Respiratory Subcommittee of PTAC meeting held 5 February 2010

(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 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 5 & 6 August 2010, the record of which is available on the PHARMAC website.

Contents

1 Anticholinergic agents 2
2 Inhaled corticosteroids 2
3 Long-acting beta-adrenoceptor agonists 3
4 Mast cell stabilisers 3
5 Methylxanthines 4
6 Montelukast 4
7 Budesonide with eformoterol – single inhaler therapy 6
8 Caffeine for apnoea of prematurity 6
9 Access to dornase alfa 7
10 Azithromycin for bronchiolitis obliterans 8

1 Anticholinergic agents

1.1 The Subcommittee noted the shift in use from ipratropium to tiotropium, and noted that this was less than was estimated at the time of listing. Members noted that one of the reasons behind this could be the requirement for spirometry. The Subcommittee noted that access to spirometers in primary care can be an issue, however considered that as spirometry is critical for diagnosing COPD, the requirement is appropriate.

1.2 Members considered that as access to combination ICS/LABA inhalers does not require spirometry, and as the level of promotional activity is much higher, some clinicians may be choosing to prescribe these in preference to tiotropium. Members noted that many clinicians consider these to provide similar levels of benefit.

1.3 The Subcommittee noted that there was a relatively low level of co-prescribing of tiotropium and ipratropium. Members noted that there was no evidence to suggest that these could not be prescribed together, although noted that Boehringer Ingelheim had previously indicated that co-prescribing may decrease the effectiveness of tiotropium.

1.4 Members noted that clinical trials were underway assessing the effect of tiotropium in addition to inhaled corticosteroids and LABAs.

1.5 The Subcommittee **recommended** that PHARMAC consider running or funding an educational program for prescribers on the diagnosis and treatment of COPD.

2 Inhaled corticosteroids

2.1 The Subcommittee noted that the average dose of inhaled corticosteroids has been reducing over time, with the proportion of people receiving a daily dose in excess of 1000 µg beclomethasone-equivalent falling steadily.

2.2 The Subcommittee noted a letter from AFT Pharmaceuticals regarding its brand of budesonide dry powder inhalers. Members noted that this letter addressed the issues raised by the Subcommittee at its last meeting, but considered that there may be some patient confusion with the new product. Members supported the listing of Budenocort on the Pharmaceutical Schedule.

3 Long-acting beta-adrenoceptor agonists

3.1 The Subcommittee noted that, while the usage of LABAs was increasing steadily, the market for LABA-only inhalers was shrinking, and there was a perception that they may not be available long-term. Members noted that the availability of these products is important for the Special Authority restriction for ICS/LABA inhalers, and that they fit well with asthma guidelines, which recommend stepwise introduction and reassessment.

3.2 Members also noted that subsidised combination ICS/LABA inhalers are only available at daily doses of 400 µg and 800 µg beclomethasone-equivalent, and the availability of a separate LABA inhaler allows steroid doses to be tailored.

3.3 Members noted that the 800 µg beclomethasone-equivalent threshold for adult patients to access combination ICS/LABA inhalers may be leading to higher ICS dosing, as many clinicians are unlikely to back-titrate the ICS component after shifting to a combination inhaler.

3.4 The Subcommittee **recommended** that the ICS threshold in the Special Authority restriction for combination ICS/LABA inhalers be amended to 400 µg beclomethasone-equivalent for adults and 200 µg for children.

4 Mast cell stabilisers

4.1 The Subcommittee noted that the mast cell stabilisers nedocromil and sodium cromoglycate are not fully funded.

4.2 Members noted that these products are not widely used asthma treatments, but do have niche uses, such as cough-variant asthma and exercise-induced asthma, when standard asthma treatments such as steroids and beta-agonists are not tolerated or are not sufficiently effective.

4.3 Members noted that fully funding these agents would be unlikely to increase usage significantly as these treatments would only be used in a small number of patients where other treatments are unable to be used due to tolerability or are not sufficiently effective; further the taste of these agents is unpleasant, and sodium cromoglycate must be used four or more times per day.

4.4 The Subcommittee **recommended** removing the part-charge from nedocromil and sodium cromoglycate.

4.5 Members considered that, if only one of these two agents was to be fully funded, it should be nedocromil.

5 Methylxanthines

5.1 The Subcommittee noted that the currently funded brand of aminophylline injection is likely to be discontinued in the next few years. Members noted that it was not a commonly used product, and that as it was more used in an acute setting, the Subcommittee recommended that PHARMAC seek advice from the intensive care unit at Starship Hospital and from the Rural General Practice Network.

5.2 The Subcommittee noted that the gradual withdrawal of theophylline had resulted in only two presentations remaining – a long-acting 250 mg tablet and the oral liquid. Members considered that theophylline was an important part of asthma treatment options, and that it was important to retain it.

5.3 Members noted that theophylline oral liquid was not used commonly in paediatrics any more, having been replaced by caffeine for apnoea of prematurity; however it may be required by older patients who are unable to swallow tablets. Member noted that, if they were available, theophylline sprinkles would also be appropriate.

5.4 The Subcommittee **recommended** removing the part-charge from theophylline oral liquid.

6 Montelukast

6.1 The Subcommittee considered a paper on montelukast. Members noted that information had been provided by PHARMAC and the supplier, Merck Sharp & Dohme.

6.2 The Subcommittee noted that PTAC had previously recommended that montelukast be funded for three groups of patients: those with aspirin-sensitive asthma, those with exercise-induced asthma, and those refractory to high dose inhaled corticosteroids. Members noted that since this recommendation was made, there had been changes to the range of asthma products subsidised and new evidence has been published relating to montelukast.

6.3 Members noted that montelukast was originally considered to be a steroid-sparing agent, and that it has mild anti-inflammatory properties equivalent to around 200 µg beclomethasone.

6.4 The Subcommittee noted that there was a lack of robust evidence to suggest that montelukast is more effective than currently funded asthma treatments. Members noted that a lot of the available trials were open-label.

6.5 The Subcommittee noted that there did not appear to be a significant unmet clinical need that would be met by montelukast. Members noted that asthma guidelines do not strongly indicate a place for montelukast in preference to other options such as theophylline.

6.6 The Subcommittee noted the results of the small study by Dahlén et al *(Am J Respir Crit Care Med. 2002 Jan 1;165(1):9-14.)* in which patients with confirmed aspirin-sensitive asthma, who were predominantly on inhaled corticosteroids, were randomised to montelukast 10 mg or placebo. Members noted that the addition of montelukast improved forced expiratory flow in 1 second (FEV_1) and peak expiratory flow rate (PEFR), and also decreased the rate of asthma exacerbations.

6.7 Members noted that in patients with aspirin-sensitive asthma, bronchospasm can be induced by naturally-occurring salicylates in food.

6.8 The Subcommittee noted that, if montelukast was funded for aspirin-sensitive asthma, the criteria for diagnosing aspirin sensitivity would be very important. Members noted that nasal polyps are usually associated with aspirin-sensitive asthma.

6.9 The Subcommittee **recommended** funding montelukast for the treatment of aspirin-sensitive asthma, subject to appropriate targeting criteria.

6.10 The Subcommittee noted that montelukast may provide some benefit in the management of exercise-induced asthma.

6.11 Members noted montelukast appears to provide some benefit above that provided by long-acting beta-adrenoceptor agonists (LABAs).

6.12 Members noted that other funded agents are also useful for exercise-induced asthma. The Subcommittee considered that if montelukast was to be funded for this indication, it should be available only after other treatments, including nedocromil, had been tried.

6.13 The Subcommittee **recommended** funding montelukast for the treatment of exercise-induced asthma, subject to appropriate targeting criteria.

6.14 The Subcommittee considered the use of montelukast in the paediatric setting. Members noted that pre-school wheeze is separated into multi-trigger wheeze and viral-induced wheeze.

6.15 Members noted that inhaled corticosteroids, LABAs and oral steroids are not considered to be very effective in the treatment of viral-induced wheeze, and that montelukast may provide benefit for children with viral-induced wheeze who have frequent exacerbations or hospital admissions.

6.16 Members noted that LABAs are not indicated for many pre-school children (eformoterol is indicated for 6 years and over, salmeterol is indicated for 4 years and over).

6.17 The Subcommittee noted that montelukast, which is indicated from 2 years of age, may be a useful addition to treatment in pre-school children with multi-trigger wheeze that is not adequately controlled with inhaled corticosteroids.

6.18 The Subcommittee deferred making a recommendation on the use of montelukast in pre-school wheeze, pending review of further information.

7 Budesonide with eformoterol – single inhaler therapy

7.1 The Subcommittee considered the application from AstraZeneca for widened access to the budesonide with eformoterol combination inhalers.

7.2 Members noted that this application had been referred to the Subcommittee by PTAC, and noted the applicant's response to the PTAC minutes.

7.3 The Subcommittee considered that the single inhaler therapy regimen can be a useful option for prescribers to consider, however considered that PHARMAC should not advocate one regimen over another.

7.4 Members noted that the single inhaler therapy regimen would not be suitable for some patients with poorly-controlled asthma or with complications of asthma where self-management strategies might delay appropriate medical assessment, nor for patients who over-use their reliever inhalers.

7.5 Members noted that the available studies excluded patients who were high users of reliever inhalers, and so provided little information on this important group of asthma patients.

7.6 The Subcommittee noted that not all patients would adhere to a 1 dose BD plus PRN regimen, and that many would take this as 2 doses BD plus PRN, which would result in increased doses of budesonide.

7.7 The Subcommittee noted the paper by Taylor et al *(N Z Med J. 2008 Nov 7; 121(1285):106-18.)*, and were in general agreement with the comments expressed by the authors. Members noted that the Subcommittee has recommended amending the inhaled corticosteroid threshold for combination ICS/LABA inhalers.

7.8 The Subcommittee noted that, for patients who meet the Special Authority criteria for combination ICS/LABA inhalers, prescribers were already able to prescribe the regimen that they considered best for their patients within the existing Special Authority criteria.

7.9 The Subcommittee did not consider it necessary or appropriate to amend the criteria as proposed by the applicant; as such the Subcommittee **recommended** declining the application to amend the restrictions applying to budesonide with eformoterol combination inhalers.

8 Caffeine for apnoea of prematurity

8.1 The Subcommittee considered a paper on the use of caffeine oral liquid in the treatment of apnoea of prematurity.

8.2 The Subcommittee noted that caffeine was commonly used in hospitals for the treatment of apnoea in infants. Members noted that the cost of caffeine is low and the number of patients accessing treatment at present is very low.

8.3 Members discussed whether it would be useful to seek expert advice from neonatologists and sleep physicians at Starship Hospital on when caffeine could be indicated. Members considered that due to the low cost and low patient numbers, listing with a comment indicating that use was primarily for apnoea of prematurity would suffice.

8.4 The Subcommittee considered that caffeine could be used in other indications including narcolepsy and in palliative care, although considered that the likelihood of significant use in these other indications would be low as the formulation being considered is a liquid form with a total dose of 250 mg caffeine per bottle.

8.5 Members noted that funded access to caffeine for apnoea of prematurity is currently only available through Hospital Exceptional Circumstances (HEC) and noted that listing caffeine would obviate the need for applications to be considered by the HEC Panel.

8.6 The Subcommittee **recommended** listing caffeine oral liquid in the Pharmaceutical Schedule with a comment in the listing noting that its intended use is for apnoea of prematurity.

9 Access to dornase alfa

9.1 The Subcommittee considered whether access to dornase alfa could be moved from application to the Cystic Fibrosis Advisory Panel (the Panel) to a standard Special Authority form.

9.2 Members noted that the Panel had indicated it was relaxed about dornase alfa moving from Panel access to Special Authority but that the Panel considered that its role in advising on cystic fibrosis treatments should be retained.

9.3 The Subcommittee noted that when funding for dornase alfa was first announced, all applications were carefully scrutinised by the Panel, but now the Panel was quite comfortable with the criteria and the outcome of an application was often obvious. PHARMAC staff noted that the majority of applications are now approved by the Panel Co-ordinator and retrospectively reviewed by the Panel.

9.4 The Subcommittee noted that PTAC were currently reviewing the dornase alfa access criteria and were keen to retain the requirement for a trial of therapy in the criteria. Members noted that it would be possible for lung function data to be entered on Special Authority forms as is currently the case with tiotropium bromide.

9.5 The Subcommittee discussed the requirement for the applicant to be part of a multidisciplinary team experienced in the management of cystic fibrosis. Members considered that this requirement could be liberally interpreted and would be difficult to monitor.

9.6 Members considered that the Panel's role had developed over time and that, after reviewing an application for dornase alfa, Panel members sometimes approached individual clinicians to discuss the management of individual patients.

9.7 The Subcommittee considered that the Panel was low cost to PHARMAC and that it would be difficult define Special Authority criteria that would provide the same utility as the Panel. Members considered that without the Panel, some applications may get through the Special Authority system inappropriately and that retaining the Panel would ensure uniformity of access across the country.

9.8 The Subcommittee **recommended** that applications for dornase alfa continue to be assessed by the Panel rather than be moved to a standard Special Authority form.

10 Azithromycin for bronchiolitis obliterans

10.1 The Subcommittee considered a paper from PHARMAC staff on the use of azithromycin in lung transplant recipients who develop bronchiolitis obliterans syndrome (BOS).

10.2 The Subcommittee considered the evidence in support of azithromycin was understandably, given the rarity of the condition, weak and of limited value, and as the patient group was small that there were unlikely to be large randomised controlled studies. Members however considered that, clinically, azithromycin appeared to slow disease progression in some patients.

10.3 The Subcommittee noted that no alternate therapies existed for the treatment of BOS, although alternate therapies such as ATG and OKT3 had been tried without much success. Members noted that azithromycin was significantly less expensive than these therapies.

10.4 The Subcommittee considered there were approximately 12 lung transplant patients per annum and that half would develop BOS. Members noted that there was a disproportionate number of Maori affected by BOS following lung transplant.

10.5 The Subcommittee **recommended** that azithromycin be funded for BOS in the Pharmaceutical Schedule under the following Special Authority criteria:

> Special Authority for bronchiolitis obliterans syndrome
>
> Application by a lung transplant specialist. Application valid for 3 months where the patient has bronchiolitis obliterans syndrome following lung transplantation.
>
> Renewal by a lung transplant specialist. Application valid without further renewal unless notified where the patient has show stabilisation or improvement of bronchiolitis obliterans syndrome symptoms.