Respiratory Subcommittee of PTAC
Meeting held 4 March 2015

(minutes for web publishing)

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

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

The Respiratory Subcommittee may:

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

These Subcommittee minutes were reviewed by PTAC at its meeting on 13 & 14 August 2015, a record of which is now available.

1 COPD Treatments and Special Authority Criteria

1.1 The Subcommittee noted that PHARMAC sought the Subcommittee's opinion on the therapeutic equivalence of the newly funded products, glycopyrronium and indacaterol, to the other fully funded treatments and advice as to where those two newly funded products may fit into treatment protocols. The Subcommittee also noted that PHARMAC sought advice from the Subcommittee on whether the funding of these two products may have an effect on the changes to the Special Authority criteria previously recommended by the Subcommittee.

1.2 The Subcommittee considered that there are more patients with undiagnosed COPD than the health sector is generally aware of and that presentations with COPD vary. The Subcommittee noted that UK data reported ~ 20% of patients admitted to hospital with the first exacerbation had severe disease despite having had a number of opportunities for a diagnosis to have been made in the previous 5 years and treatment started.

1.3 The Subcommittee considered that updated data from the NZ Health Survey, which is about to be published, would indicate the extent of COPD prevalence in primary care. The Subcommittee noted that a recent review of Hospital admissions for COPD in New Zealand (Milne & Beasley. NZ Med J 2015;128:23-35) reported 61,516 admissions in five years. The authors noted that COPD admissions are costly and are over-represented in high risk groups including rural, elderly, socioeconomically deprived and Māori and Pacific peoples, and considered that effective interventions targeted to high risk groups are required to improve equity and reduce the burden of COPD.

1.4 The Subcommittee queried whether PTAC may have misunderstood the minuted discussion held by the Subcommittee at the May 2013 meeting. The Subcommittee agreed that spirometry is the standard diagnostic tool for COPD but felt that it is an inappropriate main criterion for access to therapy as there is an unmet need for treatment amongst patients with clinical evidence of COPD who have preserved spirometry values and for highly symptomatic patients with preserved FEV_1 levels.

1.5 The Subcommittee noted that of those patients who are diagnosed and meet the GOLD criteria, patient group B may not be well treated under the current Special Authority criteria for tiotropium. These patients are defined as having mild to moderate COPD with low risk, more symptoms with ≤ 1 exacerbation per year, a CAT score of ≥ 10 and an mMRC score of ≥ 2. The FEV_1 % predicted of these patients may be anywhere from ≤ 50% to ≥ 80% but only those with an FEV_1 % of predicted ≤ 60% qualify for treatment with a LAMA. The Subcommittee considered that early intervention in this patient group would make a significant difference in the impact of the disease and would slow the rate of progression and the associated health costs.

1.6 The Subcommittee noted that the value of spirometry to assess patient need is limited in these Group B patients and considered that spirometry access criteria should be for diagnosis only with a FEV1 to FVC ratio of less than 70%. Patients should have an MRC (Medical Research Council dyspnoea scale) score of 2 or more or a CAT (COPD Assessment Test) score ≥10. The Subcommittee

considered that access to medications should be based on multiple criteria rather than spirometry on its own. The Subcommittee noted that access to spirometry is not an issue but access to quality spirometry is.

1.7 The Subcommittee recommended that the access criteria for LAMAs be changed to enable treatment of two patient groups – patients with bronchospasm and dyspnea due to COPD and who have had 2 or more exacerbations (or one exacerbation that required hospitalisation) in the last 12 months, and patients with bronchospasm and dyspnea due to COPD, and a CAT score ≥ 10. The Subcommittee considered 500 new patients may be treated in the first group and a further 750 in the second group. The Subcommittee considered that there are potential savings of $2,200 per exacerbation avoided to the total health budget.

1.8 The Subcommittee recommended removal of the FEV_1 criteria from the renewal criteria for continued treatment with LAMAs, as FEV_1 does not indicate clinical responsiveness to these pharmaceuticals.

1.9 The Subcommittee considered that indacaterol's once-a-day administration is an added advantage over other agents for COPD. The Subcommittee also noted that clinical trials for indacaterol were undertaken on study populations with less severe COPD, and queried the validity of any indirect comparisons between indacaterol and other COPD agents that had been trialled on study populations with more severe COPD.

1.10 The Subcommittee noted that the use of indacaterol and/or glycopyronium would not create any significant changes in health sector expenditure other than for direct treatment costs. The Subcommittee noted that the future funding of fluticasone furoate 100 mcg with vilanterol 25 mcg would not have significant impact on the Subcommittee's recommended amendments to the tiotropium Special Authority.

2 Pirfenidone

Application

2.1 The Subcommittee reviewed an application from a clinician at ADHB for the listing of pirfenidone on the Pharmaceutical Schedule for the treatment of idiopathic pulmonary fibrosis (IPF).

Recommendation

2.2 The Subcommittee was in general support of the application, and **recommended** the product to be listed with a high priority. The subcommittee **recommended** that PHARMAC develop a Special Authority Criteria for the treatment of patients with idiopathic pulmonary fibrosis.

2.3 The Subcommittee noted that the product is currently not available, nor registered in New Zealand.

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

Discussion

2.5 The Subcommittee reviewed the clinician application and noted that supporting evidence in the application is up to date, and robust in strength and quality.

2.6 The Subcommittee noted that there are no efficacious treatments available for idiopathic pulmonary fibrosis (IPF) listed in New Zealand. The Subcommittee also noted that there are no pharmaceuticals listed on the schedule with the same or similar effect.

2.7 The Subcommittee noted the evidence from the following studies:

Spagnolo et al (The Cochrane Library 2010). This Cochrane review examined fifteen trials involving 10 different non-steroid (corticosteroid) agents for the management IPF. The meta-analysis of 894 IPF patients in 3 studies (CAPACITY 1 and 2, and Taniguchi 2010) showed that pirfenidone reduced the risk of disease progression by 30% (HR 0.70, 95% CI 0.56 to 0.88 P=0.002). A meta-analysis of 314 patients enrolled in the two trials (Azuma 2005; Taniguchi 2010) that used pulmonary function as primary endpoint demonstrated an improved forced vital capacity in the pirfenidone group compared to placebo (mean difference 0.08, 95% CI 0.03 to 0.13, P=0.00065). The review showed pirfenidone to be the only efficacious drug at the time for the management of IPF, and there was no evidence to support the efficacy of using corticosteroids in the management of IPF.

Raghu et al (Am J Respir Crit Care Med 2011,183(6),788-824). This was a collaborative clinical guideline released by the American Thoracic Society, EU Thoracic Society and Japanese Thoracic Society in 2011. It gave pirfenidone a "weak recommendation with low-to-moderate quality evidence" in the management of IPF (Appendix 2). It also stated that the majority of patients with IPF should not be treated with pirfenidone, but it may be a reasonable choice in a minority of patients. These recommendations placed a high value on costs and side-effects and low value on the possible small reduction in pulmonary decline

King et al (N Eng J Med. 2014;370(22):2083-2092) The Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis (ASCEND) study was a randomised, double-blind, placebo-controlled trial. It found pirfenidone when compared to placebo, reduced disease progression, with the proportion of patients who had a decline of 10 percentage points or more in the percentage of the predicted FVC or who had died was reduced by 47.9% in the pirfenidone group as

compared with the placebo group (46 patients [16.5%] vs. 88 patients [31.8%], P<0.001). Furthermore, analyses on secondary end-points supported pirfenidone's effectiveness in reducing disease progression by changes in lung function, improved exercise tolerance, and progression-free survival. The study reported gastrointestinal and skin-related adverse events to be more common in the pirfenidone group than in placebo group. However, the authors concluded their findings indicate that pirfenidone is generally safe and has an acceptable side effect profile.

National Institute for Health and Clinical Excellence (NICE Pathways 2015). This NICE publication recommended pirfenidone to be an effective option for IPF only if: 1) The person has a forced vital capacity (FVC) between 50% and 80% predicted, 2) Treatment with pirfenidone that is recommended as above should be discontinued if there is evidence of disease progression (a decline in per cent predicted FVC of 10% or more within any 12 month period).

2.8 The Subcommittee considered that pirfenidone will provide benefit as, previously, treatment regimens that included corticosteroids and immunosuppressants did not provide any benefit, and could potentially cause harm. It was also noted that there was emerging evidence indicating that nintedanib, and some new monoclonal anti-bodies (in phase 2 trials) show similar efficacy to pirfenidone. The Subcommittee considered that pirfenidone would not replace any oxygen therapy, and possible future regimes would include both oxygen and GORD treatments.

2.9 The Subcommittee noted that there is no evidence to suggest there is increased risk in Māori and Pacific Island populations. An ADHB study (2006) reported a lower incidence of IPF in Māori and Pacific patients than in European/Caucasian patients.

2.10 The Subcommittee considered those patients meeting the diagnostic criteria specified in the clinical trials and NICE recommendation would benefit most from pirfenidone. The Subcommittee recommended the Special Authority criteria limit the prescribing of pirfenidone to respiratory physicians, and diagnoses confirmed by histology, CT or biopsy, with FVC of 50-80% and having 1 year trial and renewal requiring on-going benefit.

2.11 The Subcommittee did not consider there to be significant costs for the health-sector with the introduction of pirfenidone; however additional clinical and radiological examinations may incur some costs.

2.12 The Subcommittee was in general support of the application, and recommended the product be listed with a high priority. The Subcommittee noted its preference for the medication to be registered with Medsafe

3 Adherence to Asthma Treatments

3.1 The Subcommittee noted that PHARMAC has considered the area of paediatric asthma as an area where improvements could be made so that patients get the best health outcome from the products, which should lead to a reduction in overall health costs (admissions to hospital etc). The Subcommittee also noted that hospital admission rates, although improving, are still high in the paediatric age group (0-14 years) and in Māori and Pacific Island children in particular.

3.2 The Subcommittee noted that dispensings of asthma preventer medications (ICS or ICS/LABA combinations inhalers) are significantly lower per patient per year than expected if they were dispensed and used according to the recommended dose. The Subcommittee considered these medicines to be generally underused, especially in the paediatric age group and this seems sensible to concentrate on the area of treatment adherence in this group.

3.3 The Subcommittee noted two studies on asthma treatment adherence to consider. The first of these was a study report of early childhood education strategies in Early Childhood Centres (ECCs) (children 2-5 years) in four local Authority areas just north of Auckland (Space to Breathe, funded by PHARMAC, to date unpublished). The second study was a recently published inhaler adherence trial of children 6-15 years who had attended the Emergency Department (ED) in Auckland with asthma and were on ICS or needed ICS (Chan et al Lancet Respir Med 2015. Published online January 2015 doi.org/10.1016/52213-2600). .

3.4 The Subcommittee considered that the primary endpoints were not met in either of the two studies for a number of reasons.

Space to Breathe (unpublished)

3.4.1 The Subcommittee considered that education, motivation and reminders have a short term effect. Regarding the adherence to twice a day preventer every day at best it could be said that the intervention group with 28% at base improved to 47% at 12 months. This is compared to the roughly constant adherence in the control group of 32-42% in the 12 month period. The Subcommittee noted that asthma exacerbations that are not managed at home are comparatively rare in the community but probably many are managed at home especially in remote areas with limited access to Accident and Medical Centres and to hospital Emergency Departments.

3.4.2 The Subcommittee considered that the Space to Breathe study was underpowered, where while its sample size calculations had pre-specified 400 children in each arm of the study was the aim, only 341 and 334 participants respectively were analysable. In addition, the power calculation was based on a comparison of ICS vs placebo whereas in the study the control group was partial treatment (poorer compliance). The Subcommittee noted that the number enrolled was only achieved by widening the inclusion criteria from a restriction to patients diagnosed with asthma to patients who had a “high probability of asthma”, which led

to 40% of the children in the intervention group and 51% of the children in the control group being patients who had not formally been diagnosed with asthma.

3.4.3 The Subcommittee noted that the primary endpoint was a reduction in unscheduled, urgent medical or Emergency Department attendance (including hospital admission), and improved asthma outcomes at 12 months. The Subcommittee noted that although children had an improvement in their inhaler technique and a reduction in the use of reliever therapy the primary end point was not reached. Despite this it was felt that there were clinically significant benefits in the outcomes achieved.

3.4.4 The Subcommittee noted there was a high use of oral corticosteroids (Redipred) in the study and considered that most exacerbations are most likely managed at home rather than going to hospital, which may well have accounted for the high use of oral corticosteroids and the lower than expected admission rate that was seen in the study.

3.4.5 The Subcommittee considered that doses of ICS used could have been too high. Assuming that the 50 mcg dose fluticasone inhaler was the most commonly used ICS, the Subcommittee noted that 20% of children were taking 4 puffs a day, which would be equivalent to 200 mcg per day. The Subcommittee noted that explicit dose information was not provided in the study report, and therefore considered the high ostensible 200 mcg/day dosing in one fifth of children was not improbable, in the absence of evidence to the contrary.

Chan et al

3.4.6 The Subcommittee noted that in the ED study primary outcomes were the number of days absent from school for any reason, and that these did not differ significantly (median proportion of days 1.9% in the intervention group vs 1.7% in the control group, p=0.99). The Subcommittee also noted that there were no significant differences in hospital attendance either.

3.4.7 The Subcommittee noted that the authors stated that these outcomes were much less common than the rates previously reported (citing data from a 1997 study – Mitchell et al. NZMJ) when asthma admissions were more common. The Subcommittee considered that the study was underpowered for these endpoints. The Subcommittee also considered that the endpoint of days absent from school may have been suboptimal, as one of the three studies referenced in support of this endpoint showed no relationship between asthma and absenteeism at school.

3.4.8 The Subcommittee noted that the authors considered that using first ED presentation with asthma might show a significant effect, rather than using the repeat attenders (ie first and subsequent ED attendances combined).

3.4.9 The Subcommittee noted that in regard to exacerbations, parental reports of at least one asthma exacerbation were lower in the intervention group but only in the first 2 months (7% vs 24%) post baseline. This difference was not seen at 4 months (16% in the intervention group versus 15%) or at 6 months (16% versus 17%).

3.4.10 The Subcommittee noted that morbidity was improved slightly with the intervention and there was a significant improvement in the Childhood Asthma Control Test scores at each of the three time points ($p<0.0001$), with the intervention group scoring higher by an overall average of 1.57 units.

3.5 The Subcommittee considered that the low levels of adherence seen in the control groups of these studies were of concern. The Subcommittee noted that in the ECC centre study about half of children are using their ICS as prescribed. The Subcommittee also noted that in the ED based study at 2, 4, and 6 months the adherence of controls was 40%, 33% and 27% respectively, despite this being in a group that had been in hospital within the last six months.

3.6 The Subcommittee considered that many ED visits are coded as being viral lower respiratory tract infection or viral wheeze and not as asthma, which could bias those data.

3.7 The Subcommittee considered that the poor level of adherence seen in the control groups of these studies is a concern but would not be unexpected in normal practice. Members noted that in the Early Childhood Centre study only ~50% were using their ICS inhalers as prescribed and that in the ED study adherence in the control group decreased from 40% at the 2 month point to 33% at 4 months and 27% at 6 months.

3.8 The Subcommittee considered a number of actions that could be taken to try to improve adherence, eg. telephone support/follow up by an asthma nurse; mass advertising covering “How we use our medicine”; follow up by the GP/nurse on all hospital admissions; and investing in reminder systems such as Memory angel or Nexus 6 devices. The Subcommittee considered that a quality measure of recall for ICS repeat prescribing or education could be considered in primary care. Recall systems in practices could be targeted at the PHO level.

3.9 The Subcommittee considered that adherence trials could justify a case for prescribing combination inhalers and possibly for the subsidy of eformoterol/budesonide SMART regime, which the Subcommittee considered should be subject to a trial in the 6-14 year age group.

3.10 The Subcommittee considered that it would be advantageous to have the ECE study published as soon as practicable, as it highlights many of the other issues involved in pre-school wheeze/asthma control in the community.