

**Respiratory Subcommittee of the Pharmacology and Therapeutics Advisory Committee
(PTAC)**

Meeting held on 4 August 2017

(minutes for web publishing)

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

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

The Respiratory Subcommittee may:

(a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;

(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

(c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

These Subcommittee minutes will be reviewed by PTAC at its meeting on 8 & 9 February 2018, the record of which will be available in due course.

Record of the Respiratory Subcommittee of the Pharmacology and Therapeutics Committee (PTAC) meeting held at PHARMAC on 4 August 2017

1 Correspondence / Matters arising

Dornase alfa under 5s continuation

- 1.1 The Subcommittee noted that dornase alfa was a genetically engineered, recombinant human DNase that cleaves extracellular DNA found in purulent sputum secretions, increasing its viscosity and making clearance difficult. Dornase alfa hydrolyses this extracellular DNA, reducing the viscoelasticity of sputum in cystic fibrosis patients, improving lung function and lung health.
- 1.2 The Subcommittee noted that prior to 1 January 2017 the funding of dornase alfa had been only for patients aged 5 years and over who had demonstrated a good response after a 1-month trial on treatment as measured by improvements in spirometry results. The Subcommittee noted that such funding under these criteria would be lifelong.
- 1.3 The Subcommittee noted that from 1 January 2017, PHARMAC had widened access to dornase alfa to patients with cystic fibrosis who were under the age of 5 years who met specific eligibility criteria, with a renewal criteria for a further 12 months treatment per renewal.
- 1.4 The Subcommittee noted the current under 5 years age access criteria for dornase alfa. The Subcommittee considered that there would likely only be a small number of patients accessing dornase alfa using the under 5 years age criteria.
- 1.5 The Subcommittee noted correspondence from a hospital pharmacist enquiring how a patient who initiates treatment on dornase alfa using the under 5 criteria who then ages past 4 years would be able to obtain lifelong funding of dornase alfa. The Subcommittee considered that for these children it would be reasonable for them to cease treatment with dornase alfa for a period of time, for baseline lung function results to be obtained, and for these children to be reassessed using the dornase alfa 5 years age and over criteria.
- 1.6 The Subcommittee considered that upon cessation of treatment with dornase alfa, there would be a fast reversible decline in lung function to baseline. The Subcommittee considered that once baseline lung function has been reached, the 5 & over dornase alfa criteria could be used to reassess the patient's response in terms of benefit with dornase alfa, measured via spirometry.
- 1.7 The Subcommittee noted that children with cystic fibrosis generally start being trained on spirometry technique from around 4½ years old. The Subcommittee however considered that children may still have difficulty employing the correct spirometry technique at 5 years, due to the coordination and concentration that is required, making its readings unreliable. The Subcommittee considered that it may be more appropriate to change the age restriction of the dornase alfa access criteria from the current restriction of 5 years to become 7 years (ie. under 7 access criteria and 5 & over access criteria). The Subcommittee considered that increasing the age restriction to 7 years would give children with cystic fibrosis time to grow, learn, and become comfortable with doing spirometry testing for medical assessments.

- 1.8 The Subcommittee **recommended** that the age restriction in the current dornase alfa access criteria should be changed from the under 5 and 5 & over criteria, to under 7 and 5 & over criteria, with a medium priority.

Prednisone on PSO

- 1.9 The Subcommittee noted the correspondence received from a hospital pharmacist requesting prednisone 20mg tablets in addition to two other medicines (folic acid and potassium iodate), to be funded on a Practitioners Supply Order (PSO) in Section B (Community) of the Pharmaceutical Schedule. The Subcommittee noted that medicines on a PSO can be supplied directly by a primary care doctor to a patient, and are used for emergency, teaching, and demonstration purposes.
- 1.10 The Subcommittee noted that prednisone 5 mg tablets are currently available on a PSO, with a limit of up to 30 tablets. The Subcommittee considered that the indications prednisone tablets would most likely be used for on a PSO are for the acute treatment of asthma or severe allergic reactions.
- 1.11 The Subcommittee considered that the supply of prednisone 20 mg tablets on a PSO is important, especially for GPs working in clinics in remote rural areas. The Subcommittee noted that prednisone tablets were already available on PSO albeit at a lower strength, and did not consider that the availability of 20 mg strength tablets would increase the risk of inappropriate supply or harm. The Subcommittee considered that the higher 20 mg strength prednisone tablets would be more suitable for some patients.
- 1.12 The Subcommittee **recommended** that prednisone 20 mg tablets be made available on a PSO, with a limit of up to 10 tablets, only if cost neutral to the equivalent dose of prednisone 5 mg tablets.

Omalizumab for asthma – widening access

- 1.13 The Subcommittee noted that omalizumab was fully funded from 1 November 2014 with its current restrictions.
- 1.14 The Subcommittee noted that the Respiratory Subcommittee has previously reviewed the restrictions for omalizumab in March 2015 and in September 2015 with a view to widen its access criteria, as it was noted that its uptake had been lower than anticipated. The Subcommittee noted that PTAC in November 2015 reviewed the minutes of the September 2015 Respiratory Subcommittee, and recommended that a further 12 months uptake data be obtained before the Respiratory Subcommittee again reconsidered changing the Special Authority criteria.
- 1.15 The Subcommittee noted that the current omalizumab Special Authority criteria is as follows:

Special Authority for Subsidy

Initial application only from a respiratory physician. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

1. Patient is over the age of 6; and
2. Patient has a diagnosis of severe, life threatening asthma; and
3. Past or current evidence of atopy, documented by skin prick testing or RAST; and
4. Total serum human immunoglobulin E (IgE) between 76 IU/mL and 1300 IU/ml at baseline; and

5. Proven compliance with optimal inhaled therapy including high dose inhaled corticosteroid (budesonide 1600 micrograms per day or fluticasone propionate 1000 micrograms per day or equivalent), plus long-acting beta-2 agonist therapy (at least salmeterol 50 micrograms bd or eformoterol 12 micrograms bd) for at least 12 months, unless contraindicated or not tolerated; and
6. Patient has received courses of systemic corticosteroids equivalent to at least 28 days treatment in the past 12 months, unless contraindicated or not tolerated; and
7. At least four admissions to hospital for a severe asthma exacerbation over the previous 24 months with at least one of those being in the previous 12 months; and
8. An Asthma Control Questionnaire (ACQ-5) score of at least 3.0 as assessed in the previous month

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

Both

1. A reduction in the Asthma Control Questionnaire (ACQ-5) score of at least 1.0 from baseline; and
2. A reduction in the maintenance oral corticosteroid dose of at least 50% from baseline.

- 1.16 The Subcommittee noted that criterion 7, which requires patients to have had at least 4 hospital admissions in the previous 24 months and at least one in the previous 12 months, was the criterion that most patients do not meet. The Subcommittee noted that PHARMAC had received a number of such NPPA and special authority waivers requesting that the hospitalisation criterion be waived so that these patients can access to omalizumab.
- 1.17 The Subcommittee noted that many of these patients were taking high doses of systemic corticosteroids for extended periods of time and that these patients were most likely prescribed steroids with the intent of reducing hospitalisations. The Subcommittee considered that whilst patients being treated with long term steroids have reduced exacerbations and hospitalisation rates, patients were being exposed to a range of steroid-induced side effects. The Subcommittee considered that the current access criteria for omalizumab is counterintuitive, in that using prolonged high dose steroids to prevent exacerbations and hospitalisations lead to patients not meeting the eligibility criteria for omalizumab (i.e, patients were not meeting the hospitalisation criteria). The Subcommittee considered that the access criteria should be amended to enable these patients on long term, high dose steroids who do not meet the current hospitalisation criteria to access omalizumab.
- 1.18 The Subcommittee noted the restrictions for the funding of omalizumab recommended by the National Institute of Health and Clinical Excellence (NICE) in the United Kingdom and by the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia. The Subcommittee noted that neither set of restrictions had a criterion on the number of hospitalisations a patient must have had prior to being able to access omalizumab.
- 1.19 The Subcommittee considered that the omalizumab criteria should be amended so that it reflects the number exacerbations and courses of corticosteroids prescribed in the previous 12 months rather than the number of hospitalisations a patient has had. The Subcommittee considered that this change is likely to increase the number of patients accessing omalizumab.
- 1.20 The Subcommittee also considered that the Asthma Control Questionnaire (5 item version) in the proposed criteria should be replaced with the Asthma Control Test (ACT), which is a free, validated, and readily available tool used to assess asthma control. The

Subcommittee considered that when using the ACT scale in access criteria, severity scores should be 10 or less for patients to be eligible for omalizumab.

- 1.21 The Subcommittee **recommended** that the omalizumab Special Authority be amended, with a **medium priority**, to that below (deletions in strikethrough, additions in bold):

Special Authority for Subsidy

Initial application - only from a respiratory physician. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

1. **Patient must be aged 6 years or older** ~~Patient is over the age of 6;~~ and
2. Patient has a diagnosis of severe, life threatening asthma; and
3. Past or current evidence of atopy, documented by skin prick testing or RAST; and
4. Total serum human immunoglobulin E (IgE) between 76 IU/mL and 1300 IU/ml at baseline; and
5. Proven ~~compliance~~ **adherence** with optimal inhaled therapy including high dose inhaled corticosteroid (budesonide 1600 micrograms per day or fluticasone propionate 1000 micrograms per day or equivalent), plus long-acting beta-2 agonist therapy (at least salmeterol 50 micrograms bd or eformoterol 12 micrograms bd) for at least 12 months, unless contraindicated or not tolerated; and
6. **Either:**
 - 6.1 Patient has received courses of systemic corticosteroids equivalent to at least 28 days treatment in the past 12 months, unless contraindicated or not tolerated; ~~and or~~
 - 6.2 **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 steroids; or**
~~At least four admissions to hospital for a severe asthma exacerbation over the previous 24 months with at least one of those being in the previous 12 months; and~~
7. ~~An Asthma Control Questionnaire (ACQ-5) score of at least 3.0 as assessed in the previous month.~~ **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 26 weeks after the first dose to assess response to treatment.**

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

Both

1. ~~A reduction in the Asthma Control Questionnaire (ACQ-5) score of at least 1.0 from baseline~~ **An increase in the Asthma Control Test (ACT) score of at least 5 from baseline;** and
2. A reduction in the maintenance oral corticosteroid dose **or number of exacerbations** of at least 50% from baseline.

- 1.22 The Subcommittee noted that there is increasing evidence that inhaled corticosteroids reach a therapeutic ceiling, when dose escalation beyond particular levels provides little if any further meaningful clinical benefit but does generate more adverse effects, and considered that in future the criteria could be amended to reflect a reduced inhaled corticosteroid dose ceiling for what is considered optimal inhaled therapy.

- 1.23 The Subcommittee considered the prescriber type that would most likely prescribe omalizumab for the treatment of severe allergic asthma. The Subcommittee considered that severe allergic asthma is a specialised and niche disease, and that respiratory physicians and paediatricians are well placed for the initiation of treatment for this disease. The Subcommittee also considered that respiratory physicians were easier to access than other prescriber types, such as immunologists, and that there were few immunologists in New Zealand who would also specialise in the treatment of respiratory conditions. Further,

the Subcommittee noted that respiratory physicians practice in environments where other members of a multidisciplinary team, working with caregivers and primary care teams, are able to help patients improve adherence and optimise asthma therapy. The Subcommittee considered that the prescriber restriction should remain as is, as any change to this is likely to increase slippage of this product to indications other than the treatment of severe allergic asthma.

2 Therapeutic Group Review

Nintedanib

- 6.1 The Subcommittee noted that PHARMAC received an application in August 2015 from Boehringer Ingelheim for the listing of nintedanib (Ofev), a tyrosine kinase inhibitor for the treatment of idiopathic pulmonary fibrosis. The Subcommittee noted that nintedanib had a different mechanism of action to pirfenidone. The Subcommittee noted that despite the differences in mechanism of action, there was currently no evidence supporting the use of pirfenidone and nintedanib together in the treatment of IPF.
- 6.2 The Subcommittee noted that PTAC had reviewed the evidence for nintedanib at its meeting in August 2016, and made the recommendation that '*Nintedanib be listed cost-neutral to pirfenidone (if pirfenidone is listed), and that if there is a continued decline of >10% in any 12 month period following treatment initiation, treatment should be stopped.*' The Subcommittee noted that PTAC had considered that nintedanib and pirfenidone were clinically similar, and that there was no clinically significant difference between these agents for the preservation of lung function, IPF specific mortality, or all-cause mortality.
- 6.3 The Subcommittee noted that there were a high number of gastric related side effects associated with pirfenidone, and considered that patients who were intolerant of pirfenidone may benefit by switching to nintedanib. The Subcommittee considered that at the current time, there was no evidence to suggest that patients whose disease have progressed while on one agent would benefit by switching to another agent. The Subcommittee **recommended** that if nintedanib were to be listed, that nintedanib be listed in the same line as pirfenidone, using the same restrictions as pirfenidone, with the addition of the following criteria:
- 1 The patient's disease has not progressed (>10% decline in predicted FVC since starting treatment with pirfenidone); and
 - 2 Either of the following:
 - 2.1 Patient is not currently receiving treatment with pirfenidone; or
 - 2.2 Patient has received a special authority approval for pirfenidone and has discontinued pirfenidone within 12 weeks due to intolerance.
- 6.4 The Subcommittee **recommended** that if nintedanib were to be listed, that the following criteria also be included on to the current pirfenidone criteria:
- 1 The patient's disease has not progressed (>10% decline in predicted FVC since starting treatment with nintedanib); and
 - 2 Either of the following:
 - 2.1 Patient is not currently receiving treatment with nintedanib; or
 - 2.2 Patient has received a special authority approval for nintedanib and has discontinued nintedanib within 12 weeks due to intolerance.

Bevacizumab for the treatment of recurrent respiratory papillomatosis

- 1.1 The Subcommittee considered that PHARMAC should consider progressing a schedule listing of bevacizumab for the treatment of recurrent respiratory papillomatosis (RRP).
- 1.2 The Subcommittee noted that recurrent respiratory papillomatosis (RRP) is characterised by the development of exophytic proliferative lesions of connective tissue covered by epithelium which affect the mucosa of the airways. The Subcommittee noted that RRP is caused by the human papillomavirus (HPV). The Subcommittee noted that almost all cases of RRP involves the larynx (95%) although the Subcommittee noted that the papillomas may present anywhere along the respiratory tract, from the nose to the lungs. The Subcommittee noted that patients with RRP can have difficulty breathing, that it can affect the quality of the patient's voice and the ability of the patient to speak, and that affected patients have a small increased risk of squamous cell carcinoma of the head and neck.
- 1.3 The Subcommittee considered that whilst the disease can be benign, it causes a significant amount of morbidity in affected patients. The Subcommittee noted that papilloma growth is not proportional to body size, and that some children can have very severe disease. The Subcommittee noted that current treatment comprises of largely of surgical debulking, and that the main purpose of debulking surgery is to secure airway patency, to preserve the underlying laryngeal tissues, and to maintain an acceptable quality of voice. The Subcommittee noted that surgery is performed via microscopic or endoscopic rigid laryngoscopy using a variety of lasers to debulk the papillomatous lesions however noted that due to the tendency for the papillomas to relapse, frequent surgeries are often required (>6 times a year).
- 1.4 The Subcommittee noted a study by Carifi et al 2015 (Ther Clin Risk Manag;11:731-8) which reported a bimodal age distribution with RRP, with peaks in young children and in adults. The Subcommittee noted that in children, RRP mostly came about as a result of vertical transmission from an infected mother during vaginal delivery or in utero and that in adults, HPV infection might occur following oral sex. The Subcommittee noted that of the NPPAs received by PHARMAC for bevacizumab for RRP, patients' age ranged from 7 to 83 years old and that the majority (65%) of patients were under 30 years old and male.
- 1.5 The Subcommittee noted that the prevalence of RRP in Australia is around 0.8 per 100,000 people, and considered that the prevalence in New Zealand is likely to be similar.
- 1.6 The Subcommittee noted that cidofovir, an anti-viral agent, is currently listed in the HML and is sometimes used in the hospital setting for the management of RRP. The Subcommittee however noted that there is no accepted dosage regimen for cidofovir, that there are concerns around the risk that cidofovir may be associated with the secondary development of oral and throat cancers, and that the cost per treatment with cidofovir is high (approximately \$6,000 per dose). The Subcommittee therefore considered that it would be important to have another agent for the management of RRP.
- 1.7 The Subcommittee noted the association between HPV infection and the development of RRP, and considered that uptake of the HPV vaccine may reduce the longterm incidence of RRP in the population. The Subcommittee noted that the HPV vaccine is currently funded for people aged between 11 and 26, and that it covers 9 strains of the virus, including HPV strains 6 and 11 which are implicated in the majority of RRP cases. The Subcommittee considered that the HPV vaccine should be available to people undergoing

debulking surgery for RRP who have not yet had the vaccine, as the vaccine may reduce the size of future papilloma growths.

- 1.8 The Subcommittee noted that bevacizumab is a recombinant humanised monoclonal immunoglobulin G1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor in vitro and in vivo. The Subcommittee noted that whilst bevacizumab is registered with Medsafe in New Zealand for a number of oncological indications, it is currently listed in Section II of Part H of the Pharmaceutical Schedule for various ophthalmological diseases. The Subcommittee noted that should bevacizumab also be listed for the treatment of RRP, that this indication would also be off-label.
- 1.9 The Subcommittee noted a small number of published studies that reported the effectiveness of bevacizumab when used for the treatment of RRP.
- Sidell et al. Ann Otol Rhinol Laryngol 2014;123(3):214-21
 - Zeitels et al. Ann Otol Rhinol Laryngol 2011;120(10):627-34
 - Best et al. Ann Otol Rhinol Laryngol 2012;121(9):587-93
- 1.10 The Subcommittee noted Sidell et al. 2014, which reported that patients treated with bevacizumab had a median improvement of 58% (Derkay score), and that all patients demonstrated an increased time interval between surgery and injections, with a median extension of the injection interval being 2.05 times the usual median treatment interval (42 days). The Subcommittee noted the results of Zeitels et al. 2011, which reported that after 4 injections, 15% of patients (3 of 20) treated with bevacizumab had no discernible disease, and that 80% of patients (16 of 20) had less disease, and that 5% (1 of 20) of patients had more disease. The Subcommittee noted that Best et al. 2012 reported the safety and dosing of intralesional bevacizumab when used for the treatment of RRP, and found that using an average of 30 mg per dose intralesionally resulted in no significant observable local or systemic complications.
- 1.11 The Subcommittee noted that the above studies used bevacizumab as an adjuvant to surgery, that an average dose of 15 – 30 mg bevacizumab were used intra-lesionally, and that the injections were initiated at frequencies of every 4 to 6 weeks. The Subcommittee noted that overall, using bevacizumab as an adjuvant to surgery reduced the growth of the papillomas, improved patient's voice quality, and increased the time interval between surgical procedures reducing the number of surgical procedures each year.
- 1.12 The Subcommittee considered that whilst the above studies were small, of low power and of low quality, in the context of RRP being a rare disease, the above studies were reasonable to demonstrate the effectiveness of bevacizumab in the treatment of RRP.
- 1.13 The Subcommittee **recommended** that access to bevacizumab be widened with a **high priority** for the treatment of RRP, when prescribed by an ENT specialist.

3 PAH treatment algorithm

- 2.1 The Subcommittee noted a paper from PHARMAC staff outlining that a number of applications had been received regarding the widening of access of pulmonary arterial hypertension (PAH) treatments, which PTAC had reviewed at its May 2016, November 2016 and February 2017 meetings. The Subcommittee also noted that PTAC had reviewed applications for macitentan (May 2015) and selexipag (May 2016).

- 2.2 The Subcommittee noted that at the PTAC meeting held in February 2017, PTAC recommended that the Respiratory and Cardiovascular Subcommittees and the PHARMAC PAH Panel should review a suitable framework for the treatment of patients with PAH and epoprostenol's place in this framework. The Subcommittee noted PHARMAC's request for advice was regarding the practical use of the treatments in the clinical setting, and that further review of the evidence for existing and new treatments was not being sought. The Subcommittee was informed that its advice was also to inform cost utility analyses, as part of the usual process for assessing funding applications.
- 2.3 The Subcommittee noted that the widening of access of PAH treatment funding applications were made by members of the PAH Panel and specialist clinicians. Members noted PTAC's recommendations for these applications in the context of the 2009 eligibility criteria for pulmonary arterial hypertension treatments.
- 2.4 Members considered that PAH had lower overall survival than most cancers, that patients with this disease had a significant health need, and that New Zealand treatment regimens were significantly behind other OECD countries.
- 2.5 The Subcommittee considered that, based on the currently available PAH treatments used in clinical practice (and the respective funding applications for widening of access of PAH treatments), sildenafil could be used as a first line treatment in the New Zealand setting, followed by add-on treatments bosentan or ambrisentan, then nebulised iloprost. It considered that for patients with PAH who were unable to take sildenafil as a first line treatment, it was reasonable that bosentan or ambrisentan would be commenced, followed by nebulised iloprost.
- 2.6 The Subcommittee considered that all patients with PAH would eventually need to use all available treatments, as PAH was a progressive disease and treatments would be aimed at slowing progression. As such, the Subcommittee considered that because all patients' disease would progress so they would eventually all need to use all available treatments, this should be reflected in PHARMAC's cost-utility analysis. The Subcommittee was unable to comment on the likely proportions of patients who would be on a given treatment.
- 2.7 The Subcommittee considered that the PHARMAC PAH Panel would be best placed to define the parameters that indicated stable or worsening disease, as current members of the Subcommittee felt they did not have specialist experience with patients who had PAH. However, it considered that the parameters in Charalampopoulos et al. (*Pulm Circ* 2014;4:669-678) and Borrie et al. (*Can Respir J* 2011;18:230-234) were reasonable. In particular, the Subcommittee considered that if both a patient's NYHA functional class did not improve after treatment or a failure to improve from NYHA functional class IV plus a decrease in 6 minute walk distance of greater than or equal to 15%, may indicate deterioration of their PAH while on treatment. However, it considered that it would be difficult to differentiate such deterioration from stabilisation of disease or slowing of disease progression. It considered that improvement of treatment could be defined as a combined improvement in NYHA functional class plus and increase in 6 minute walk distance of greater than or equal to 15% compared with baseline, and that patients who did not meet these criteria could be classified as having no improvement on treatment.
- 2.8 The Subcommittee considered that some patients with PAH and evidence of vasoreactivity derive long term clinical benefit and disease stability from treatment with calcium channel blockers. Members considered a trial of a calcium channel blocker can be first line therapy

for patients with PAH and vasoreactivity, but those with PAH but without vasoreactivity do not benefit from calcium channel blocker therapy.

- 2.9 The Subcommittee considered that right heart catheterisation (RHC) measurements had a place in PAH treatment monitoring, and that this procedure should be done by an experienced specialist due to the significant inter- and intra-rater variability. Members considered that the increased mortality in children, due to the requirement of a general anaesthetic for the right heart catheterisation, was significant, rendering the use of RHC for routine monitoring inappropriate clinically. The Subcommittee considered that an echocardiogram would suffice to monitor children who were being initiated on monotherapy and dual therapy, however a right heart catheter may also be necessary at renewal.
- 2.10 The Subcommittee considered that there would be differences in the Special Authority criteria for adults compared to children, however, the members considered that they did not have enough experience with patients with PAH to comment on specific criteria.
- 2.11 The Subcommittee considered that the use of PAH treatments in intensive care units differs from how PAH treatments are used in the community and that this should be taken into consideration. For example, in intensive care units, add-on treatments may be given if there is a lack of treatment response after a few days, versus the 3-6 month therapeutic trial that may occur in the community.
- 2.12 The Subcommittee was unable to indicate where epoprostenol would fit in this framework, but considered that this treatment should be available and for individual clinicians to determine its use. It considered it possible that epoprostenol could be used as a fourth line treatment in approximately 10 patients per year, and that given that all patients with PAH would progress, it may be used by all patients eventually.
- 2.13 The Subcommittee also noted the impending availability of tadalafil, and that this might also be considered by PHARMAC in future.

4 Pirfenidone widening access

- 3.1 The Subcommittee noted that on 1 January 2017, PHARMAC listed pirfenidone fully funded, with restrictions, for the treatment of idiopathic pulmonary fibrosis (IPF). The Subcommittee noted that IPF is a progressive interstitial lung disease affecting mostly the elderly population, with a median survival duration of 2-3 years after diagnosis. The Subcommittee noted that pirfenidone was the first anti-fibrotic agent to be funded in New Zealand for the treatment of IPF. The Subcommittee noted that nintedanib (supplied by Boehringer Ingelheim) is another medicine registered for the treatment of IPF in New Zealand and has a different mechanism of action compared with pirfenidone. The Subcommittee noted that there are no medicines that reverse the decline of lung function in IPF, however, anti-fibrotic agents slowed the rate of progression and decline in lung function.
- 3.2 The Subcommittee noted PHARMAC data showing that, in the first 6 months of listing, approximately 87 patients had special authorities approved for pirfenidone. The Subcommittee noted that PHARMAC had forecasted that, with the current restriction, that around 150 patients would be expected to use this medicine in the first 12 months.

- 3.3 The Subcommittee noted that the New Zealand access criteria for pirfenidone was similar to that currently recommended by the National Institute of Health and Clinical Excellence (NICE) in the UK, and was as follows:

**Retail Pharmacy - Specialist
Special Authority for Subsidy**

Initial application – (idiopathic pulmonary fibrosis) only from a respiratory specialist. Approvals valid for 12 months for applications meeting the following criteria:

All of the following:

1. Patient has been diagnosed with idiopathic pulmonary fibrosis as confirmed by histology, CT or biopsy; and
2. Forced vital capacity is between 50% and 80% predicted; and
3. Pirfenidone is to be discontinued at disease progression (See Notes).

Renewal application – (idiopathic pulmonary fibrosis) only from a respiratory specialist. Approvals valid for 12 months for applications meeting the following criteria:

Both:

1. Treatment remains clinically appropriate and patient is benefitting from and tolerating treatment.
2. Pirfenidone is to be discontinued at disease progression (See Notes).

Notes: disease progression is defined as a decline in percent predicted FVC of 10% or more within any 12 month period.

- 3.4 The Subcommittee noted that PHARMAC had received feedback from a number of respiratory clinicians during the consultation period at the time of listing pirfenidone, requesting that PHARMAC review the above access criteria of pirfenidone at a later date. The Subcommittee noted that the respiratory clinicians were concerned that there were patients with IPF who had a high FVC and were both symptomatic and deteriorating, who would benefit from treatment but were not eligible under the current criteria. The Subcommittee noted that these patients would currently have to wait until their FVC declined to below 80% to access funded treatment, and considered that for some of these patients they may never be eligible to receive treatment. The Subcommittee also noted clinicians' feedback that the stopping rule should be removed (when patients experience a 10% decline in FVC in the last 12 months).

- 3.5 The Subcommittee noted the new evidence provided by Roche (supplier of pirfenidone), which included the following papers:

- Albera et al. Eur Respir J. 2016;48(3):843-51
- Ley et al. Am J Respir Crit Care Med. 2017;196(6):670-671
- Nathan et al. Thorax 2016;71(5):429-35
- Nathan et al. Lancet Respir Med. 2017;5:33-41
- Nobel et al. Eur Respir. 2016;47:243-53

- 3.6 The Subcommittee noted that evidence provided was a combination of pooled data of trials considered in the initial recommendation to fund pirfenidone. The Subcommittee noted that the evidence provided and considered at this meeting were not new but was retrospective analysis of data previously considered by the Subcommittee. The Subcommittee noted that the same data has been considered by a number of jurisdictions overseas.

- 3.7 The Subcommittee noted Nobel et al. 2016, a pooled study of the three Phase III clinical trials for pirfenidone and Albera et al. 2016, which analysed the benefits of pirfenidone in patients stratified by whether patient's baseline FVC were $\geq 80\%$ predicted or $< 80\%$ predicted. The Subcommittee noted that the trials included patients with %FVC of between

- 48% to 124% and noted that the effect of pirfenidone on reducing disease progression and death was the same in FVC<80% and FVC≥80% subgroups.
- 3.8 The Subcommittee noted Table 2 in Nathan et al. 2016, which conducted a subgroup analysis on patients who had experienced a >10% decline in FVC in the first three and six months of treatment with pirfenidone and placebo, who subsequently continued on treatment with pirfenidone and placebo. The Subcommittee noted that in this subgroup who continued treatment with pirfenidone had a lower risk of subsequent FVC decline or death compared to placebo. The Subcommittee noted that these data indicated ongoing benefit with treatment, however there was no clear direct comparison between patients who continued treatment with pirfenidone versus those who had stopped pirfenidone after a >10% decline in FVC. The Subcommittee considered that based on the evidence reviewed, there was still a place in therapy for treatment with pirfenidone even when the patient experiences a >10% decline in FVC in the prior 12 months.
 - 3.9 The Subcommittee noted Ley et al. 2017 reported that treating with pirfenidone reduced the number of non-elective respiratory related hospitalisations versus placebo (7% vs 12%, p=0.001), and Nathan et al. 2017, which reported a 45% reduction in IPF related all-cause mortality over 120 weeks for pirfenidone versus placebo. However, the Subcommittee considered that these studies were not directly relevant and did not address whether and how the access criteria for pirfenidone should be amended.
 - 3.10 The Subcommittee noted that there was little direct evidence of starting pirfenidone in patients with FVC <50% predicted.
 - 3.11 The Subcommittee noted the current estimates of pirfenidone use, and considered that there would unlikely be significant budgetary risks if the upper 80% FVC limit for pirfenidone eligibility was removed, as the majority of patients with IPF were already captured by the 50-80% predicted FVC criterion, for whom treatment is already funded.
 - 3.12 The Subcommittee considered that removal of the stopping criteria however, would likely increase the duration that patients remain on treatment, and that this would likely see the prevalent number of patients treated with pirfenidone double in the medium to long term. The Subcommittee however noted the heavy pill burden associated with pirfenidone, and considered that few patients would continue treatment if no benefits were observed.
 - 3.13 The Subcommittee noted the NICE (UK) recommendation and the PBS (Australian) restrictions for access to pirfenidone. The Subcommittee considered that the restrictions used in Australia for accessing pirfenidone were pragmatic.
 - 3.14 The Subcommittee noted the wording of the IPF diagnosis criterion currently used in the NZ criteria for pirfenidone, which states 'Patient has been diagnosed with idiopathic pulmonary fibrosis as confirmed by histology, CT or biopsy'. The Subcommittee noted the risks associated with lung biopsies, and considered that biopsies are seldom conducted for the diagnosis of IPF. The Subcommittee considered that this criterion should be amended and reworded so that diagnosis is made via a multi-disciplinary team (MDT) including a radiologist. The Subcommittee noted that smaller centres around New Zealand may not have access to a full MDT, however considered that regular teleconferences of these centres with larger tertiary centres would ensure that patients with suspected IPF are discussed.

- 3.15 The Subcommittee **recommended** that special authority criteria for pirfenidone be amended by removing the upper limit of the FVC 80% predicted criterion, removal of the criteria requiring pirfenidone to be discontinued at disease progression, and reword the diagnosis criterion to be by a MDT, **with high priority**.

5 Mepolizumab for severe eosinophilic asthma

- 4.1 The Subcommittee noted the funding application from GlaxoSmithKline NZ Ltd for mepolizumab for the treatment of severe refractory eosinophilic asthma.
- 4.2 Andrew Corin had declared that he was an investigator in the TERRANOVA trial for benralizumab, a potential competition product to mepolizumab, and that he had received information from GlaxoSmithKline New Zealand Limited (GSK Ltd) for a trial on mepolizumab in June 2017. It was determined that Dr Corin would participate in the discussion of the funding application for mepolizumab for severe eosinophilic asthma (agenda item 5), however he would abstain from voting.
- 4.3 The Subcommittee noted that mepolizumab targets human IL-5, the major cytokine responsible for the growth and differentiation, recruitment, activation and survival of eosinophils. Mepolizumab selectively and effectively inhibits eosinophilic airway inflammation by inhibiting IL-5 signalling and reducing the production and survival of eosinophils. The Subcommittee noted that mepolizumab is formulated as a sterile lyophilised powder for injection, and is reconstituted with water for injection to 100 mg/mL prior to use. The Subcommittee noted that mepolizumab is administered as a subcutaneous injection every 4 weekly. The Subcommittee considered that mepolizumab may be a treatment that patients would be able to self-administer with the appropriate training.
- 4.4 The Subcommittee noted that there were a number of other monoclonal antibodies currently in development for the treatment of severe asthma, such as reslizumab, benralizumab, and lebrikizumab. The Subcommittee noted that mepolizumab is currently the only Medsafe-registered monoclonal antibody for the treatment of severe eosinophilic asthma. The Subcommittee noted that mepolizumab was not similar to any currently listed pharmaceutical for the treatment of severe eosinophilic asthma.
- 4.5 The Subcommittee noted that severe asthma comprises a minority of the asthmatic population (5–10%) but contributes disproportionately to morbidity, healthcare expenditure and societal costs of disease. The Subcommittee considered that a typical person with severe eosinophilic asthma would experience daily symptoms that include cough, wheeze, chest tightness, chest pain, shortness of breath, exercise limitation and night waking. The Subcommittee noted that patients are currently managed on a multitude of broad spectrum asthma treatments, and are often receiving long term maintenance treatment at maximal doses or at doses above the recommended daily dosing limit. The Subcommittee noted that long term use of oral corticosteroids can lead to a number of side effects.
- 4.6 The Subcommittee noted that the impact of asthma on Māori is significantly greater than the general population of New Zealand, with an incidence just over twice the rate of the general population. The Subcommittee noted that while asthma deaths are uncommon, they are largely preventable and that Māori are over three times more likely to die of asthma than non-Māori (Asthma Respiratory Foundation NZ, 2016). The Subcommittee also noted that Māori, Pacific peoples and people living in the most deprived localities have by far have the highest rates of hospitalisations for asthma. The Subcommittee noted

that Māori are 3.4 times and Pacific peoples 3.9 times more likely to be hospitalised than Europeans or other New Zealanders, and people living in the most deprived localities are 3.7 times more likely to be hospitalised than those in least deprived localities (Asthma Respiratory Foundation NZ, 2016).

- 4.7 The Subcommittee noted the following trials that studied the safety and efficacy of mepolizumab:
- Pavord et al. *Lancet* 2012; 380(9842): 651-9
 - Ortega et al. *N Eng J Med* 2014;371(13):1198-1207
 - Bel et al. *N Eng J Med* 2014;371(13):1189-97
 - Chupp et al. *Lancet Respir Med* 2017;5:390-400
- 4.8 The Subcommittee noted that Pavord et al. 2012 studied the effects of three different doses of mepolizumab (75mg, 250mg, and 750mg) versus placebo. The Subcommittee noted that all doses of mepolizumab reduced exacerbations and delayed time to first exacerbation by a similar amount, compared to placebo.
- 4.9 The Subcommittee noted Ortega et al. 2014, which compared 75mg IV mepolizumab and 100mg subcutaneous mepolizumab against placebo. The Subcommittee noted that the authors estimated rates of clinically significant exacerbations per patient per year were 0.93 in the 75 mg intravenous-mepolizumab group, 0.83 in the 100 mg subcutaneous-mepolizumab group, and 1.74 in the placebo group. The Subcommittee noted that the relative reduction in exacerbation rate compared to placebo was 47% (95% CI, 28-60%) in the intravenous-mepolizumab group and 53% (95% CI, 36-65%) in the subcutaneous mepolizumab group ($P < 0.001$ for both comparisons). The Subcommittee noted that the proportion of patients with an exacerbation that resulted in an emergency department visit or hospitalisation was 9% in the intravenous-mepolizumab group, 6% in the subcutaneous-mepolizumab group, and 13% in the placebo group. The Subcommittee noted that the use of mepolizumab resulted in a relative reduction in the rate of exacerbations requiring hospitalisation or an emergency department visit of 32% in the intravenous-mepolizumab group ($P = 0.30$) and 61% in the subcutaneous-mepolizumab group ($P = 0.02$).
- 4.10 The Subcommittee noted Bel et al. 2014, which compared the steroid sparing effects of mepolizumab versus placebo. The Subcommittee noted that the authors reported more patients in the mepolizumab group than in the placebo group had a reduction of 90% to 100% in the oral glucocorticoid dose (23% vs. 11% respectively) and a reduction of 70% to 90% in the oral glucocorticoid dose (17% vs. 8% respectively). The Subcommittee noted that the median percentage reduction from baseline in the daily oral glucocorticoid dose was 50% among patients in the mepolizumab group, as compared with no reduction among those in the placebo group ($P = 0.007$).
- 4.11 The Subcommittee noted that Chupp et al. 2017 was a study that examined the effect of add-on mepolizumab versus placebo on the health-related quality of life (HRQOL) of patients with severe eosinophilic asthma. The Subcommittee noted that the mepolizumab group reported significant improvements at week 24 from baseline in St George's Respiratory Questionnaire (SGRQ) total score (least squares mean (SE) change from baseline $-15.6 (1.0)$ vs $-7.9 (1.0)$ compared to placebo, a treatment difference of $-7.7 (95\% \text{ CI } -10.5 \text{ to } -4.9; p < 0.0001)$). The authors reported that improvements in SGRQ total

score exceeded minimal clinically important difference (MCID) from week 12 onwards for mepolizumab versus placebo.

- 4.12 The Subcommittee noted the strength and quality of evidence, considering that there were several moderate sized well-conducted RCTs with consistent results. The studies had a high quality trial design (randomisation, blinding, trial design appropriate, choice of outcomes all appropriate), were almost exclusively industry sponsored trials, and had limited post-marketing surveillance data. The Subcommittee noted that there were multicentre studies, mostly European individuals with an average age of 50 years. The Subcommittee noted that although not fully representative, the studies were likely to be as relevant to New Zealand patients as any other global industry-sponsored trials. The Subcommittee considered that omalizumab would not be the appropriate comparator for mepolizumab, as mepolizumab is used to treat a different group of patients.
- 4.13 The Subcommittee noted that mepolizumab primarily offered benefit to the patient. However, members considered there were also minor health benefits to family/ whānau that could be expected in terms of reducing carer anxiety and stress. The Subcommittee noted that there was no evidence supplied about the magnitude of these benefits.
- 4.14 The Subcommittee noted the restrictions for mepolizumab proposed by the supplier and considered that the proposed criteria were too loose. The Subcommittee considered that an additional criterion should be included to exclude diseases with similar presentations to asthma. The Subcommittee noted that from the evidence presented, patients with higher blood eosinophil counts are those that are most likely to benefit, and considered that the blood eosinophil count in the last 6 weeks criterion should be increased from 150 cells/ μ L to 500 cells/ μ L. The Subcommittee also considered that the Asthma Control Questionnaire (5 item version) in the proposed criteria should be replaced with the Asthma Control Test (ACT), which is a free, validated, and readily available tool used to assess asthma control. The Subcommittee considered that when using the ACT scale for access criteria, severity scores should be 10 or less for patients to be eligible for mepolizumab. The Subcommittee also considered that the restriction should require patients to be on at least 1000 mcg of inhaled fluticasone, or adult/beclomethasone equivalent, per day. The Subcommittee also considered that the initiation criteria should be for 52 weeks treatment instead of 32 weeks, for ease of administration.
- 4.15 The Subcommittee noted the renewal criteria for mepolizumab proposed by the supplier, and considered that the wording in its current form to be ambiguous and subjective. The Subcommittee noted the mepolizumab restrictions recommended by the National Institute of Health and Clinical Excellence (NICE) in the UK. The Subcommittee considered that, in terms of response to treatment, improvements should be in the ACT score, and that exacerbations frequency should be reduced by at least 50% from baseline (in line with the NICE criteria) or oral steroid dosing should be reduced by at least 50% or more than >10 mg/day.
- 4.16 The Subcommittee proposed the following restrictions for mepolizumab:

Special Authority for Subsidy – Severe eosinophilic asthma

Initial application – respiratory physician. 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 > 500 cells/ μ L in the last 6 weeks, 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, 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 steroids; or
 - 6.2 Patient has received continuous oral corticosteroids of at least the equivalent of 10 mg per day over the previous 3 months
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. Approvals valid for 24 months 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.

- 4.17 The Subcommittee noted that there is increasing evidence that inhaled corticosteroids reach a therapeutic ceiling, when dose escalation beyond particular levels provides little if any further meaningful clinical benefit but does generate more adverse effects, and considered that in future the criteria could be amended to reflect a reduced inhaled corticosteroid dose ceiling for what is considered optimal inhaled therapy.
- 4.18 The Subcommittee noted the proposed costs and savings of mepolizumab. The Subcommittee considered that mepolizumab would be used as add-on therapy with patients stabilised on ICS+LABA and possibly other medicines such as prednisone, theophylline, montelukast etc. The Subcommittee noted that there were no significant indirect costs expected. The Subcommittee considered that the number of patients eligible for mepolizumab in New Zealand would likely be around 500, but noted that this number is difficult to correctly estimate. The Subcommittee considered that patients generally preferred oral or inhaled treatments, and that it was likely that approximately half of the total eligible patients will be treated with mepolizumab.
- 4.19 The Subcommittee considered that mepolizumab is the first registered treatment for severe eosinophilic asthma, and that it targets a disease with a high unmet health need which particularly affects Maori and Pacific populations. The Subcommittee considered that there was good quality evidence demonstrating the benefit of mepolizumab, and that treating with mepolizumab is likely to result in reduced exacerbations, hospital visits, and oral steroid use. The Subcommittee noted the subcutaneous formulation of mepolizumab and considered that this treatment may be administered in the community setting. The Subcommittee **recommended** funding of mepolizumab for the treatment of severe allergic eosinophilic asthma, subject to restrictions, with high priority.