide education to patients, in particular when historically there has been little supplier-provided education to inform past switches.

8.48. The Subcommittee considered that, when evaluating different types of inhalers, it is important that variation in both the delivery device and the formulation be taken into account (eg. that there may be more variation in some cases within groups of inhalers [DPIs or pMDIs] than between DPIs and pMDIs).The Subcommittee considered that splitting inhalers into the categories, such as DPIs and pMDIs, can be of limited practical clinical relevance, given the variation within categories.

8.49. The Subcommittee considered that the preferred commercial approach for budesonide/eformoterol DPIs would include principal supply status, and that it would be important to allow some patients to remain on their previous inhaler by virtue of the discretionary variance allowance. The Subcommittee considered that an allowance of up to 5% would be appropriate for this transition. The Subcommittee considered that patient and clinician education will be key in transitioning patients to ensure similarity and familiarity of use to aid with adherence. The Subcommittee noted that inhaler technique training specific to the new devices would be important for transitioning patients.

9. High dose ICS/LABA (fluticasone propionate/salmeterol; fluticasone furoate/vilanterol)

Interests

9.1. The Subcommittee reported no conflicts of interest for this item

Application

9.2. The Subcommittee reviewed the application for fluticasone furoate/vilanterol 200/25 mcg (Breo Ellipta 200).

9.3. The Subcommittee noted the consultation feedback received regarding fluticasone propionate with salmeterol (high dose) for severe asthma when this had been proposed for decline.

9.4. The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

9.5. The Subcommittee **recommended** that fluticasone furoate/vilanterol 200/25 mcg (Breo Ellipta 200) be funded for the treatment of severe asthma with a **medium priority**

within the context of respiratory disease, subject to the following Special Authority criteria:

> **Initial application** – (severe asthma) from any relevant practitioner on the recommendation of a paediatrician or respiratory physician. Approvals valid for 12 months for applications meeting the following criteria:
> Both:
> 1. Despite adherence to optimised asthma therapy including inhaled corticosteroids (equivalent to at least 500 mcg per day of fluticasone propionate) plus long acting beta-2 agonist, or budesonide/formoterol as part of the anti-inflammatory reliever plus maintenance regimen including previous trials of appropriate meds, the patient has experienced an asthma exacerbation in the previous 6 months that required oral corticosteroids; and
> 2. Conditions that mimic asthma (e.g., vocal cord dysfunction, central airway obstruction etc.) have been excluded or managed.
>
> **Renewal** – (severe asthma) from any relevant practitioner on the recommendation of a paediatrician or respiratory physician. Approvals valid without further renewal where the treatment remains appropriate and the patient continues to benefit from treatment

9.6. In making this recommendation, the Subcommittee considered the health need of this patient group with severe disease, the potential benefits of fluticasone furoate/vilanterol 200/25 mcg, and the risks associated with use of high dose inhaled corticosteroids in this patient group.

Discussion

9.7. The Subcommittee noted that a quarter of patients with asthma of any severity cannot adequately control their asthma with currently funded inhaler therapy at standard doses. The Subcommittee considered that patients with severe uncontrolled asthma can be very unwell, experiencing shortness of breath and requiring hospital stays for management, all of which impacts on the families/whānau of people with severe uncontrolled asthma. The Subcommittee noted that Māori and Pacific people are disproportionately affected by asthma, have more than two times the mortality rate as non-Māori and are more likely to be hospitalised due to severe asthma (Ministry of Health, 2013/14 New Zealand Health Survey and National Minimum Data Set [NMDS]).

9.8. The Subcommittee noted that approximately 25% of patients with severe asthma are uncontrolled and considered that about 5-10% patients with severe, uncontrolled asthma despite all other options (e.g. optimisation of current treatments through asthma nurse support; a trial of high-dose inhaled corticosteroids) may be eligible to commence a biologic treatment with a monoclonal antibody i.e. mepolizumab or omalizumab. The Subcommittee considered that actual uptake of these biologics is only about 2% of patients with severe, uncontrolled asthma despite all other options due to patient preference for inhaled over biological therapy as well as the logistical complexity of biological therapy. The Subcommittee noted that mepolizumab and omalizumab are given as an injection and require admission to a day stay unit (at a cost of $500 per admission) for at least the first few treatments; subsequent doses of omalizumab may be given in the community via prefilled syringes, and mepolizumab is expected to be able to be delivered in the community after Medsafe approval in 2021.

9.9. The Subcommittee noted that the Special Authority criteria for mepolizumab and omalizumab each require a patient to have trialled high-dose oral corticosteroids (1000 mcg per day or equivalent) with a long-acting beta agonist (LABA); current funded options are such that this high dose of steroid cannot be achieved without using two separate devices. The Subcommittee noted that a proportion of patients who trial higher doses of an inhaled corticosteroid may benefit from anti-inflammatory reliever therapy with maintenance (Hardy et al. Lancet. 2019;394:919-28).

Fluticasone propionate (FP) / with salmeterol (Sal) (high dose) for asthma and chronic obstructive pulmonary disease

9.10. The Subcommittee noted that the application for fluticasone propionate (FP) with salmeterol (Sal) (high dose) was considered by PTAC and recommended for decline in November 2007, November 2010 and in August 2011. In May 2013, the Respiratory Subcommittee had reviewed and agreed with PTAC's recommendation to decline the application. Overall, the rationale for the recommendation to decline was concern about the high dose of corticosteroid in the combination product, which could cause significant side effects (e.g. pneumonia) and it was noted that high-dose inhaled steroid regimens could be achieved by combining existing funded inhalers (e.g. an inhaled corticosteroid [ICS]/ long-acting beta agonist [LABA] plus an ICS).

9.11. The Subcommittee noted that the application was included in PHARMAC's December 2019 consultation proposing to decline inactive funding applications and that a responder had noted that the Special Authority for omalizumab requires that patients be adherent to an inhaled corticosteroid dose equivalent to 1000 mcg FP per day or equivalent (where currently, this threshold cannot be reached without prescribing two separate inhalers, one containing the combination FP/Sal and another containing FP only; the responder considered that having FP/Sal (high dose) available would resolve the need for two inhalers to satisfy this Special Authority criterion for this population). The Subcommittee noted that no further evidence has been provided regarding FP/Sal (high dose), and considered that a daily dose of 1600 mcg budesonide would also satisfy the Special Authority requirement for omalizumab.

9.12. The Subcommittee considered that the patient population who require high dose inhaled corticosteroids, or biologics, for severe asthma are a high need group with impaired quality of life and an increased risk of death, experiencing multiple exacerbations per year and often requiring hospital admission to manage their disease. The Subcommittee considered that these patients could benefit from a move to one high-dose inhaler, which could reduce the risk of critical errors associated with use of multiple devices

9.13. The Subcommittee considered that the unmet need of patients with severe asthma that was identified by the consultation respondent regarding FP/Sal (high dose) could be addressed by amending the Special Authority criteria for mepolizumab and omalizumab to state that a patient had trialled a medium or high dose of high-potency inhaled corticosteroid according to the relevant treatment guidelines, as an alternative to specifying a particular dose. The Subcommittee however considered that adjusting the criteria for high dose corticosteroids would likely increase the number of patients eligible for biological treatment

Fluticasone furoate/vilanterol 200/25mcg (Breo Ellipta 200) for severe asthma

9.14. The Subcommittee noted that fluticasone furoate/vilanterol (FF/VI) 200/25 is approved by Medsafe for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination product (ICS/LABA) is appropriate. The Subcommittee noted that FF/VI 200/25 (Breo Ellipta 200) would be taken as one inhaled dose daily and had been proposed to enable patients to receive the high ICS dose without receiving excess LABA, as would occur with two puffs of a 100/25 inhaler.

9.15. The Subcommittee considered that the FF/VI 200/25 has the same (or similar) therapeutic effect as other inhaled corticosteroids (i.e. a combination of an inhaler providing ICS/LABA and an additional inhaler with the same ICS e.g. fluticasone

propionate or budesonide) that are currently listed on the Pharmaceutical Schedule, however, the FF/VI 200/25 provides this dose in one inhaler only. In addition, the Subcommittee considered that it may reduce the number of patients that could require treatment with a long-acting muscarinic agonist.

9.16. The Subcommittee noted that previously high-dose fluticasone furoate with vilanterol (200/25 mcg) was recommended for decline by PTAC in November 2014 and by the Respiratory Subcommittee in September 2015 due to the risk of adverse events associated with high-dose corticosteroids and a lack of evidence of harm associated with using two devices.

9.17. The Subcommittee noted the results of the double-blind, randomised, parallel-group, phase III study CAPTAIN study, which included 2,436 patients with uncontrolled asthma despite treatment with ICS/LABA with pre-bronchodilatory FEV_1 (forced expiratory volume in 1 second) between 30% and <85% of predicted normal value (Lee et al. Lancet Respir Med. 2020;S2213-2600(20)30389-1. [Epub ahead of print]). The Subcommittee noted that participants were randomised (1:1:1:1:1:1) to receive one of the following treatments administered once daily via Ellipta dry powder inhaler for between 24 to 52 weeks:

- Fluticasone furoate (FF) / vilanterol (VI) 100/25 mcg
- FF/VI 200/25 mcg
- FF/ umeclidinium (UMEC) / VI 100/31.25/25 mcg
- FF/UMEC/VI 100/62.5/25 mcg
- FF/UMEC/VI 200/31.25/25 mcg
- FF/UMEC/VI 200/62.5/25 mcg

9.17.1. The Subcommittee considered that FF/VI 100/25 was the most relevant comparator for the New Zealand context. However, the Subcommittee noted that the long-acting muscarinic agonist (LAMA) combination therapies were relevant to the evaluation of the efficacy of FF/VI 200/25, although in New Zealand they are not funded for patients with asthma.

9.17.2. The Subcommittee noted that the primary outcome was the change from baseline in clinic trough FEV_1 and that at week 24, the least squares mean improvement in FEV_1 was 110 mL (95% CI: 66 to 153; P<0.0001) for FF/UMEC/VI 100/62.5/25 mcg versus FF/VI 100/25 mcg, and was 92 mL (95% CI:49 to 135; P<0·0001) for FF/UMEC/VI 200/62.5/25 mcg versus FF/VI 200/25 mcg. The Subcommittee considered that the high-dose FF/VI 200/25 mcg improved FEV_1 compared with FF/VI 100/25 mcg, but not as much as adding umeclidinium. The Subcommittee considered that the results did not meaningfully differ between groups according to eosinophil count.

9.17.3. The Subcommittee noted that the mean annualised moderate and/or severe asthma exacerbation rate was 0.87 with FF/VI 100/25 mcg and 0.57 with high dose FF/VI 200/25 mcg and 0.55 with FF/VI/UMEC 200/62.5/25 mcg. The Subcommittee considered that the exacerbation rate reduction observed was due to the increased dose of fluticasone furoate, however, the Subcommittee noted a similar effect with the addition of umeclidinium.

9.17.4. The Subcommittee noted that there was no evidence directly comparing the efficacy of ICS + ICS/LABA (FF/VI 100/25) with FF/VI 200/25 mcg and that this lack of evidence was unlikely to change. The Subcommittee considered that the benefit observed from FF/VI 200/25 mcg in this population compared

to the FF/VI 100/25 mcg was relevant to patients requiring additional ICS beyond their current ICS/LABA dose.

9.17.5. The Subcommittee noted that a pre-specified subgroup analysis in the CAPTAIN study, provided by the supplier as a poster, reported that higher dose FF/VI had a greater effect on trough FEV_1 and moderate-severe exacerbations in patients with elevated eosinophil counts (Pavord_205715_ATS-2020).

9.18. The Subcommittee noted that a systematic literature review of single combination inhalers compared with multiple inhalers in patients with asthma or chronic obstructive pulmonary disease (COPD) reported that observational studies suggested clinical benefit of receiving treatment from one inhaler rather than multiple inhalers. The Subcommittee noted that 18 of the randomised controlled trials included in this analysis reported no effect on lung function and six reported no effect on exacerbations (Zhang et al. 2020. Int J Chron Obstruct Pulmon Dis. 2020; 15: 417–38). The Subcommittee noted that the review reported a decrease in medicine costs with use of a single inhaler, based on observational studies and two open-label randomised controlled trials, as well as reductions in emergency room visits, oral corticosteroid use and use of short-acting bronchodilator.

9.19. The Subcommittee noted that a randomised, controlled, cross-over, dose-response comparison trial measuring airway responsiveness and cortisol levels in 54 patients with asthma reported that the therapeutic effect of fluticasone furoate was equivalent to or better than high-dose fluticasone propionate or budesonide, and that cortisol levels with fluticasone furoate were the same as those with low-dose fluticasone propionate or budesonide (Daly-Yates et al. Br J Clin Pharmacol. 2020. doi: 10.1111/bcp.14406. [Epub ahead of print]).

9.20. The Subcommittee considered that there remains a clinical risk of systemic exposure from high dose corticosteroids and an increased risk of pneumonia (which significantly suppresses lung function) associated with high-dose fluticasone furoate, noting that there is clinical trial data suggesting that the rate of pneumonia was increased in patients who received fluticasone furoate 200 mcg daily compared to fluticasone furoate 100 mcg daily (Fluticasone furoate/Vilanterol periodic benefit risk evaluation report. GSK. 2015 [unpublished]). The Subcommittee noted that the extent of cortisol suppression differs among molecules, with a 14% decrease in cortisol with FF 200 mcg and about a 30% decrease with FP 1000 mcg (Daly-Yates et al. Br J Clin Pharmacol. 2020. doi: 10.1111/bcp.14406. [Epub ahead of print]); the Subcommittee considered that this difference was substantial.

9.21. The Subcommittee noted that the supplier's 2015 submission included evidence for changes in urine cortisol levels from integrated asthma clinical trials that used FF/VI 100/25, FF/VI 200/25, FF 100, FF 200, FP 200, FP 500, FP 1000, placebo, or placebo plus oral corticosteroid (Fluticasone furoate/vilanterol supplier application. 2015). The Subcommittee noted that the more recent evidence reported serum cortisol and considered that this indicated there was no difference in the effect of increased fluticasone furoate dose on serum cortisol. The Subcommittee considered that the evidence from the 2015 submission provided more clear evidence that fluticasone furoate doses of 100 and 200 mcg did not significantly affect urine cortisol levels. The Subcommittee considered that this sufficiently addressed the safety concerns about the use of high-dose corticosteroids in this setting.

9.22. The Subcommittee noted that the published literature for the FF/VI 200/25 does not include the risk of pneumonia with either strength of the Breo inhaler, comparison with

other doses of inhaled corticosteroids, and the relative hospitalisation rates due to exacerbations.

9.23. The Subcommittee considered that there are theoretical risks of mis-prescribing or dosing errors that could result in patients receiving excessively high doses of inhaled corticosteroid. The Subcommittee considered that because of this risk, it would be necessary to limit who could recommend prescribing this medicine to respiratory physicians and paediatricians. The Subcommittee considered that once commenced on FF/VI 200/25, it would be unlikely that patients would have their dose titrated down.

9.24. Overall, the Subcommittee considered that there was evidence of moderate strength and quality (from one large clinical trial) that the FF/VI 200/25 provides a clinically significant benefit for patients with severe uncontrolled asthma and the ability to receive a high dose of inhaled corticosteroid in a single inhaler. However, the Subcommittee noted that this was associated with some potential risks, and considered that this evidence suggested efficacy of FF/VI 200/25 with a reported difference compared with the lower dose product (FF/VI 100/25).

9.25. The Subcommittee considered that patients with poorly controlled asthma who are currently using the FF/VI 100/25 and those using moderate ICS/LABA combination inhalers could benefit most from a transition to the FF/VI 200/25. The Subcommittee noted that the supplier had estimated that about 7% of patients with severe uncontrolled asthma would be eligible for the FF/VI 200/25 according to the proposed eligibility criteria. The Subcommittee considered that the requirement for access to be provided in consultation with a paediatrician or respiratory physician was to ensure that the risks associated with FF/VI 200/25 would be minimised and access be provided to only those patients with sufficient need to warrant the use of the high dose of FF.

9.26. The Subcommittee considered that an inhaled corticosteroid dose equivalent to at least 500 mcg per day of fluticasone propionate was more appropriate as a requirement for access than a dose equivalent to 1000 mcg per day. The Subcommittee considered that it was not appropriate for patients to require two inhalers to achieve the required ICS dose.

9.27. The Subcommittee noted that Māori and Pacific people are evidenced to have a high burden of disease for asthma compared to non-Māori. The Subcommittee considered that a single inhaler high dose inhaled corticosteroid would contribute to reducing the barriers to access for population groups known to be experiencing inequities such as Māori, Pacific and people from more socioeconomically deprived areas. The Subcommittee considered that the requirement to pay only a single co-payment when collecting a prescription would be a meaningful consideration for these patients, but that this would be of benefit to all patients requiring high dose corticosteroids.

9.28. The Subcommittee considered that the Ellipta inhaler is easier to use than other dry powder inhalers (DPIs), that additional benefit could be provided from patients only needing to use this inhaler once daily, and that the patient education for use of the one inhaler would be simpler than that for two inhalers. The Subcommittee considered that it would be a popular option for this patient group and that uptake would be high, however this would be impacted by the uptake of other treatment regimens promoted in the recent update to the adult and adolescent asthma guidelines, such as budesonide/eformoterol containing inhalers.

9.29. The Subcommittee noted that the proposed annual cost of the FF/VI 200/25 was significantly greater than the annual cost of two inhalers (i.e. ICS and ICS/LABA), and

considered that this would constitute a significant increase in pharmaceutical expenditure for this patient group.

9.30. The Subcommittee considered that a reduction in exacerbation rates would likely have benefits for the health system due to a reduction in costs, although the evidence to suggest that the FF/VI 200/25 could reduce the frequency of hospital admissions for this patient population compared to treatment administered from two inhalers was weak. The Subcommittee considered that FF/VI 200/25 could reduce medicine costs (e.g. salbutamol and oral corticosteroids). The Subcommittee noted that no additional tests or treatment costs would be expected, if the FF/VI 200/25 were to be funded for patients with severe uncontrolled asthma.

9.31. The Subcommittee considered that appropriate comparators for cost-effectiveness modelling of the FF/VI 200/25 would be a combination ICS/LABA (either budesonide/formoterol 400/12, fluticasone furoate/vilanterol 100/25, or fluticasone propionate/salmeterol 250/50), in combination with an additional ICS; either beclomethasone dipropionate inhaler 250 mcg, budesonide powder for inhalation 400 mcg, and fluticasone 250 mcg (both powder for inhalation and aerosol inhaler).

10. Mepolizumab for severe eosinophilic asthma (widening access)

Interests

10.1. The Subcommittee reported no conflicts of interest with regard to this agenda item

Application

10.2. The Subcommittee reviewed the application from GlaxoSmithKline NZ (GSK) for widening access to mepolizumab for the treatment of severe eosinophilic asthma in patients with a blood eosinophil count of greater than 300 cells/µL and to remove the Asthma Control Test (ACT) requirement.

10.3. The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

10.4. The Subcommittee **recommended** that the application for widening access to mepolizumab for the treatment of severe eosinophilic asthma in patients with <u>a blood eosinophil count of greater than 300 cells/µL</u> be funded with a **high priority**, in the context of treatment for respiratory disease, as follows (additions in **bold**, deletions in ~~strikethrough~~ to the current special authority for mepolizumab):

> Initial application — (Severe eosinophilic asthma) only from a respiratory physician or clinical immunologist. Approvals valid for 12 months for applications meeting the following criteria:
> All of the following:
> 1. Patient must be aged 12 years or older; and
> 2. Patient must have a diagnosis of severe eosinophilic asthma documented by a respiratory physician or clinical immunologist; and
> 3. Conditions that mimic asthma e.g. vocal cord dysfunction, central airway obstruction, bronchiolitis etc. have been excluded; and
> 4. Patient has a blood eosinophil count of greater than **0.3 × 10^9 cells/L** ~~0.5 × 10^9 cells/L~~ in the last 12 months; and
> 5. Patient must be adherent to optimised asthma therapy including inhaled corticosteroids (equivalent to at least 1000 mcg per day of fluticasone propionate) plus long acting beta-2 agonist, or budesonide/formoterol as part of the single maintenance and reliever therapy regimen, unless contraindicated or not tolerated; and
>
> 6 Either:

6.1 Patient has had at least 4 exacerbations needing systemic corticosteroids in the previous 12 months, where an exacerbation is defined as either documented use of oral corticosteroids for at least 3 days or parenteral corticosteroids; or
6.2 Patient has received continuous oral corticosteroids of at least the equivalent of 10 mg per day over the previous 3 months; and
6.3 Patient has an Asthma Control Test (ACT) score of 10 or less. Baseline measurements of the patient's asthma control using the ACT and oral corticosteroid dose must be made at the time of application, and again at around 52 weeks after the first dose to assess response to treatment.

Renewal — (Severe eosinophilic asthma) only from a respiratory physician or clinical immunologist. Approvals valid for 2 years for applications meeting the following criteria:
Both:
1 An increase in the Asthma Control Test (ACT) score of at least 5 from baseline; and
2 Either:
2.1 Exacerbations have been reduced from baseline by 50% as a result of treatment with mepolizumab; or
2.2 Reduction in continuous oral corticosteroid use by 50% or by 10 mg/day while maintaining or improving asthma control.

10.5. In making this recommendation, the Subcommittee considered that widening the blood eosinophil count would enable funded access to treatment for a patient group with a high health need who are not currently able to access this funded treatment and the quality of the evidence indicating a benefit in this patient group.

10.6. The Subcommittee **recommended** that the initial and renewal criteria for mepolizumab for the treatment of severe eosinophilic asthma be amended to remove the Asthma Control Test (ACT) with a **medium priority**, in the context of treatment for respiratory disease, as follows (additions in **bold**, deletions in ~~strikethrough~~ to the current special authority for mepolizumab):

Initial application — (Severe eosinophilic asthma) only from a respiratory physician or clinical immunologist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:
1 Patient must be aged 12 years or older; and
2 Patient must have a diagnosis of severe eosinophilic asthma documented by a respiratory physician or clinical immunologist; and
3 Conditions that mimic asthma e.g. vocal cord dysfunction, central airway obstruction, bronchiolitis etc. have been excluded; and
4 Patient has a blood eosinophil count of greater than 0.5 × 10^9 cells/L in the last 12 months; and
5 Patient must be adherent to optimised asthma therapy including inhaled corticosteroids (equivalent to at least 1000 mcg per day of fluticasone propionate) plus long acting beta-2 agonist, or budesonide/formoterol as part of the single maintenance and reliever therapy regimen, unless contraindicated or not tolerated; and
6 Either:
6.1 Patient has had at least 4 exacerbations needing systemic corticosteroids in the previous 12 months, where an exacerbation is defined as either documented use of oral corticosteroids for at least 3 days or parenteral corticosteroids; or
6.2 Patient has received continuous oral corticosteroids of at least the equivalent of 10 mg per day over the previous 3 months**.** ~~; and~~
~~7 Patient has an Asthma Control Test (ACT) score of 10 or less. Baseline measurements of the patient's asthma control using the ACT and oral corticosteroid dose must be made at the time of application, and again at around 52 weeks after the first dose to assess response to treatment.~~

Renewal — (Severe eosinophilic asthma) only from a respiratory physician or clinical immunologist. Approvals valid for 2 years for applications meeting the following criteria:
~~Both:~~
~~1 An increase in the Asthma Control Test (ACT) score of at least 5 from baseline; and~~
~~2~~ Either:
~~2.1~~ **1** Exacerbations have been reduced from baseline by 50% as a result of treatment with mepolizumab; or

~~2.2~~ **2** Reduction in continuous oral corticosteroid use by 50% or by 10 mg/day while maintaining or improving asthma control.

10.7. In making this recommendation, the Subcommittee considered that removing the Asthma Control Test (ACT) from the initial application and renewal would be reasonable to enable treatment in a group with a health need who meet the intent of the current Special Authority criteria as it relates to blood eosinophil count.

Discussion

10.8. The Subcommittee noted that in August 2017, the Respiratory Subcommittee considered a funding application for mepolizumab in patients with severe eosinophilic asthma with a blood eosinophil count of ≥150 cells/µL. At that time, the Subcommittee recommended mepolizumab be funded for severe allergic eosinophilic asthma, subject to restrictions including a blood eosinophil count of >500 cells/µL with a high priority. In April 2020, mepolizumab was funded subject to Special Authority criteria (including a blood eosinophil count of greater than 0.5 x 10^9 cells/L [equivalent to >500 cells/µL]).

10.9. The Subcommittee noted that in August 2020, GSK, submitted an application to widen access to mepolizumab to patients with a blood eosinophil count of 300 cells/µL and to remove the requirement for the asthma control test (ACT) from both the initial and renewal access criteria.

10.10. The Subcommittee considered that the health need, undertreatment, exacerbation rates and hospitalisation rates of patients with severe eosinophilic asthma (including the disproportionate burden of this disease on Māori, Pacific people and other groups experiencing health disparities) has been well described in previous meeting records.

10.11. The Subcommittee noted that healthcare costs after an exacerbation in patients with severe uncontrolled eosinophilic asthma have been reported at US$2,040 per exacerbation (Suruki et al. 2017). The Subcommittee considered that use of the mepolizumab prefilled syringe would reduce day stay unit costs because of self-injection by patients at home.

10.12. The Subcommittee considered that widening access to mepolizumab to patients with a blood eosinophil count of 300 cells/µL and removing the requirement for the ACT were actions that would help address the highest unmet needs of this patient group and inequities in access to this medicine.

10.13. The Subcommittee considered that patients would be expected to receive about 13 doses of mepolizumab per year, and that montelukast as add-on therapy would be appropriate to include as a comparator, when modelling the cost-effectiveness of widening access to mepolizumab to patients with a blood eosinophil count of 300 cells/µL and removal of the requirement for the asthma control test (ACT).

10.14. The Subcommittee considered it important to ensure alignment of all listed biological treatments for patients with severe asthma, with respect to the eosinophil count criterion and/or the ACT score criterion as relevant.

Blood eosinophil count of >300 cells/ µL

10.15. The Subcommittee noted that increased asthma severity is associated with higher rates of exacerbations and hospitalisations, and that there is evidence of a ten-fold increase in exacerbations in patients with uncontrolled eosinophilic asthma and blood

eosinophil counts >300 cells/µL in the UK and USA (Suruki et al. BMC Pulm Med. 2017;17:74).

10.16. The Subcommittee noted that mepolizumab is funded for severe eosinophilic asthma patients with blood eosinophils ≥300 cells/µL in Australia, England/Wales and Canada. The Subcommittee noted that the 2020 Global Initiative for Asthma (GINA) guidelines use a blood eosinophil count threshold of >300 cells/µL for adding treatment with anti-IL5 at Step 5 (and state that the evidence for this is reasonably weak), whereas the 2020 European Respiratory Society/American Thoracic Society guidelines suggest a threshold of ≥150 cells/µL (Holguin et al. Eur Respir J. 2020;55:1900588). The Subcommittee noted that the New Zealand Adolescent and Adult Asthma Guidelines (2020) do not refer to eosinophil count when recommending treatment of severe uncontrolled asthma with monoclonal antibodies (Beasley et al. N Z Med J. 2020;133:73-99).

10.17. The Subcommittee noted that there are challenges in obtaining accurate blood eosinophil counts in routine blood testing due to variation in the accuracy of the cell count and rounding of results. The Subcommittee noted that many local laboratories round blood eosinophils to fewer decimal places than occurs in clinical trials, and that the current specification of a blood eosinophil count greater than 0.5 x 10^9 cells/L would, with rounding up to the nearest digit, require a blood eosinophil count of at least 550 cells/µL.

10.18. The Subcommittee noted that the evidence provided in support of this application for widened access comes from the DREAM (Pavord et al. Lancet. 2012;380:651-9), MENSA (Ortega et al. N Engl J Med. 2014;371:1198-207) and MUSCA trials (Chupp et al. Lancet Respir Med. 2017;5:390-400). The Subcommittee noted that DREAM included patients with a clinical diagnosis of asthma and subsequently analysed outcomes in patients with blood eosinophil counts of >150 cells/µL, whereas MENSA and MUSCA was confined to patients with blood eosinophils >150 cells/µL.

10.19. The Subcommittee noted that post-hoc analyses of DREAM and MENSA, and of MENSA and MUSCA reported a reduced exacerbation frequency and greater treatment effects in patients with greater blood eosinophil counts (Ortega et al. Lancet Respir Med. 2016;4:549-56; Albers et al. Respir Med. 2019;159:105806). The Subcommittee considered that these analyses provided evidence of clinical benefit with mepolizumab in patients with a blood eosinophil count >150 cells/µL, however the Subcommittee noted that the difference in frequency of clinically significant exacerbations in patients with a blood eosinophil count between 150 and <300 cells/µL in the analysis by Albers et al. did not reach statistical significance (the 95% confidence interval crossing one) (relative risk (RR) 0.70, 95% CI 0.45-1.08, Albers et al. Table 2).

10.20. The Subcommittee noted a non-experimental single arm before-and-after cohort study of 368 patients with severe eosinophilic asthma (about three-quarters with blood eosinophils ≥300 cells/µL) who received at least one dose of mepolizumab, which compared exacerbation rates on the study versus exacerbation rates in the previous year. The Subcommittee noted that clinically significant exacerbations were reduced by 69% and exacerbations requiring hospitalisation and/or ED visits were reduced by 77%, and that the median daily dose of oral corticosteroid was decreased in patients who received oral corticosteroid maintenance treatment (Harrison et al. Eur Respir J. 2020;56:2000151). The Subcommittee considered that the patients in this study had comparable baseline disease severity and rates of exacerbations and hospitalisations to the New Zealand population with severe eosinophilic asthma.

10.21. The Subcommittee considered that widening access to patients with severe eosinophilic asthma with a blood eosinophil count of greater than 300 cells/µL would result in approximately double the number of patients eligible for access to mepolizumab in this setting.

10.22. The Subcommittee considered that the supplier's estimates of 917 patients who may be eligible for mepolizumab in year 1 if access were widened (blood eosinophil count of 300 cells/µL) to 959 eligible patients in year 5, and the assumptions underlying these estimates, were reasonable. The Subcommittee considered that previous estimates of the number of patients with blood eosinophils >500 cells/µL may have been overestimated; and considered that uptake of mepolizumab since its funding may have been affected by patient transfer from compassionate access schemes, the COVID-19 lockdown in early 2020, and the availability of prefilled syringes. The Subcommittee considered that its previous consideration of uptake was still relevant, in that approximately half of all eligible patients would eventually be treated with mepolizumab.

Asthma Control Test (ACT) score

10.23. The Subcommittee noted that the health-related quality of life data collected in all mepolizumab trials had been previously reviewed by the Subcommittee, that more impaired quality of life was seen in patients with more severe disease, and that mepolizumab improved quality of life compared with standard of care.

10.24. The Subcommittee noted the inclusion of the ACT score criterion in the access criteria for mepolizumab due to it being a practical measure of self-reported asthma control, and that the trials providing evidence of benefit in patients with severe eosinophilic asthma did not provide evidence for a benefit from the use of this criterion.

10.25. The Subcommittee considered that the requirement for an ACT score of <10 at baseline may exclude a subset of patients with severe eosinophilic asthma who were controlled only due to their regular administration of high dose oral corticosteroids.

10.26. The Subcommittee noted that both the initial and renewal criteria require the ACT assessment; the assessment of response per ACT therefore requires the ACT to be conducted at baseline. The Subcommittee considered that the initial inclusion of the ACT in the mepolizumab criteria was a cautious and reasonable action to ensure appropriate funded access of a new treatment. The Subcommittee considered that ensuring that treatment continues only for patients who continue to receive clinical benefit (rather than response measured by change in ACT score) would be appropriate, given both that prescribing would occur by a respiratory physician or clinical immunologist and that the ACT instrument has not been validated as a measure of treatment response/change over time.

10.27. The Subcommittee noted that the ACT criteria affect access in current practice. The Subcommittee considered that it was unclear how the removal of the ACT from the Special Authority criteria for mepolizumab might change the number of patients with severe eosinophilic asthma who are eligible to access mepolizumab in this setting. On balance, the Subcommittee considered that removing the ACT would likely increase the number of patients who accessed mepolizumab by approximately 30%.

11. Benralizumab for severe eosinophilic asthma

Interests

Andrew Corin noted that:

- He was an investigator in the TERRANOVA trial for benralizumab. The Chair deemed this as a conflict, but participation permitted under Board Chair's Standing Permission.

Application

11.1. The Subcommittee reviewed the application from AstraZeneca for benralizumab for the treatment of severe uncontrolled eosinophilic asthma.

11.2. The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

11.3. The committee **recommended** that benralizumab for the treatment of severe eosinophilic asthma be funded within the context of respiratory disease only if **cost-neutral** to mepolizumab, subject to Special Authority criteria.

BENRALIZUMAB
Initial application — (Severe eosinophilic asthma) only from a respiratory physician or clinical immunologist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:

1. Patient must be aged 12 years or older; and
2. Patient must have a diagnosis of severe eosinophilic asthma documented by a respiratory physician or clinical immunologist; and
3. Conditions that mimic asthma eg. vocal cord dysfunction, central airway obstruction, bronchiolitis etc. have been excluded; and
4. Patient has a blood eosinophil count of greater than 0.5 × 10^9 cells/L in the last 12 months; and
5. Patient must be adherent to optimised asthma therapy including inhaled corticosteroids (equivalent to at least 1000 mcg per day of fluticasone propionate) plus long acting beta-2 agonist, or budesonide/formoterol as part of the single maintenance and reliever therapy regimen, unless contraindicated or not tolerated; and
6. Either:
    a. Patient has had at least 4 exacerbations needing systemic corticosteroids in the previous 12 months, where an exacerbation is defined as either documented use of oral corticosteroids for at least 3 days or parenteral corticosteroids; or
    b. Patient has received continuous oral corticosteroids of at least the equivalent of 10 mg per day over the previous 3 months; and
7. Patient has an Asthma Control Test (ACT) score of 10 or less. Baseline measurements of the patient's asthma control using the ACT and oral corticosteroid dose must be made at the time of application, and again at around 52 weeks after the first dose to assess response to treatment.

Renewal — (Severe eosinophilic asthma) only from a respiratory physician or clinical immunologist. Approvals valid for 2 years for applications meeting the following criteria:
Both:

1. An increase in the Asthma Control Test (ACT) score of at least 5 from baseline; and
2. Either:
3. Exacerbations have been reduced from baseline by 50% as a result of treatment with benralizumab; or
4. Reduction in continuous oral corticosteroid use by 50% or by 10 mg/day while maintaining or improving asthma control.

11.3.1. In making this recommendation, the Subcommittee considered that both benralizumab and mepolizumab were addressing a health need in the same patient population and that it would be appropriate for the Special Authority criteria for benralizumab to define the same patient group as mepolizumab.

Discussion

11.4. The Subcommittee noted that severe uncontrolled eosinophilic asthma has a major impact on a patient's quality of life and their key activities and responsibilities, including their ability to work, study and/or care for their children. The Subcommittee considered that the disease and the side effects of treatment, including effects of oral corticosteroids, can substantially affect a patient and their family/whānau. The Subcommittee noted that severe eosinophilic asthma disproportionately affects Māori and Pacific people.

11.5. The Subcommittee noted that patients with severe uncontrolled eosinophilic asthma require frequent courses of oral corticosteroids to manage their disease, experience poor health and are at increased risk of exacerbations and mortality.

11.6. The Subcommittee considered that there remains an unmet need for patients with severe uncontrolled eosinophilic asthma who have not experienced a response with other funded treatments for severe uncontrolled eosinophilic asthma (i.e. mepolizumab).

11.7. The Subcommittee noted that the benralizumab prefilled syringe (30 mg/mL) is Medsafe approved for use as add-on therapy in patients aged 12 years and over with severe eosinophilic asthma, defined as having a blood eosinophil count of ≥300 cells/μL or ≥150 cells/μL if the patient is on oral corticosteroid treatment.

11.8. The Subcommittee noted that benralizumab is a monoclonal antibody (biologic) that binds with high affinity and specificity to the alpha subunit of the human interleukin-5 receptor (IL-5Rα), which is specifically expressed on the surface of eosinophils and basophils. Members noted that benralizumab takes effect within a few hours, resulting in undetectable levels of blood eosinophils. The Subcommittee noted that benralizumab is recommended to be used at a dose of 30 mg (via subcutaneous injection) every four weeks for the first three doses and then every eight weeks thereafter.

11.9. The Subcommittee noted that benralizumab has a different mechanism of action to mepolizumab, another biologic which inhibits IL-5 signalling. The Subcommittee noted that mepolizumab was recommended with a high priority by the Respiratory Subcommittee in August 2017 and the 100 mg vial of powder for injection has been funded for eosinophilic asthma since 1 April 2020. The Subcommittee noted that mepolizumab is administered at a dose of 100 mg via subcutaneous injection every four weeks. The Subcommittee noted that an application to widen access to mepolizumab to include patients with blood eosinophil counts greater than 300 cells/μL and to remove the ACT requirement was also being considered at this meeting.

11.10. The Subcommittee noted that this application seeks funding of benralizumab with the same Special Authority criteria as that of mepolizumab and that benralizumab is proposed to sit alongside mepolizumab for the treatment of the same population, as an add-on therapy for patients with severe eosinophilic asthma stabilised on an inhaled corticosteroid (ICS) plus long-acting beta agonist (LABA). The Subcommittee considered that this patient population may also use medications such as prednisone, theophylline, or montelukast as add-on therapy.

11.11. The Subcommittee noted that the key evidence for the clinical efficacy of benralizumab for the treatment of severe uncontrolled eosinophilic asthma comes from two large, multi-centre, randomised controlled trials and an open label-extension study, as follows:

11.11.1. CALIMA: A randomised (1:1:1), double-blind, parallel-group, placebo-controlled, phase III trial investigating subcutaneous benralizumab 30 mg Q4W vs subcutaneous benralizumab 30 mg Q4W for 12 weeks then Q8W for 16 weeks vs subcutaneous placebo Q4W in 1,306 patients aged 12–75 years with severe asthma uncontrolled by medium dosage to high-dosage ICS and LABA, and a history of ≥2 exacerbations in the previous year (Fitzgerald et al. Lancet. 2016;388:2128-41). Patients were stratified (2:1) by baseline blood eosinophil counts 300 cells/µL or greater and less than 300 cells/µL, respectively, and received treatment for 56 weeks.

11.11.2 SIROCCO: A phase III, randomised (1:1:1), multi-centre, placebo-controlled trial investigating subcutaneous benralizumab 30 mg Q4W vs subcutaneous benralizumab 30 mg Q8W vs matching placebo in 1,205 patients aged 12-75 years diagnosed with asthma requiring treatment with medium- or high-dose ICS plus LABA for at least one year (Bleecker et al. Lancet. 2016;388:2115-27). Patients were stratified (2:1) by baseline blood eosinophil counts 300 cells/µL or greater and less than 300 cells/µL, respectively, and received treatment for 48 weeks.

11.11.3 BORA: A phase III, randomised, double-blind extension study of 1,576 patients who had completed the CALIMA or SIROCCO trials and remained on subcutaneous benralizumab, which investigated subcutaneous benralizumab 30 mg either Q4W or Q8W according to previous assigned treatment or according to 1:1 randomisation for patients who were previously assigned to placebo (Busse et al. Lancet Respir Med. 2019;7:49-59). The Subcommittee noted that BORA provided follow-up data up to 3 years

11.12. Members considered that both CALIMA and SIROCCO followed essentially the same trial protocol despite having different methods and were conducted well. The Subcommittee noted that the two clinical trials were sufficiently powered to detect a reduction in exacerbation with benralizumab. Members noted that participants had blood eosinophils over 300 cells/µL, that many participants with mild-moderate disease were able to meet the requirements for inclusion (e.g. exacerbation frequency of two per year) and some had airflow restriction (FEV_1 <80%). Members considered that the patient population included in these trials had comparatively less severe disease than the New Zealand patient population with severe eosinophilic asthma. In addition, the Subcommittee noted the Hawthorne effect observed in these trials in the reduction in exacerbation rate for patients receiving placebo, given that patients were required to have had at least two exacerbations in the 12 months preceding inclusion on these trials. The Subcommittee noted that this was most profound in the CALIMA study, in which the exacerbation rate reduced to 0.93 in the placebo group.

11.13. The Subcommittee noted that there was a substantial reduction in annual exacerbation rate with benralizumab compared with placebo in the SIROCCO trial (Q8W rate estimate 0.65 [95% CI 0.53 to 0.80], Q4W rate estimate 0.73 [95% CI: 0.60 to 0.89] and placebo rate estimate 1.33 [95% CI: 1.12 to 1.58] with a rate ratio of 0.49 (0.37 to 0.64; P<0·0001) for Q8W compared with placebo (Bleecker et al. 2016).

11.14. The Subcommittee noted a small reduction in annual exacerbation rate was reported with benralizumab in the CALIMA trial (Q4W rate 0.60 [95% CI 0.48 to 0.74], P=0.0018, N=241; Q8W rate 0.66 [95% CI 0.54 to 0.82], P=0.0188, N=239) compared with placebo (rate 0.93 [95% CI 0.77 to 1.12], N=248), with a rate ratio of 0.72 (95% CI 0.54 to 0.95) for benralizumab Q8W vs placebo (Fitzgerald et al. 2016). However, the Subcommittee considered that the lower exacerbation rate of the

placebo group in CALIMA suggested that group included in the trial had milder disease than those in SIROCCO.

11.15. The Subcommittee noted that there was evidence of a minor improvement in quality of life with benralizumab compared with placebo (0.35 and 0.24, for SIROCCO and CALIMA, respectively, both assessed using the Standardised Asthma Quality of Life Questionnaire for 12 years and older, AQLQ[S]), and noted that these average improvements were less than the reported minimal clinically important difference (MCID) of 0.5.

11.16. The Subcommittee considered that the BORA long-term extension data provides support for a consistent response to treatment that is durable over three years.

11.17. Members considered that there was some uncertainty around the true effect of benralizumab on exacerbation rates from the CALIMA, SIROCCO and BORA trials due to significant heterogeneity of response in the trial populations between countries, trials and subgroups.

11.18. The Subcommittee noted that the ZONDA trial; a smaller (N=220), randomised (1:1:1) double-blind, placebo-controlled clinical trial with the same treatment interventions as the CALIMA trial, investigated the impact of benralizumab on the ability of adult patients with eosinophil count of ≥150 cells per cubic mm, whose asthma was treated with medium- to high-dose inhaled glucocorticoid and LABA therapy for at least 12 months and who were receiving prednisone or prednisolone, to reduce their oral corticosteroid dose (Nair et al. N Engl J Med. 2017;376:2448-58). The Subcommittee noted that a small number of patients received benralizumab Q8W (N=73) and noted that the authors report a reduction in median oral corticosteroid use from 10 mg per day to 5 mg per day with benralizumab compared to no change with placebo.

11.19. The Subcommittee also noted the following evidence regarding benralizumab:

- Bourdin et al. Eur Respir J. 2018;52:1801393
- Busse et al. J Allerg Clin Immunol. 2019;143:190-200
- Busse et al. J Allerg Clin Immunol. 2020;AB174 [Abstract only]
- Ferguson et al. J Asthma Allergy. 2018;11:63-72
- Fitzgerald et al. Lancet. 2018;6:51-64
- Fitzgerald et al. J Asthma Allerg. 2019;12:401-13
- Harrison et al. Am J Respir Crit Care Med. 2020;201:A4274 [abstract only]
- Jackson et al. Am J Respir Crit Care Med. 2020;201:A3028 [abstract only]
- Ramonell and Iftikhar. Lung. 2020;198:95-103
- Zeitlin et al. J Asthma Allergy. 2018;11:181-92

11.20. Members considered that evidence of benralizumab from real-world case series described generally good results in clinic populations from large treatment centres with experience treating severe asthma and considered that their results were indicative of the disease severity of patients outside of a clinical trial. The Subcommittee also noted that there were network meta-analyses indirectly comparing the outcomes in severe asthma with the use of different biologics (i.e. benralizumab and mepolizumab) and considered that these analyses suggested perhaps equal efficacy between benralizumab and mepolizumab in reducing exacerbations when adjusted for patient-related predictors of response (Bourdin et al. 2018; Busse et al. 2019; Ramonell and Iftikhar. 2020).

11.21. The Subcommittee considered that the consequences of reduced blood eosinophils and basophils were not fully understood and that some safety signals may not yet have been identified in the clinical trials (e.g. relating to possible cardioprotective and cancer-preventative effects of these blood cells), and that they may be important in responding to helminths. However, the Subcommittee noted that these trials were not powered for safety follow-up and low-frequency events may only be identified post-marketing. Members were made aware of a single case report of disseminated herpes zoster infection in a patient receiving benralizumab and considered that such infections like this were rare in immunocompetent individuals; however, this was not reviewed in detail.

11.22. The Subcommittee considered that any benefit could decrease over time if neutralising anti-drug antibodies (ADAs) were to develop. However, the Subcommittee considered that it was unclear how frequently neutralising ADAs occur in patients who have received mepolizumab, although ADAs have been detected and there is evidence out to 5-years with mepolizumab suggesting that there is no loss of therapeutic effect. Members considered that patients could consider a switch from one medicine to another (i.e. mepolizumab to benralizumab, or vice versa) if neutralising ADAs developed.

11.23. The Subcommittee noted that increased incidence of fever, arthralgia and nausea were reported after treatment with benralizumab compared with placebo. The Subcommittee considered that there is additional uncertainty and risk associated with the clinical trials' design due to being powered for a reduction in exacerbations, but not for hospital attendances, symptoms or rare safety signals. However, the Subcommittee considered that there was evidence of a consistent reduction in the rate of exacerbations, and considered that this may be a good surrogate for hospitalisation rates, in the absence of evidence for hospitalisations.

11.24. The Subcommittee noted that the evidence base for benralizumab for severe eosinophilic asthma was limited to a relatively small number of placebo-controlled trials that were included in many analyses and that had not investigated effects on quality of life in any detail. The Subcommittee noted there were no head-to-head trials of biologic agents for severe asthma, and considered that appraisal of the current evidence is reliant on indirect comparison which inherently has high degrees of uncertainty. The Subcommittee considered that direct comparative evidence in the form of a direct head-to-head trial between benralizumab and mepolizumab would not be forthcoming in this setting.

11.25. The Subcommittee considered that evidence suggested that the patients with severe eosinophilic asthma who received the greatest benefits from treatment with benralizumab had high eosinophil counts (≥300 cells/μL), experienced more frequent exacerbations, had nasal polyps, had persistent airway obstruction (FEV1 <65%) or were requiring high doses of oral corticosteroids. The Subcommittee considered that the patient population who may receive the greatest benefit from benralizumab is the same population who are currently eligible for mepolizumab. However, the Subcommittee considered that participants in the benralizumab clinical trials had less severe disease than those patients included in the mepolizumab clinical trials (previously reviewed by the Subcommittee for in August 2017 and which reported a 61% reduction in exacerbations with mepolizumab), although the Hawthorne effect would have influenced the exacerbation rate of the benralizumab trial's placebo group.

11.26. The Subcommittee considered it would be reasonable for benralizumab to have the same Special Authority criteria as mepolizumab, which defines a similar patient group

and similar predictors of response to treatment, including appropriate criteria regarding blood eosinophil counts and ACT scores.

11.27. Members considered that both benralizumab and mepolizumab would likely be equally effective in a significant proportion of patients with severe asthma, but that some patients may only benefit from one or the other and the outcomes experienced by individual patients may vary. However, members considered that there is no evidence to support efficacy of one treatment over the other in the same patient.

11.28. The Subcommittee noted that the funding application requested 8-weekly dosing of benralizumab and considered that this dosing regimen would be appropriate, given the clinical trial evidence suggesting similar efficacy between the two dosing regimens.

11.29. The Subcommittee considered that after the initial 4-weekly dosing, the 8-weekly dosing and formulation (prefilled syringe) of benralizumab offered benefits to the health system which would administer this treatment at a cost of approximately $500 if given in a hospital day stay unit, although members noted that some centres are shifting this treatment from day stay units into general practice or to patient self-administered treatment in the community.

11.30. The Subcommittee considered that the 8-weekly dosing regimen of benralizumab could be preferable to the ongoing 4-weekly administration of mepolizumab, and noted that patients who self-administer treatment with mepolizumab would be self-funding water for dilution at this time. The Subcommittee considered that these differing treatment frequencies should be taken into account when modelling treatment costs of benralizumab and mepolizumab.

11.31. The Subcommittee considered that, if multiple prefilled syringe options were available, patient preference regarding administration frequency would be a key factor driving uptake, rather than health costs, and clinician familiarity with an existing funded treatment may also be a factor. However, the Subcommittee noted that Medsafe approval and availability of prefilled syringe and autoinjector formulations of mepolizumab is expected in 2021.

11.32. The Subcommittee considered that the supplier's estimates of eligible patient uptake for benralizumab of 8% at 1 year up to 26% after 5 years, based on the proposed Special Authority criteria, were reasonable, although this could depend on marketing activity. The Subcommittee considered that patients who were currently receiving treatment with mepolizumab would be unlikely to change to benralizumab, if funded, unless they experienced a waning response on mepolizumab.

11.33. The Subcommittee considered that patients experiencing a reaction to one biologic agent or who have experienced loss of efficacy may choose to switch to another agent with a different mechanism of action, however, switching patients with stable disease onto a different biologic treatment could expose patients to significant risks (e.g. a patient could lose disease control and may experience a potentially life-threatening exacerbation).

11.34. The Subcommittee noted that there is no evidence for concurrent use of biologics targeting different pathways (e.g. benralizumab and mepolizumab), and considered that as most clinicians would reserve an agent with a different mechanism of action for use when a patient experiences loss of efficacy, this would not need to be incorporated into the funding criteria.

11.35. The Subcommittee noted that there was an absence of evidence for benralizumab as a second-line biologic, although members were aware of evidence for second-line use of other biologics for severe eosinophilic asthma. The Subcommittee considered that some use of benralizumab as a second-line treatment for patients who did not receive a response from mepolizumab would be likely if funded.

Chair Date

Chair