

Pharmaceutical Benefits Scheme

**Post-market Review**

**PBS Medicines Used to Treat Asthma in Children**

**Report to PBAC**

**Final Report**

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## Glossary

ABS	Australian Bureau of Statistics
ACAM	Australian Centre for Asthma Monitoring
AIHW	Australian Institute of Health and Welfare
AMSTAR	Assessment of Multiple Systematic Reviews
BEACH	Betting the Evaluation and Care of Health
Co-dispensing	Supply, as determined from prescription quantity supplied, of two or more medicines for a minimum of one month
Commonwealth	Commonwealth of Australia as represented by the Department of Health and Ageing
COPD	Chronic Obstructive Pulmonary Disease
DUSC	Drug Utilisation Sub-Committee (of the PBAC)
DVA	Department of Veterans' Affairs
ESC	Economics Sub-Committee (of the PBAC)
FDA	Food and Drug Administration
FEV <sub>1</sub>	Forced expiratory volume in one second
FDC	Fixed dose combination of inhaled corticosteroid and long acting beta <sub>2</sub> agonist
GINA	Global Initiative for Asthma
GP(s)	General Practitioner(s)
GRADE	Grading of Recommendations Assessment Development and Evaluation
The Handbook	The Australian Asthma Handbook 7 <sup>th</sup> ed. Version 1.0, 2014
HTA	Health Technology Assessment
ICS	Inhaled corticosteroid
LABA	Long-acting beta <sub>2</sub> -agonist
LTRA	Leukotriene Receptor Antagonist
mcg	Micrograms
MDI	Metered Dose Inhaler
NAC	National Asthma Council of Australia
NICE	National Institute for Health and Clinical Excellence
NHMRC	National Health and Medical Research Council

NHS	National Health Survey
NMP	National Medicines Policy
NPS	National Prescribing Service
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PBD	Pharmaceutical Benefits Division
PEF	Peak expiratory flow
PIN	Patient Identifier Number
PMAG	Paediatric Medicines Advisory Group
PMM	Post-market monitoring
PMR	Post-market review
PPB	Pharmaceutical Policy Branch
QoL	Quality of Life
QUM	Quality Use of Medicines
QUMPRC	Quality Use of Medicines and Pharmacy Research Centre
RCT	Randomised Control Trial
The Review	The Post-Market Review of PBS Medicines Used to Treat Asthma in Children
Reference Group	Reference Group for the Post-Market Review of PBS Medicines Used to Treat Asthma in Children
RPBS	Repatriation Pharmaceutical Benefits Scheme
SABA	Short-acting beta <sub>2</sub> -agonist
SMART	Symbicort® Maintenance and Reliever Therapy
TGA	The Therapeutic Goods Administration
The Department	The Department of Health
The Government	The Australian Government
ToR	Terms of Reference
WHO	World Health Organization

## Consumer Summary

- Asthma is a chronic disease which affects approximately 2.3 million Australians and is most common in children and adolescents.
- Asthma causes breathing difficulties from narrowing of the airways due to inflammation and swelling of the airway lining, tightening of the airway muscles and the production of excess mucus.
- There are two broad groups of asthma medicines, relievers which are used to reduce breathlessness and preventers which are used daily to either prevent or reduce the severity of asthma symptoms and flare-ups.
- Many children will only need to use a reliever now and then; however children who have frequent symptoms that are not controlled when using a reliever will need to use a preventer.
- This Review focuses on fixed dose combination inhalers (FDC) of an inhaled corticosteroid (ICS) and a long acting beta2 agonist (LABA). FDCs are generally recommended as second line preventer medicines when the child has poorly controlled asthma while using a low dose of ICS and a short acting reliever.
- In Australia, over 90% of asthma preventer therapy is initiated by GPs and GPs manage asthma treatment for the majority of children.
- The national guidelines recommend most children start with an ICS then move onto a FDC if asthma symptoms remain poorly controlled. The PBAC has recommended use of a FDC where people have continuing symptoms in spite of optimal doses of an ICS, oral corticosteroids or are currently having an ICS and a LABA at the same time.
- The PBAC has only considered cost effectiveness in children who are stabilised on both components of the FDC or who have continuing symptoms on regular ICS therapy.
- In Australia, the use of FDC in children is higher than any other preventer medicine, such as ICS or montelukast.
- The majority of children used a FDC as their first preventer treatment.
- Utilisation analysis of pharmacy prescription data shows that approximately 79% of initiating PBS prescriptions for FDCs were prescribed outside PBS restrictions.
- Over 25% of FDC prescriptions in children, are supplied to children below the age recommended by the national guidelines.
- Despite FDC being a long term preventer treatment used to manage more severe asthma, more than half of the children who started a FDC only filled the one script. There is no research evidence to support the benefit of FDC in this way.
- FDC were found to provide slightly better lung function in children than ICS, but children still had the same number of flare ups and visits to hospital. The difference in lung function is difficult to interpret when not supported by outcomes valued by patients and payers.
- Studies looking at adverse effects of the LABA component of FDCs provide uncertain results in terms of the potential for harm.

- A wide range of educational interventions for asthma are used across Australia, including teacher and carer training, professional development for health care professionals and skills and management education for children with asthma.
- Evidence of the effect of educational interventions for asthma management is mixed.

## Executive Summary

Asthma is a chronic disease that results in inflammation and narrowing of the air passages in the lungs. Approximately 2.3 million Australian have asthma and it is most prevalent in children and adolescents. Asthma flare-ups affect the patients' and carers' quality of life and can be fatal.

The objective of the Post-market Review of PBS Medicines Used to Treat Asthma in Children (the Review) is to systematically evaluate the body of clinical evidence regarding asthma medicine interventions to ensure the most appropriate management of children living with asthma in the community. The Terms of Reference (ToR) for the Review were approved by the PBAC following consideration of a number of utilisation reports that identified concerns about the proportion of children supplied with a fixed dose combination inhaler (FDC) of inhaled corticosteroid (ICS) plus long acting beta agonist (LABA) without prior experience with an ICS. These concerns were echoed by the Paediatric Medicines Advisory Group and the National Medicines Policy Committee.

The five ToR were addressed through specific reviews of evidence for medicines, utilisation and asthma interventions. A Reference Group provided advice on the Report and there were opportunities for additional stakeholder consultation throughout the review period.

### *ToR 1: Safety and efficacy of LABA and ICS combination inhalers.*

A review of all available randomised controlled trials published since 2000 in children and adolescents provided evidence of effectiveness and safety in study subjects with frequent symptoms of asthma managed on preventer therapy, usually an ICS.

In children and adolescents with poorly controlled asthma and moderate to severe symptoms a FDC was more effective in improving lung function (measured as change in %FEV<sub>1</sub> from baseline) but there was no reduction in the number of asthma exacerbations or hospitalisations when compared to the same dose of ICS. The commissioned safety and efficacy literature review reported that studies in adults show a reduction in exacerbations where adults received a FDC compared to the same dose of ICS. This may show an important difference between how adults and children should be treated for asthma.

In those studies comparing a FDC and an increased dose of ICS there was no difference in change of FEV<sub>1</sub>, exacerbations of symptoms or hospitalisations; however there was an increase in PEF morning and night for subjects taking FDC. Again, the literature suggested a differential effect between adults and children, with trends in opposite directions for the risk of exacerbations. There were no similar quality studies in children with less severe symptoms or who used a FDC without prior preventer therapy only.

The literature review reported a reduction in the rate of growth associated with ICS in higher doses and an increase in hospitalisations where patients received a LABA alone. There are conflicting studies regarding the development of tolerance to treatment and no evidence to support differential effectiveness on lung function (FEV<sub>1</sub>) over time

between a FDC or ICS. Stakeholders reported that non-responsiveness to treatment may be associated with tolerance to FDC. Studies exploring the effect of genetic polymorphism on treatment efficacy have been published but the results are inconclusive. There are no studies of FDCs in very young children and stakeholders considered that children five years or less should not use a FDC.

The utilisation analyses suggest that a proportion of children receive FDC for conditions other than asthma; for which the medicines are not PBS subsidised. The safety and efficacy literature review did not identify any studies that assessed the safety and effectiveness in any other conditions other than moderate to severe asthma.

A number of small studies compared FDC to either ICS or montelukast in exercise induced asthma. The size of effect reported was highly variable between studies. Stakeholders noted that there is other literature regarding effectiveness of ICS plus montelukast noting this use is only subsidised on the PBS for children 6 – 14 years.

#### *ToR 2: Utilisation of FDC in Australia*

The 2013 PMR analysis reviewed and updated the work undertaken in the 2011 DUSC analysis. The new analysis found that around 79% of children (0-18 years) who started treatment with a FDC had not trialled a PBS-subsidised ICS or oral corticosteroid. A large number (59-79%) of children, with no prior ICS use, had only one FDC prescription filled in a 12 month period. Children who had prior ICS treatment were slightly more likely to have more than one FDC prescription per year but the difference between groups on the basis of prior ICS therapy was small.

Fluticasone was the most commonly prescribed ICS for younger children and fluticasone/salmeterol was the most commonly prescribed FDC.

Stakeholders noted that the utilisation analyses were not able to take into account the individual patient circumstances and this makes interpretation of the analysis difficult.

Although stakeholders considered that FDC were not suitable for children five years or less the utilisation analyses showed that a small proportion of this group received a supply of FDC. Use of LABA as a single component inhaler remains negligible and most use of LABA is as part of a FDC.

#### *ToR 3: clinical practice and clinical guidelines comparison.*

Over 25% of FDC prescriptions are supplied to children below the age recommended in Australian clinical guidelines. The supply of FDCs to children in Australia is inconsistent with the observed epidemiology of asthma and guideline recommendations for treatment. Many children are likely to be prescribed FDC for other respiratory conditions or have less severe symptoms than those who participated in the clinical trials. Therefore the comparative effectiveness and cost effectiveness of FDCs in managing these patients is unknown.

Stakeholders noted that treatment guidelines are not adhered to in many cases. Reasons included lack of diagnostic effort, priority for symptom management, social and clinical factors and a lack of awareness of differences between paediatric and adult asthma management.

*ToR 4: Healthcare professional and consumer education medication management.*

A range of programmes promoting improved asthma management were identified during the Review. There remains a demand for information about asthma treatment as evidenced by the large volume of calls to the national asthma phone service. Some stakeholders reported that patients may remain confused about the differences between preventers and relievers despite the education in this area. It was also noted that delivery of education at a time when consumers were receptive and able to understand the information was more likely to be beneficial.

There is evidence that education of prescribers using the Practitioner Asthma Communication Education (PACE) programme improves prescribing practice in relation to the use of inhalers. Some stakeholders noted that GPs were not always as aware of the differences in managing childhood asthma and adult asthma, and tended to apply adult management techniques when uncertain.

*ToR 5: Effectiveness of community setting interventions*

A systematic review of interventions to improve prescribing and quality use of medicines in children with asthma identified that consumer education and behaviour interventions may have slight benefits on health care utilisation, specifically on the number of emergency department and hospital visits. There are a number of interventions with little research into effectiveness, these include educational outreach visits, audit and feedback, reminders and patient mediated interventions. Overall the literature review was not able to isolate intervention types that clearly and consistently improved prescribing, preventer use or healthcare utilisation in all settings.

Stakeholders noted anecdotal reports of benefits from home visiting programmes conducted by pharmacists and/or nurses but no published evidence is currently available.

In general, stakeholders supported interventions that were multifaceted, involved a range of settings, and engaged a number of stakeholders, including health professionals, parents/carers and children.

Interventions that promote positive behaviours in managing asthma generally show a benefit in reduced healthcare resource use. Such interventions can include coaching, monitoring of medication adherence, support programs and education interventions that include all health professionals and consumers. Further research may be needed to identify the critical factors for successful education interventions.

## Report Structure

This Report is presented in seven separate parts, as briefly outlined below. The Report has been structured in this way to address the Terms of Reference of the Review.

**Section 1**– Provides the context for the Review, background information on asthma in children including its prevalence and impact in Australia, and a synopsis of the guidelines for the management of asthma in children.

**Section 2 – ToR 1:** Provides a review of the evidence on the efficacy and safety of FDCs in children compared to alternative preventer medicines not previously considered by the PBAC.

**Section 3 – ToR 2:** Provides a comparison of findings to the original DUSC report, and supplements the analysis with more recent data.

**Section 4 – ToR 3:** Aims to identify areas of prescribing for childhood asthma in Australia where clinical practice is inconsistent with clinical guidelines; and if there is evidence that supports this practice.

**Section 5 - ToR 4:** Presents a review of recent (past five years) healthcare professional and consumer education in the area of medication management in children with asthma.

**Section 6 – ToR 5:** Presents a review of effective interventions from Australia and overseas that have resulted in improvement of prescribing and quality use of medicines in the context of childhood asthma.

# Section 1

## Background

### 1.1 Context for the Review

#### **1.1.1 The National Medicines Policy (NMP)**

The NMP is a broad framework that aims to improve health outcomes for all Australians through improving both access to, and appropriate use of, medicines.

The four central objectives of the policy are:

- timely and affordable access to medicines for all Australians;
- appropriate standards of quality, safety, and efficacy of medicines;
- quality use of medicines; and
- maintenance of a responsible and viable medicines industry in Australia.

Post-market reviews contribute to the quality use of medicines objective of the NMP.

*Quality use of medicines* is defined as:

- selecting management options wisely;
- choosing suitable medicines if a medicine is considered necessary; and
- using medicines safely and effectively.

The definition of quality use of medicines applies equally to decisions about medicine use by individuals and decisions that affect the health of the population.

#### **1.1.2 Australian Commission on Safety and Quality in Health Care (ACSQHC)**

The ACSQHC was established to lead and coordinate national improvements in the safety and quality of health care. (1)

Post-market reviews contribute to the stated goals and standards of the ACSQHC, primarily through goal three (1) and standard two(2) which focus on partnering with consumers in planning, designing and evaluating health care.

This is achieved in post-market reviews by providing multiple opportunities for consumers, and other stakeholders, to provide input into the review, via public consultation and through the consumer advocate who is appointed as part of the review reference group.

#### **1.1.3 Pharmaceutical Benefits Scheme (PBS)**

The PBS provides reliable, timely and affordable access to a wide range of medicines for all Australians. Under the PBS, the Australian Government subsidises medicine costs to help people afford prescription medicines for most medical conditions.

#### **1.1.4 The Pharmaceutical Benefits Advisory Committee (PBAC)**

The PBAC is an independent expert body appointed by the Australian Government, comprised of doctors, health professionals, health economists and consumer representatives. The PBAC meets three times a year, usually in March, July and November. Additional special meetings may be held as required.

The PBAC is responsible for evaluating the clinical and cost-effectiveness of medicines in order to make recommendations to the Government to list a medicine on the PBS.<sup>(3)</sup> Recommendations for new listings are informed by evidence of a medicine's clinical effectiveness, safety, and cost-effectiveness ('value for money') compared with other treatments.

The PBAC has a broad statutory function under the *National Health Act 1953*, to advise the Minister on any matters concerning the operation of the PBS. This includes making further recommendations regarding the safety, effectiveness and cost-effectiveness of medicines after they have been listed. Therefore, the PBAC considers the need for, and provides recommendations on, post-market reviews.

The PBAC has two sub-committees to assist with analysis and advice: the Drug Utilisation Sub-Committee (DUSC) and the Economics Sub-Committee (ESC). Information relating to the PBS, and the PBAC, DUSC and ESC meeting dates, agendas and outcomes are available on the [PBS website](#).

#### **1.1.5 Post-market monitoring**

The Post-Market Review (PMR) programme is a systematic approach to monitoring medicines subsidised by the PBS. PMRs were initiated under the 2011-12 Budget measure '*Improving sustainability of the PBS through enhanced post-market surveillance*'.

PMRs are established under the quality use of medicines objective of the National Medicines Policy framework; promoting the safe and effective use of medicines, with the aim to improve health outcomes for all Australians.

The PMR programme contributes to the following:

- Improved patient safety through better understanding of adverse events and medicine-related harms, including hospitalisations;
- A more sustainable Pharmaceutical Benefits Scheme (PBS) through better targeting of medicines, and avoidance of preventable wastage, or inappropriate prescribing;
- A better knowledge base to understand medicines utilisation, to validate the intended clinical benefit which will inform medicines evaluation processes; and
- A strengthened approach to medicine pricing management, including through better management of clinical and economic uncertainty.

Post-market reviews can be initiated when concerns related to the quality use of a medicine, cost-effectiveness, clinical effectiveness, higher than predicted utilisation

and/or international differences are raised. A full post-market review will only proceed following PBAC agreement and Ministerial approval.

## 1.2 About the Asthma Medicines Post-Market Review

In November 2012, following a request by the Minister, the PBAC agreed on the Terms of Reference (ToR) for the Post-Market Review of PBS Medicines Used to Treat Asthma in Children (the Review), and to consider the Review's findings. The objective of this Review is to systematically evaluate the body of clinical evidence regarding asthma medicine interventions to ensure the most appropriate management of children living with asthma in the community.

The need for this Review was first identified in 2010 by Merck Sharp and Dohme (MSD), the sponsor of montelukast, an asthma preventer medicine. MSD provided a report to the Paediatric Medicines Advisory Group (PMAG).

This report found that a substantial proportion of the children supplied with a fixed dose combination (FDC) inhaler containing a long-acting beta<sub>2</sub>-agonist (LABA) and inhaled corticosteroid (ICS), had not first been prescribed a single ingredient product (such as an ICS) in accordance with the then current recommendations of Australian guidelines.

PMAG considered that the extent of FDC use in children reported in the study commissioned by MSD was a potentially serious quality use of medicines issue and required further investigation. The PMAG referred the matter to the DUSC of the PBAC.

In June 2011, the DUSC considered the MSD findings and an additional analysis of the PBS data undertaken by the DUSC Secretariat. Using additional data the DUSC report ([Appendix A](#)) indicated that there was a very high rate (78%) of children and adolescents commencing a FDC without prior use of a single ingredient corticosteroid inhaler. This appeared contrary to asthma management guidelines in the Asthma Management Handbook 6<sup>th</sup> ed. 2006. The DUSC reviewed the report, noted the issues raised, and advised sponsors that this is a complex area of treatment and further clarification of the issues surrounding asthma management in children was needed. The DUSC referred the issues raised with the available reports and comments from the industry to the PBAC.

In August 2011, the PBAC agreed that the data indicated a mismatch between current guidelines, quality use of medicines messages and use in actual practice. The PBAC wrote to the National Medicines Policy (NMP) Committee. In April 2012, the NMP Committee recommended to the Minister for Health the initiation of a post-market review of Pharmaceutical Benefits Scheme (PBS) listed medicines used for treating asthma in children, to ensure that these medicines continue to be used safely and appropriately. The NMP Committee developed draft ToR for this Review.

The Minister wrote to the PBAC in September 2012 requesting their consideration of the Review ToR at the November 2012 meeting and to subsequently consider the Review findings and provide advice upon completion of the Review.

### 1.2.1 Overview of the Review Process

The PMR process is detailed on the PBS website:

<http://www.pbs.gov.au/info/reviews/subsidised-medicines-reviews>

**Table 1.1. Key dates of the Post-Market Review of PBS Medicines Used to Treat Asthma in Children**

12 February 2013	Public announcement of the Review on pbs.gov.au	
12 February 2013 2 April 2013	Period for submissions on the Terms of Reference closes	16 submissions received,
April 2013	Reference Group formed from health professionals, researchers and members from key stakeholder groups, including consumer, pharmacist, general practitioner and specialist.	Made up of 12 Members. The group was formed to provide expert input to the Review
17 June 2013	14 of 16 submissions available publically on website  Further details regarding who made submissions can be found on the <a href="#">Asthma Review webpage</a> .	2 submissions requested confidentiality for their submissions
28 August 2013	First Reference Group meeting	Discussed: Terms of Reference DUSC analysis Literature Review Stakeholder Submissions
18 November 2013	Stakeholder forum (representatives from consumer groups, pharmaceutical industry, health professionals and Department of Health staff)	21 stakeholders attended
27 November 2013	Second Reference Group meeting	Discussed: Stakeholder Forum Literature Review PMR analysis PMR Interventions Review
6 February 2014	DUSC considered the commissioned PMR analysis which was conducted to supplement the original DUSC analysis	Positive feedback was received with no additional work required.
28 March 2014	Third Reference Group meeting	Discussed: Draft Review Report Options for the Review
5 May 2014	Outcomes of the stakeholder forum publically available	
12 May 2014 26 May 2014	Final Report publically available on the web. Additional period for further comments (two weeks)	
June 2014	Report finalised and ratified by the Reference Group and submissions to final report collated.	
8 – 11 July 2014.	Final Report and submissions considered by the PBAC	

### **1.2.2 Review Reference Group**

A Reference Group was formed to assist in reviewing the evidence and forming options for the report. Members of the Reference Group were appointed as either individuals or organisational representatives and included experts in clinical management of asthma and representatives of health professional and consumer organisations, a full list of members is at [Appendix B](#).

### **1.2.3 Report Sources**

This Report has been compiled from a wide range of sources including scientific literature, data analysis and stakeholder input.

In the course of the review two literature reviews have been conducted covering; questions around the comparative safety and effectiveness of medicines, questions of alternate usage of asthma medicines and evidence of educational interventions for the treatment of asthma.

In addition the Report considered both the 2011 DUSC analysis and the 2013 PMR analysis which were conducted on the basis of PBS data and provided evidence of usage of medicines outside of PBS restrictions.

Finally extensive open stakeholder consultation was conducted; this included an open invitation to submit comments on the ToR, an open stakeholder forum for further comment and an open invitation to submit comments on the Report before it is presented to the PBAC for consideration. In addition to this open consultation the Reference group provided extensive feedback on all aspects of the evidence considered within the Report.

## **1.3 Asthma in Children**

### **1.3.1 What is asthma?**

Asthma is a chronic disease of the air passages of the lungs which inflames and narrows them.(4) It is characterised by recurrent attacks of breathlessness and wheezing, which vary in severity and frequency. The frequency of symptoms can vary from occurring several times per day to only a few times per year and can worsen during physical activity or at night. An asthma flare-up involves contraction of the smooth muscle and swelling of the lining of the bronchial tubes, constricting the airway which reduces the flow of air into and out of the lungs.

While asthma has a low fatality rate compared to other chronic diseases, its impacts include sleeplessness, daytime fatigue, reduced activity levels and school and work absenteeism.(4)

The causes of asthma are not fully understood, however the strongest risk factors for developing the disease is believed to be a combination of genetic predisposition with environmental exposure to inhaled substances that may provoke allergic reactions or

irritate the airways.(4) Triggers include cold/dry air, extreme emotion, physical exercise and cigarette smoke.(5)

Asthma is a common chronic disease among children worldwide.(4)

### ***1.3.2 Prevalence of asthma in Australian children***

In 2011-12, the ABS estimated that 2.3 million Australians had;(6) considered high compared to international prevalence.(7) However, the prevalence of asthma in Australian children and young adults has lowered in the last decade; a similar trend has been observed in other English-speaking countries.(7)

Asthma is most frequently reported in children and adolescents. The reported prevalence varies slightly depending on the source of data collection according to the Australian Centre for Asthma Monitoring (ACAM) approximately one in ten of adults and children have asthma.(7) In a cross-sectional community study an estimated 10.4% of children aged 15 years or less had current asthma.(8)

### ***1.3.3 Impact in Australia***

Children with asthma have a poorer quality of life and have significantly higher school absenteeism than those who do not have asthma.(7)

The ACAM determines that children aged 0 to 4 years are the group with the most frequent general practitioner consultations, emergency department visits or number of hospitalisations.(7)

In Australia in 2011, asthma was the underlying cause of death for 378 people across all age groups.(9) The majority of these deaths are in people are aged over 65 years; although asthma leads to a higher proportion of deaths in younger age groups when considering deaths from all causes.(7) Morbidity and mortality can be reduced by education, self-monitoring, appropriate drug therapy, regular medical review and a written asthma action plan.(10)

In terms of financial impact, asthma expenditure accounted for 0.9% (\$655 million) of the total Australian health expenditure in 2008-09. Of this, 50% of asthma expenditure was on pharmaceuticals, compared to 14% across all diseases. (11)

Hospitalisation for asthma decreased between 1998-99 and 2010-11. During this time, there was an overall reduction in the rate of hospitalisation reported for asthma (-33%) among children. This is in the context of the reduction in all-cause hospitalisations among children (-2%).(11)

The Australian Health Survey Report 2011-12 provided updated results showing 73.2% of children with asthma in the 0-14 years age group had consulted a GP, 10.9% had consulted a specialist and 14.2% had consulted other health professionals. The findings of the report showed 46.4% of children with asthma in the 0-14 years age group had visited a hospital or emergency department at least once due to their asthma becoming worse or out of control. The report also reported that 40.9% of children with asthma in the 0-14 years age group had a written asthma action plan. Of children with asthma in

the 0-14 years age group who were of school age, 42.4% had one or more days of school absence in the previous 12 months.(12)

#### **1.3.4 Types of asthma in children**

The Australian Asthma Handbook (7<sup>th</sup> Ed.) classifies childhood asthma on two measures of severity depending on whether the child has initiated preventer treatment or not. Prior to initiating a preventer severity is assessed in terms of the asthma pattern and ranges from infrequent intermittent asthma to severe persistent asthma. Once a child is receiving regular preventer treatment the severity of their asthma is classified in terms of control ranging from good control to poor control. (5)

#### **1.3.5 Criteria for diagnosis**

Diagnosis of asthma is based on the patient's history, physical examination and supportive diagnostic testing (such as spirometry). Spirometry can be used in most children six years and over.(5)

Recurrent non-specific cough, chronic suppurative lung disease and exercise-induced respiratory symptoms are often mistakenly diagnosed as asthma.(10)

There are a number of measures of lung function that are used in studies of medicines for asthma and other respiratory diseases. Forced Expiratory Volume in one second (FEV<sub>1</sub>) is the volume of air that can forcibly be blown out in one second, after full inspiration following administration of a bronchodilator. Peak expiratory flow (PEF) is the maximal flow (or speed) achieved during the maximally forced expiration initiated at full inspiration, measured in liters per minute or in liters per second.(13) The change in these measures in an individual patient shows the effectiveness of medicines in reducing the resistance or 'stiffness' of the airways.

### **1.4 Treatment options for asthma in children**

The following treatment options are considered in this Review.

#### **1.4.1 Relievers**

Relievers relieve symptoms of breathlessness quickly by dilating the smooth muscle of the airways in the lungs. These medicines stimulate beta<sub>2</sub>-receptors in the bronchi and bronchioles, which in turn, relaxes the bronchial smooth muscle and makes air flow into the lungs more easily. The most commonly used relievers are short acting beta<sub>2</sub>-agonists (SABA) (salbutamol, terbutaline). Eformoterol (also known as formoterol in USA and Europe), a longer acting beta<sub>2</sub>-agonist can also relieve symptoms of breathlessness quickly but is not recommended by Australian guidelines for use on its own. For children older than 12 years, low-dose budesonide/eformoterol FDC may be used as the reliever medication.

#### **1.4.2 Long-Acting Beta<sub>2</sub>-Agonists**

LABA have a longer duration of action on the smooth muscle of the airways than SABA, some such as eformoterol have quick onset and can therefore be used as a reliever,

while others such as salmeterol have slower onset and must be used in conjunction with a reliever to provide extended relief from symptoms. LABA is not recommended for monotherapy (i.e. without ICS) because of the high risk of exacerbations. The two most commonly used LABAs are salmeterol and eformoterol.

### 1.4.3 Preventers

Preventers provide longer term protection and effectively reduce asthma flare-ups. Preventers include ICS and non-steroidal products including leukotriene antagonists (montelukast) and cromones (sodium cromoglycate and nedocromil sodium).

### 1.4.4 Inhaled corticosteroid comparative potency.

ICS vary in potency and therefore doses are not directly equivalent, Table 1.2 from the Handbook outlines the comparative doses for high and low dose ICS treatment in children.(5)

**Table 1.2. ICS Comparative Potency Table.**

Inhaled corticosteroid	Daily dose (mcg)	
	Low	High
Beclomethasone dipropionate †	100–200	>200 (up to 400)
Budesonide	200–400	>400 (up to 800)
Ciclesonide ‡	80–160	>160 (up to 320)
Fluticasone propionate	100–200	>200 (up to 500)

† Dose equivalents for Qvar® (CFC-free formulation of beclomethasone dipropionate currently available in Australia)

‡ Ciclesonide is registered for use in children aged six and over.

Source: adapted from the Australian Asthma Handbook ID 21.(5)

### 1.4.5 Fixed dose combinations

Fixed dose combinations (FDC) for management of asthma combine a LABA with an ICS in a single device for inhalation. The current combinations listed on the PBS are salmeterol and fluticasone, and eformoterol and budesonide and fluticasone and eformoterol.

### 1.4.6 PBS listed medicines

The list of PBS subsidised medicines and their costs in Australia as of March 2014 is included at [Appendix C](#).

## 1.5 History of PBS Listings

### 1.5.1 Fluticasone

The PBAC listed Fluticasone (Flixotide®) in 1989.

### 1.5.2 Montelukast

The PBAC considered montelukast sodium tablets (Singulair®) on nine occasions between June 1998 and July 2009. In December 2001 PBAC recommended the montelukast sodium 4 mg and 5 mg tablets for listing for use in children with frequent intermittent or mild persistent asthma, the PBAC recommended an authority required listing. In December 2003 the PBAC recommended that the authority required listing should remain. At the July 2009 meeting PBAC recommended a second restriction for the 5mg tablets: prevention of exercise-induced asthma in a child aged 6-14 years as an alternative to adding a LABA for symptom relief.

### 1.5.3 Fluticasone / salmeterol FDC

Salmeterol (Serevent®) was first considered by PBAC in May 1993, it was accepted that salmeterol was cost effective in reducing nocturnal wakefulness in patients who were taking maximal doses of inhaled corticosteroid. The studies considered by the PBAC were all in adult patients with a range of conditions including uncontrolled symptoms of moderate or severe asthma. Salmeterol was first listed in February 1995.

PBAC recommended fluticasone propionate with salmeterol xinafoate fixed dose combinations (Seretide®) in March 2000. The PBAC concluded that there would be no difference in clinical effectiveness or safety between the combination product and the individual component products administered separately and that the combination was a convenient product, and titration of doses was manageable.

### 1.5.4 Budesonide / eformoterol FDC

Eformoterol (Oxis®) was considered in December 1996 and recommended for listing on the basis of cost minimisation to salmeterol. Eformoterol was listed on the PBS in May 1997.

PBAC recommended budesonide with eformoterol fixed dose combinations (Symbicort®) in March 2002. Initially the budesonide/eformoterol 200/6 mcg formulations was listed, then subsequently the 400/12 mcg (August 2004) and 100/6 mcg (April 2005). PBAC recommended a further application to amend the restrictions of the two lower strengths to include use as reliever as well as for maintenance in patients with uncontrolled asthma symptoms (March 2007).

### 1.5.5 Mometasone / eformoterol FDC

The PBAC considered a submission to list mometasone with eformoterol (Zenhale®) on the PBS in July 2013. The product is currently not listed on the ARTG.

### 1.5.6 Fluticasone / vilanterol FDC

The PBAC considered fluticasone furoate with vilanterol trifenate (Breo Elipta®) at the March 2014 meeting. The PBAC recommended PBS listing on a cost minimisation basis to fluticasone propionate with salmeterol

## 1.6 Guidelines for management of asthma in children

Asthma cannot be cured but appropriate management can control the disease and enable people to enjoy a good quality of life.(4) In addition to using medication, children with asthma are advised to avoid their asthma triggers. These triggers vary and may include allergy, irritants (air pollutants, tobacco smoke), gases and chemicals, cold air exposure, exercise, viral respiratory infections and gastro-oesophageal reflux disease.(5)

The National Asthma Council of Australia (NAC) provides clinical guidelines for Australia. The most recent version of the Australian Asthma Handbook (The Handbook) was released in March 2014.(5)

There is broad international consensus on the therapeutic management of asthma. The United Kingdom (14) and Canada (15) publish national guidelines. The Global Initiative for Asthma (GINA) publishes a global strategy report.(16) These guidelines all recommend a step-wise approach to asthma management and provide similar recommendations at each step.

Step 1: Inhaled short-acting beta<sub>2</sub>-agonists (SABA) are recommended as intermittent first line reliever treatment in both adults and children.

Step 2: When asthma is not well controlled with a reliever alone, the addition of low dose ICS is recommended. The Handbook recommends leukotriene receptor antagonists (LTRA) over low-dose ICS as first line preventer treatment in children with frequent intermittent or mild persistent asthma, while low-dose ICS is recommended over LTRA as first line preventer treatment for all age groups in the UK and GINA guidelines, in adults and children over six in the Canadian guidelines.

Step 3: When asthma is not well controlled with ICS alone:

- In adults, all guidelines recommend adding LABA to ICS. LABAs are approved for use in adults and children over five years. Safety concerns related to an increased risk of severe asthma exacerbations with LABAs led to recommendations for LABAs to only be used in combination with ICS and only in patients who are already on ICS (17).
- In children four years and under, the use of LABAs in combination with ICS is never recommended because of the lack of data.
- In children between 6 to 12 years of age, the guidelines all provide the option to the prescriber to add LABA to ICS when the child is not adequately controlled on ICS alone, although the non-stabilising dose of ICS varies slightly across guidelines.
- The use of a single combination inhaler of budesonide with eformoterol (18) as a rescue medication and a preventer therapy is also considered in the British and GINA guidelines for the management of patients 12 years and over. This

combination is not licensed for use in children less than 12 years. The individual international guideline recommendations appear in [Appendix D](#).

## **1.7 Review Terms of Reference**

1. Review the evidence on the efficacy and safety of single ingredient and combination product use of inhaled long-acting beta<sub>2</sub>-agonist in children not previously considered by the PBAC in making recommendations to the Minister.
2. Review the DUSC report on utilisation of combination inhaled corticosteroid (ICS)/ long-acting beta<sub>2</sub>-agonists (LABA) considered by PBAC and supplement this analysis with any additional data and clinical information sources available in Australia.
3. Identify areas of prescribing for childhood asthma in Australia where clinical practice is inconsistent with clinical guidelines; and if there is evidence that supports this practice.
4. Identify and review recent (past five years) healthcare professional and consumer education in the area of medication management in children with asthma.
5. Identify effective interventions that have resulted in improvement of prescribing and quality use of medicines in the context of childhood asthma using overseas or Australian literature.

## Section 2: ToR 1

### Safety and efficacy of LABA and ICS combinations

Review the evidence on the efficacy and safety of single ingredient and combination product use of inhaled long-acting beta<sub>2</sub>-agonist in children not previously considered by the PBAC in making recommendations to the Minister.

#### 2.1 Key findings for ToR 1

##### **Literature review part one**

- *In children with poorly controlled asthma no improvement was found when LABA was added to ICS over treatment with same dose ICS in preventing asthma exacerbations requiring corticosteroids or hospitalisation. This differs from evidence in adults which shows that commencing a LABA/ICS does significantly reduce the risk of exacerbations requiring oral corticosteroids compared to same dose ICS.*
- *The addition of LABA to ICS is more effective than same dose ICS for improving lung function (FEV<sub>1</sub>) but this was not found to translate into a reduction of other symptoms in children. No difference was found when LABA added to ICS was compared to higher dose ICS in preventing exacerbations requiring corticosteroids or hospitalisation, or in changing measures of FEV<sub>1</sub> in children.*
- *ICS/LABA was found to significantly improve morning and evening PEF compared to higher dose ICS, but this was not found to translate into a reduction in other symptoms in children*
- *Higher doses of ICS were found to reduce short term rate of growth in children more than ICS/LABA.*
- *A meta-analysis of trials reported a higher risk of hospitalisation for children taking LABA alone; however there is no significant difference in hospitalisations for the group taking the FDC.*

##### **Literature review part two**

- *A review of the published literature since 2000 did not find any trials or studies that assessed the efficacy and/or safety of combination LABA/ICS used intermittently for asthma symptoms or respiratory conditions other than asthma.*
- *There is trial evidence to support the maintenance of effect (measured as improvement in FEV<sub>1</sub>) of LABA/ICS compared to same dose ICS; however there is insufficient data to draw any conclusions regarding the maintenance of effect when compared to higher dose ICS over 28 weeks.*
- *The comparability of FDC with ICS and/or montelukast in exercise-induced asthma is difficult to interpret owing to the reliance on heterogeneous small studies of short duration.*
- *The development of tolerance to LABA (e.g. through down-regulation of beta receptors) has limited support. In one study of 8 weeks duration comparing FDC to the same dose of ICS the primary outcome was salbutamol (a SABA) response following cold-air challenge. The comparative results showed that there was no significant difference in lung function (FEV<sub>1</sub>) following cold air challenge at eight weeks, however*

*there was a significant reduction in response to SABA in the LABA/ICS group at 8 weeks.*

- *There is conflicting evidence on the association between genetic polymorphism and asthma outcomes in children and adults treated with LABA/ICS.*

### **Stakeholder input from the Forum and submissions on Terms of Reference**

- FDCs should not be used to treat children under the age of five years as there is a lack of evidence on effectiveness and safety in this age group.
- LTRA have shown promise in the treatment of exercise induced bronchoconstriction. Based on the current evidence, the PBS restriction that prevents use in combination with an ICS should be reviewed.
- The impact of ICS on growth and other side effects are of concern to both parents and prescribers. However stakeholders noted that any concerns about using FDCs in children were not widely discussed.
- A perception of greater risk is associated with older established treatments such as ICS when comparing with the potentially incomplete side effect profile of FDCs. The selection of patients in whom there is evidence of the risk and benefit of treatment with ICS alone and FDC is well known and well covered in guidelines but prescribers, considering a range of clinical, social and other factors may choose to disregard the guidelines.
- Use of FDCs has been associated with non-responsiveness to treatment, based on development of tolerance to the LABA component. Tolerance to reliever medication can make treating asthma flare-ups difficult.
- The child relevant outcomes identified by stakeholders are not routinely measured in clinical trials.

## **2.2 Published evidence**

The literature review *Efficacy and safety of LABA and ICS for asthma in children* was conducted by the Quality Use of Medicines and Pharmacy Research Centre (QUMPRC) at the University of South Australia. The literature review was conducted in two parts, part one addresses the efficacy and safety of LABA/ICS versus ICS, while part two deals with additional research questions which arose during the course of the Review. The literature review including the detailed search strategy and located articles is appended at [Appendix E](#).

The PBAC has previously considered only one study conducted in children treated with FDCs. This study compared the use of FDC with the individual components administered concomitantly in children 4-11 years (Van den Burg et al; 1998). Studies comparing the use of a FDC or concomitant LABA plus ICS to increased doses of an ICS enrolled adolescents and adults only. All studies enrolled subjects who had symptomatic asthma requiring treatment with an ICS and either LABA or SABA or both. Therefore the literature searching for this review has been conducted from 2000 onwards.

### **2.2.1 Literature review part one**

1. What is the evidence on the efficacy of combinations of LABAs and ICS as preventers versus same or higher doses of ICS in children with asthma (children <5, 5 to 12 years, ≥12 to <18 years) according to severity of asthma?
  - a. Addition of LABA to ICS versus same dose of ICS
  - b. Addition of LABA to ICS versus higher dose of ICS
  - c. Corticosteroid-naive children with uncontrolled asthma
2. What is the evidence on the safety of combinations of LABAs and ICS in children (children <5, 5 to 12 years, ≥ 12 to < 18 years) according to severity of asthma?
  - a. Asthma-related deaths and other harms
  - b. Effect on growth rates

### **2.2.2 Literature review part two**

1. What is the evidence on the efficacy and safety of intermittent or episodic use of the combination of LABA with ICS for asthma in children?
2. What is the evidence on the efficacy and safety of the combination LABA/ICS for respiratory conditions other than asthma in children?
3. What is the evidence on the possible down-regulation of beta receptors in children taking LABA/ICS that may render SABA less effective and results in loss of protection in exercise induced asthma?
  - a. Is the effect of ICS/LABA maintained over time, in respect to asthma outcomes such as asthma exacerbations and FEV<sub>1</sub>?
  - b. What is the evidence on the efficacy of LABA/ICS treatment for exercise induced bronchoconstriction?
  - c. What is the evidence on the association between genetic polymorphisms and asthma outcomes in children receiving LABA/ICS?

## **2.3 Summary of review methodology**

### **2.3.1 Search strategy literature review**

The literature search for part one involved a two-tier process:

- identification of systematic reviews and meta-analyses of the literature from January 2000 to August 2012; and
- identification of randomised controlled trials (RCTs) and large (>500) observational studies not included in the systematic reviews to August 2012. The search for observational studies was updated up to the end of November 2013.

Only English language references were sought. The search strategy comprised four electronic databases (Cochrane Library, Medline, Embase, PubMed). Two manufacturer's clinical trial websites, Glaxo Smith Kline and AstraZeneca, were also searched to identify other published or unpublished RCTs, individual companies were not approached.

Titles and abstracts of publications identified in the search were reviewed independently by two reviewers. Citations that clearly did not fit the inclusion criteria below were excluded. Full text of all remaining citations were obtained and assessed for eligibility.

The criteria considered for inclusion of evidence included:

- Populations: children with asthma;
- Interventions: LABA and ICS;
- Comparisons: LABAs and ICS versus same or higher doses of ICS;
- Outcomes:
  - Standardised outcomes for clinical research in asthma have been recently proposed by the National Institutes of Health (NIH) and the Agency for Healthcare Research and Quality (19). Recommendations for core asthma outcomes for efficacy in trials where children are participants include exacerbations (requiring use of systemic corticosteroids or hospitalisations or emergency department visits), death, and spirometry results such as FEV<sub>1</sub>.
  - Primary outcomes: exacerbations (requiring use of systemic corticosteroids or hospitalisation), lung function (FEV<sub>1</sub>),
  - Secondary outcomes: lung function (measured as PEF), quality of life, symptom scores, symptom-free days, use of relief medication, withdrawals, adverse effects, growth.

A similar search strategy was undertaken for part two of the literature review: for further detail see [Appendix E](#).

### **2.3.2 Quality assessment**

Quality of the systematic reviews was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.(20) Quality was assessed by two reviewers independently and any discrepancy was resolved by discussion.

Quality of RCTs was assessed using the Cochrane Collaboration's Tool for assessing risk of bias.(21) The assessment of quality for articles included in a Cochrane Review was accepted in this report. For RCTs not included in the Cochrane systematic reviews, quality was assessed by two reviewers independently and any discrepancy was resolved by discussion.

The overall quality of evidence for each question and primary outcome was graded using the GRADE guidelines.(22)

The overall quality of evidence was assessed by two reviewers independently and any discrepancy was resolved by discussion. The GRADE assessment was done by the authors of the literature review based on the information provided in the Cochrane Reviews when the GRADE assessment was not reported in the reviews.

### **2.3.3 Data extraction and analysis**

Characteristics of systematic reviews and RCTs and results for all outcomes were extracted and cross-checked by a second reviewer. Evidence synthesis of all the existing systematic reviews and additionally identified RCTs was carried out using a narrative review for each research question. Where there was incomplete reporting of information in the systematic reviews data were verified using the original papers.

## **2.4 Efficacy of adding LABA to ICS versus same dose of ICS**

*Research question 1a: does adding LABA to ICS increase the effectiveness of therapy compared to the same dose of ICS alone?*

*The evidence: In people aged 17 years or under with poor asthma control while being treated with regular ICS there is:*

- *no statistically significant reduction in the number of exacerbations of asthma through the addition of a LABA to ICS; and*
- *a statistically significant improvement in measures of lung function.*

*The studies have substantial heterogeneity and the reported effectiveness in the meta-analyses in the Cochrane Reviews have wide confidence intervals.*

*The clinical importance of the observed differences in lung function results is poorly quantified. The differences are expected as the currently available LABAs are bronchodilators.*

The search extracted two Cochrane Reviews (23, 24) with the same 20 paediatric trials in each publication. Two additional studies (25, 26) were also extracted, the children in all the studies had established corticosteroid treatment of at least 28 days duration.

The outcomes of interest were reported in a limited number of the 20 studies extracted for the Cochrane Reviews. The outcomes of exacerbations of asthma requiring oral corticosteroids and/or hospitalisation were reported in 11 studies. (23, 26) There was no significant difference in the number of exacerbations (defined as requiring oral corticosteroid or hospital admission) as a result of adding a LABA to the ICS compared to maintaining children on the same dose ICS (Table 2.1). For the outcome of change in number of exacerbations the quality of the studies in the Cochrane Review is considered low as measured by GRADE method. Because of the low number of RCTs and inconsistent reporting, the authors of the Cochrane Reviews stated that the impact of

baseline severity of airway obstruction, baseline dose of ICS, type of LABA (salmeterol or eformoterol), or trial duration could not be examined on the primary outcome of exacerbations requiring systemic steroids. There was only one trial of 32 participants with eformoterol that examined exacerbations requiring systemic steroids.

The measures of lung function (FEV<sub>1</sub> change at endpoint or change in % predicted at endpoint) were reported in 14 studies in the Cochrane Review and in Carroll 2010. There was a significant increase in FEV<sub>1</sub> following addition of a LABA to an ICS (no dose escalation). (Table 2.1).

**Table 2.1. Results for exacerbations and changes in FEV<sub>1</sub> in RCTs comparing addition of LABA to ICS versus same doses of ICS in children with poor asthma control**

Outcomes	Comparative risks		Relative effect (95% CI) p value	No participants (No. RCTs)	Quality of the evidence (GRADE)
	LABA with ICS	ICS			
Exacerbations (requiring systemic corticosteroids )	63 per 1000	68 per 1000	RR 0.92 (0.60,1.40) p = 0.69	1084 (8 studies)*	Low
Exacerbations (requiring hospital admissions)	31 per 1000	19 per 1000	RR 1.65 (0.83, 3.25), p = 0.15	1266 (6 studies)*	Low
Exacerbations (systemic corticosteroid urgent care, emergency room visit, and admission)			HR = 0.971	339 (GSK 113872)	Not provided
FEV <sub>1</sub> Changes in L at endpoint			<b>WMD 0.08 L (0.06, 0.11) p &lt; 0.00001</b>	Not able to be determined for all studies (9 studies)	Moderate
FEV <sub>1</sub> % predicted at endpoint			<b>WMD 2.35% (0.07, 4.64) p = 0.044</b>	476 (5 studies)	Moderate
FEV <sub>1</sub> % predicted			<b>MD 1.6%</b>	39 (Carroll W)	Not provided
Change in morning PEF at endpoint			<b>MD (L/min) 10.38 (8.23,12.52) P&lt;0.0001</b>	2934 (14 studies)	Not provided
Change in evening PEF at endpoint			<b>MD (L/min) 9.37 L/min (6.96,11.79) P,0.00001</b>	2636 (11 studies)	Not provided

RR: risk ratio; WMD: weighted mean difference. Compiled from information in Appendix E

\* 3 studies reported exacerbations requiring hospital admissions and systemic corticosteroids

Additional endpoints were measured in a number of trials and are reported in the Cochrane Review reported in the previous paragraph. There was a significantly greater improvement in morning and evening PEF in a number of studies. There were no statistically significant differences across a number of patient relevant outcomes including mean symptom scores, number of symptom-free days, percentage of days

where relief medication was not required, quality of life, adverse effects, serious adverse events, or withdrawals due to poor asthma control. Withdrawals for any reason were 21% less likely to occur in the groups where LABA was added to ICS compared to maintaining children on same dose ICS (RR 0.79, 95% CI 0.67 to 0.93,  $p = 0.006$ ). Two RCTs (25, 26) that were not included in the Cochrane Review found results consistent with these findings.

Another Cochrane Review (24) included a comparison of adults and children for the same outcomes. This review reported that evidence suggests there are differential effects of adding LABA to ICS in children compared to those seen in adults. This review found no significant difference in asthma exacerbations requiring oral corticosteroids when LABA was added to ICS in children (RR 0.89, 95% CI 0.58 to 1.39,  $P = 0.61$ ). In contrast, asthma exacerbations were reduced by 23% when LABAs were added to ICS in adults (RR 0.77, 95% CI 0.68 to 0.88,  $p=0.000052$ ).

## 2.5 Efficacy of addition of LABA to ICS compared to higher dose of ICS

*Research question 1b: does adding LABA to ICS increase the effectiveness of therapy compared to a higher dose of ICS alone?*

*The evidence: when adding LABA to ICS in people 17 years or less with poor asthma control was compared with increasing the dose of the ICS there was:*

- *no significant difference in the risk of exacerbations (low strength of evidence);*
- *or in change in FEV<sub>1</sub> (high strength of evidence) between group, and*
- *a greater improvement from baseline in the change in morning or evening PEF compared to increasing the dose of ICS.*

*The studies have substantial heterogeneity and the reported effectiveness in the meta-analyses in the Cochrane Reviews has wide confidence intervals.*

*The clinical importance of the observed differences in only one measure of lung function (morning and evening PEF) is poorly quantified.*

A 2009 Cochrane review (23) pooled the results of seven RCTs that assessed the addition of LABA to ICS versus an escalating dose of ICS alone in children. Five of the trials assessed salmeterol and two trials assessed eformoterol.(23) The control groups received double the ICS dose in all studies except one where the ICS dose was higher than double. A total of 1,082 children were randomised. All children in the studies had poor asthma control (prior treatment with ICS for 28 days). In most of the studies asthma was considered to be poorly controlled.

There was no significant difference in asthma exacerbations among children when LABA was added to ICS or the ICS dose was doubled (Table 2.2). The evidence also shows no significant difference in FEV<sub>1</sub>. Adding LABA to ICS was associated with a significantly greater improvement in morning PEF (MD 7.55 L/min 95%CI,

3.57 to 11.53,  $p=0.0002$ ) and evening PEF (MD 5.5 L/min, 95% CI, 1.21 to 9.79,  $p=0.012$ ). There was no difference in adverse effects, serious adverse effects, total withdrawals or withdrawals due to adverse effects.

**Table 2.2. Results for exacerbations in trials comparing addition of LABA to ICS versus higher doses of ICS in children with asthma (23, 27)**

Outcomes	Comparative risks		Relative effect (95% CI, P value)	No of participants (RCTs)	Quality of the evidence (GRADE)
	LABA with ICS	ICS			
Exacerbations (requiring oral corticosteroids)	54 per 1000	36 per 1000	RR 1.5 (0.65 to 3.48) $p = 0.34$	441 (2 studies)	Low
Exacerbations (requiring hospital admissions)	17 per 1000	6 per 1000	RR 2.21 (0.74 to 6.64) $p = 0.16$	1026 (4 studies)	Low
Morning PEF			<b>MD 7.55L/min (3.57, 11.53)</b> <b><math>p=0.0002</math></b>	4 studies	Not provided
Evening PEF			<b>MD 5.5L/min (1.21, 9.79)</b> <b><math>P=0.012</math></b>	3 studies	Not provided
FEV <sub>1</sub> Changes in L at endpoint			WMD 0.01 L (-0.03 to 0.05) $p < 0.47$	544 (2 studies)	High

RR: risk ratio; WMD: weighted mean difference. MD mean difference . Compiled from information provided in Appendix E.

The evidence suggests there are differential effects of adding LABA to ICS in children compared to those seen in adults. There is a separate Cochrane Review that included trials in adults and children.(28) It included the same paediatric trial data as the review described above (23) and additional data from one study that included both children and adults. Consistent with the previous findings, the evidence showed no difference in asthma exacerbations requiring oral corticosteroids in children when either adding a LABA to ICS or increasing the dose of ICS (RR 1.24, 95% CI 0.58, 2.66,  $p=0.59$ ). When limiting the analysis to adults, the evidence showed that adding a LABAs to an ICS resulted in a 13% decrease in the risk of asthma exacerbations requiring oral corticosteroids compared to increasing the dose of ICS (RR 0.87, 95% CI 0.78, 0.97,  $p=0.01$ ). For exacerbations requiring hospitalisation, there was no-statistically significant difference overall but the effects were in opposite directions in adults compared to children: RR was 0.87 (95% CI 0.54, 1.38,  $p=0.55$ ) in adults, showing a trend towards decreased risk of hospitalisation with the combination of ICS and LABA, and 2.21 (95% CI 0.74, 6.64,  $p=0.16$ ) in children (<18 years old), showing an increased risk of hospitalisation with the combination of ICS and LABA.

### **2.5.1 Corticosteroid-naive children with uncontrolled asthma**

*Research question 1c: what is the comparative effectiveness of using LABA plus ICS compared to ICS alone in corticosteroid-naive children with uncontrolled asthma.*

*Evidence: There is insufficient published data to enable any conclusion regarding the comparative benefit of selecting a combination of LABA and ICS compared to ICS.*

One Cochrane Review was identified in the search (27), no additional studies were identified. This Cochrane Review compared the efficacy of LABA plus ICS with ICS alone in corticosteroid-naive children and adults with persistent asthma. The review included 27 trials of which five trials were in children but only one or two trials in children contributed data to any outcome, thus preventing any subgroup analyses on age.

## 2.6 Safety of single use and combinations of ICS and LABA in children

*Research question 2a: are there any differences in the safety profiles of single or separate use ICS and LABA compared to fixed dose combinations of ICS and LABA?*

*The Evidence:*

- *Use of LABA alone is associated with an increased risk of asthma related death;*
- *There is weak evidence that the use of regular LABA with intermittent ICS is associated with an increased risk of asthma related deaths in young children. The FDA has required the manufacturers of LABAs to conduct five RCTs comparing the addition of LABA to ICS versus ICS alone and one of these studies is in children. These results will be available in 2017; and*
- *There is no reported difference in asthma related deaths for people taking a LABA and ICS concomitantly or an ICS with non-LABA therapy.*

*The FDA meta-analysis was undertaken on RCTs provided by drug companies, but was limited to products and doses approved for use in the US. These studies are predominantly in children with persistent asthma and in adults with moderate to severe asthma requiring regular therapy. The results in children rely on a small number of studies but are consistent with the evidence on exacerbations requiring hospital admissions in clinical trials.*

The literature search identified a meta-analysis undertaken by the US Food and Drug Administration (FDA) in 2008 that included patient-level and trial-level data provided by sponsors of LABAs.(29) The meta-analysis included a total of 110 trials involving 60,954 patients of which 9,807 were children less than 18 years.

The main outcome reported was a combined end point of asthma-related deaths, intubations and hospitalisations. The analysis assessed risk by age groups including 4 to 11 years and 12 to 17 years. Asthma-related hospitalisations represented the majority of events of the combined endpoint (95% to 99% in all age groups). An extended meta-analysis of these data using incidence difference estimates (events per 1,000 patient-years) per age group was also reported.(30)

The FDA meta-analysis showed that the use of LABAs alone in both adults and children with asthma significantly increased the risk of asthma-related hospitalisations and death compared to non-LABA treatment (ICS, SABA, other non-LABA treatments, placebo, or a combination of treatments)

The risk of death (risk difference) associated with LABA alone was greatest in younger patients. Similarly the incidence difference was greatest however interpretation of this result is limited by the small number (2) of asthma-related deaths in children under 18 which made it impossible to draw any conclusion on this outcome. The incidence difference for the whole population was not significant when comparing studies where the LABAs and ICS were both randomly assigned to one group and ICS with other treatments were randomly assigned to the other group: incidence difference 0.4 events, (95% CI -3.8, 4.6,  $p = 0.685$ ). The analysis also found a statistically significant incidence increase of 6.1 events per 1000 patient-years (95% CI 0.9, 11.4,  $p=0.006$ ) in studies of LABAs with concomitant ICS (defined as randomly assigned or recorded to have taken ICS at baseline) in comparison to concomitant ICS without LABAs. The authors suggested that the apparent different findings between concomitant and randomly assigned ICS use may be due to a lack of power in the studies to detect a difference or that concomitant ICS use was primarily occasional ICS use.

**Table 2.3. Incidence and risk difference estimates for combined end point according to age for LABA versus no-LABA therapy.(29, 30)**

Age group (years)	Risk difference estimate Events per 1000 patients (95% CI) (29)			Incidence difference estimate Events per 1000 patient-years (95% CI) (30)		
	Overall effect (LABA with or without randomly assigned ICS versus non LABA)	LABA without randomly assigned ICS versus non LABA	LABA with randomly assigned ICS versus non LABA	Overall effect (LABA with or without randomly assigned ICS versus non LABA)	LABA with randomly assigned ICS versus non LABA with assigned ICS	LABA with concomitant ICS (randomly assigned or recorded to have taken ICS at baseline) versus non LABA with concomitant ICS
<b>4 to 11</b>	14.83 (3.24 to 26.43)*	NR	NR	30.4 (5.7,55.1)*	-7.5 (-30.3, 15.4)**	48.5 (7.2, 89.7)*
<b>12 to 17</b>	5.57 (0.21 to 10.92)*	NR	NR	11.6 (- 0.5, 23.7)**	7.6 (-4.5, 19.7)**	11.1 (-5.4, 27.5)**
<b>18 to 64</b>	2.13 (0.34 to 3.91)*	NR	NR	4.8 (0.5, 9.1)**	- 1.6 (-6.3, 3.1)**	5.1 (-0.6, 10.7)**
<b>≥ 65</b>	- 3.58 (-10.47 to 3.32)**	NR	NR	- 10.6 (- 28.4, 7.3)**	21.1 (1.8, 40.5)*	-8.4 (-30.1, 13.3)**
<b>Total</b>	2.80 (1.11, 4.49)*	3.63 (1.51, 5.75)*	0.25 (-1.69, 2.18)**	6.3 (2.2, 10.3)*	0.4 (-3.8, 4.6)**	6.1 (0.9, 11.4)*
<b>Statistical significance between age groups</b>				p = 0.020	p = 0.685	p = 0.006

\*Statistically significant, P value not reported

\*\*Non statistically significant, P value not reported

The literature search identified a Cochrane overview of Cochrane systematic reviews (31) that included an assessment of serious adverse events reported in clinical trials reported on manufacturers' website, in FDA submissions, and in medical journals. A serious adverse event was defined as 'any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect'. The occurrence of non-fatal serious adverse events from combination therapy of LABAs and ICS compared to ICS alone in children was not statistically significant (Table 2.4). A single child died in all the studies so mortality could not be assessed.

**Table 2.4. Summary of findings - children with a serious adverse event(31).**  
**Note: table modified from Cochrane Review.**

Comparison	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	LABA and ICS	ICS			
<b>Children with a non-fatal serious adverse event of any cause</b>					
<b>Regular eformoterol &amp; ICS versus ICS Cates 2009b</b> Follow-up: mean 13 weeks	<b>8 per 1000</b>	<b>14 per 1000</b> (7 to 27)	<b>OR 1.62</b> (0.80 to 3.28)	2788 (7 studies)	⊕⊕⊕⊖ <b>moderate</b> <sup>1</sup>
<b>Regular salmeterol &amp; ICS versus ICS Cates 2009a</b> Follow-up: mean 15 weeks	<b>5 per 1000</b>	<b>6 per 1000</b> (2 to 19)	<b>OR 1.20</b> (0.37 o 3.91)	1862 (5 studies)	⊕⊕⊕⊖ <b>moderate</b> <sup>1</sup>
<b>Children with a non-fatal serious adverse event related to asthma</b>					
<b>Regular eformoterol &amp; ICS versus ICS Cates 2009b</b> Follow-up: mean 13 weeks	<b>4 per 1000</b>	<b>6 per 1000</b> (2 to 17)	<b>OR 1.49</b> (0.48 to 4.61)	2788 (7 studies)	⊕⊕⊕⊖ <b>low</b> <sup>1,2</sup>
<b>Regular salmeterol &amp; ICS versus ICS Cates 2009a</b> Follow-up: mean 15 weeks	<b>1 per 1000</b>	<b>1 per 1000</b> (0 to 17)	<b>OR 0.99</b> (0.06 to 15.85)	1862 (5 studies)	⊕⊕⊕⊖ <b>low</b> <sup>1,2</sup>

\*The basis for the **assumed risk** was the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).  
CI: Confidence interval; OR: Odds ratio; SAE: serious adverse event

1. Confidence intervals include the possibility of an increase and a decrease in SAEs on regular LABA
2. Considerable heterogeneity between trial results

Uncertainty still exists regarding the safety of LABAs combined with ICS compared to ICS alone. For this reason, the FDA has required the manufacturers of LABAs to conduct five randomised, double-blind, controlled clinical trials comparing the addition of LABAs to ICS versus ICS alone(32). Four clinical trials will be conducted in adults and adolescents over 12 years enrolling a total of 46,800 patients. One trial of fluticasone and salmeterol will be conducted in children aged 4 to 11 years and will include 6,200 patients. This sample size of 6,200 will provide 90% power to rule out a 2.7-fold

increase in relative risk in children(33). Patients in all trials will be treated for six months, and the primary endpoint will be a composite of serious asthma outcomes: asthma-related death, intubation, or hospitalisation. The paediatric trial will also assess other relevant quality of life endpoints such as days of school missed and emergency room visits because of asthma related illness. Results of these trials are expected to be available in 2017.

### **2.6.1 Effects on growth**

*Research question 2b: Is there any evidence of a change in growth rates in children who receive combination LABA compared to ICS alone?*

*The Evidence: There is limited evidence to conclude that ICS alone compared to combination LABA with ICS results in differential growth rates. The dose of ICS is likely to be an important factor.*

There are concerns raised in the literature and by consumers that prolonged or increased exposure to ICS reduces the rate of growth in children and can result in lower than expected height.

The literature review identified two studies,(34, 35) included in a Cochrane Review.(23) A single trial comparing the effect of LABA (salmeterol) and ICS (400 mcg beclomethasone) with same dose ICS on growth reported no statistically significant group difference in growth velocity over 52 weeks in 117 children with a mean age of 10 to 11 years (5.1cm versus 4.5 cm respectively).(34)

Two trials comparing LABA and ICS versus double dose of ICS in 343 children measured growth over one year.(34, 35) Growth was significantly greater in children treated with combination therapy (MD 1.2 cm/year; 95% CI 0.72, 1.7, p<0.00001).

## **2.7 Literature review part two**

*Research question 1: What is the evidence on the efficacy and safety of intermittent or episodic use of the combination of LABA with ICS for asthma in children?*

- *A review of the published literature between 2000 and 2014 did not find any trials or studies that assessed the safety and/or efficacy of short term or intermittent use of combination LABA/ICS in children for asthma.*

While not directly answering this question, the following study is discussed briefly as it presents evidence on the use of intermittent LABA/ICS in addition to maintenance treatment according to the Symbicort Maintenance and Reliever Therapy (SMART) protocol. This 12-month randomised controlled trial compared the combination of LABA/ICS as maintenance treatment plus additional inhalations for symptom relief (SMART) versus a fixed dose of the combination LABA/ICS and versus ICS in children with persistent asthma (35). The third arm of the study, a comparison of the fixed dose of combination LABA/ICS versus fixed dose ICS is included in a Cochrane systematic review previously reported (23) The comparison of the SMART combination LABA/ICS

versus fixed dose ICS is reported in another recent Cochrane systematic review (36). In both LABA/ICS groups, children were receiving a minimum fixed daily dose of the combination. Therefore, the results of this trial cannot answer the question of the clinical relevance of intermittent or episodic use of LABA/ICS for asthma in children.

*Research question 2: What is the evidence on the efficacy and safety of the combination LABA/ICS for respiratory conditions other than asthma in children?*

- *There were no trials or studies identified between 2000 and 2014 that assessed the safety and/or efficacy of combination LABA/ICS in respiratory conditions other than asthma in children.*

*Research question 3: What is the evidence on the possible down-regulation of beta receptors in children taking LABA/ICS that may render SABA less effective and results in loss of protection in exercise induced asthma?*

Development of tolerance to the effect of beta<sub>2</sub> agonists has been proposed as a possible explanation for the increased risk of asthma-related deaths and hospitalisation observed in children receiving LABAs only. These findings led to the development of the current clinical guidelines for asthma which recommend against the use of regular SABAs and against the use of regular LABAs without concomitant use of ICS treatment (refer to [Appendix E](#): Literature review part A, report p.17).

Research question 3 has been addressed by the following three sub-questions.

*Research question 3a. Is the effect of ICS/LABA maintained over time, in respect to asthma outcomes such as asthma exacerbations and FEV<sub>1</sub>?*

- *There is trial evidence to support the maintenance of effect (measured as improvement in FEV<sub>1</sub>) of LABA/ICS compared to same dose ICS from 6 to 28 weeks in children (as reported in part 1), however there is insufficient data to draw any conclusions regarding the sustained effect of combination LABA/ICS compared to higher dose ICS over the same period.*

The previous report presented the results of a Cochrane review comparing LABA/ICS to the **same** dose of ICS alone in children with uncontrolled asthma who had required treatment with ICS for at least 28 days prior to commencing the study (23). The authors sought to assess the impact of trial duration on the magnitude of effect. A meta-analysis could not be performed for the primary outcome of exacerbations requiring systemic steroids because of the low number of trials and inconsistent reporting of characteristics. The duration of treatment did not affect the magnitude of improvement in FEV<sub>1</sub> over time (Chi<sup>2</sup> = 0.08, p = 0.96). The authors concluded that the sustained effect of LABA, in combination with ICS, from six to 24 weeks did not support the development of tolerance.

The same Cochrane review (23) compared the combination of ICS with LABA to higher doses of ICS. The results, reported in section 2.5, found a trend towards an increased risk of asthma exacerbations and a modest improvement in morning and evening PEF but no difference in FEV<sub>1</sub> observed with the combination LABA/ICS compared to ICS. An analysis of the impact of trial duration could not be performed because of the low number of trials. The authors suggested that either persisting inflammation related to the use of a lower dose of ICS in the combination product or tolerance caused by the prolonged use of LABA may explain these results.

*Research question 3b. What is the evidence on the efficacy of LABA/ICS treatment for exercise induced bronchoconstriction?*

- *Five small trials report conflicting results on the efficacy of LABA/ICS compared to ICS or montelukast for exercise induced asthma.*
- *These trials were conducted over a maximum of four weeks and provide insufficient evidence to determine if any inferior effect was caused by the development of tolerance to LABAs because of the limited data available over the treatment course and variability in conducting and measuring response to respiratory challenges.*
- *One small trial of 8 weeks duration compared combination LABA/ICS to the same dose of ICS. (25) The primary outcome was salbutamol response following cold-air challenge. The comparative results showed that there was no significant difference in lung function (FEV<sub>1</sub>) following cold air challenge at eight weeks, however there was a significant reduction in response to SABA in the LABA/ICS group at 8 weeks.*
- *These results suggested a possible tachyphylaxis to the bronchoprotector properties of LABA as shown by the results to cold-air challenge but no tachyphylaxis to the bronchodilator responses as shown by the sustained improvement in FEV<sub>1</sub>.*

Five trials examined the efficacy of LABA/ICS versus several comparators. Although the combination LABA/ICS may be less effective than other treatments such as ICS, montelukast or the combination montelukast/ICS for prevention of exercise-induced bronchoconstriction, there was limited evidence (in the absence of longitudinal data collection over the treatment course) that this inferior effect could be caused by the development of tolerance to LABAs (Table 2.5). Only one small cross-over trial in 14 children included a comparison of the broncho-protective effect at the start and the end of treatment that suggested a smaller effect of LABA/ICS at the end of a 28-day treatment (37).

**Table 2.5. Maximum % fall in FEV<sub>1</sub> after exercise-induced challenge.**

Comparator	Study	Time of exercise challenge	Maximum % fall in FEV <sub>1</sub>		
			LABA/ICS	Mean (SEM) comparator	P value
Placebo	Stelmach (2008)	4 weeks after start treatment	18.9 (0.65)	26.6 (0.61)	< 0.001
ICS	Stelmach (2008)	4 weeks after start treatment	18.9 (0.65)	16.9 (1.00)	0.71
	Simons (1997)	Day 1 (1 hour after dose)	-7	24	0.0001
		Day 1 (9 hours after dose)	6	18	0.0002
		Day 28 (1 hour after dose)	4	16	0.0002
		Day 28 (9 hours after dose)	10	15	0.1
	Pearlman (2009)	4 weeks after start treatment	9.5 (0.8)	12.7 (1.1)	0.021
Murray (2011)	4 weeks after start treatment	9.9 (1.01)	11.1 (1.02)	0.158	
Montelukast	Stelmach (2008)	4 weeks after start treatment	18.9 (0.65)	11.5 (0.97)	< 0.001
Montelukast/ICS	Stelmach (2008)	4 weeks after start treatment	18.9 (0.65)	12.1 (1.13)	< 0.001
	Fogel (2010)	4 weeks after start treatment	13.8	10.6	0.009

Source: Literature Review Part 2, p.22

Another trial of 37 children, average age 10-11 years, assessed the efficacy of FDC versus ICS following cold-air challenge over an eight-week period. (25) The primary outcome was salbutamol response following cold-air challenge. The cold air challenge was undertaken 6 to 8 hours following the morning dose of the medication. Spirometry measurements were done before and three minutes after the cold air challenge, and then 15 minutes after the administration of 1000 µg salbutamol in order to assess salbutamol reversibility. There was no significant difference in the mean maximum percentage decrease in FEV<sub>1</sub> after cold-air challenge with the combination versus ICS alone at eight weeks (3.7% versus 4.6%, p=0.5755). There were reductions in salbutamol reversibility in both groups but the effect was only significant in the combination group at week eight (reduction of 11.4%, p=0.0010). At eight weeks, there were significant improvements in basal FEV<sub>1</sub> (% predicted) (+6.4 %, 95% CI 2.4, 10.5, p=0.0033) in the salmeterol/fluticasone group but not in the fluticasone group (+ 1.2 %, 95% CI -3.4, 5.8, p=0.59). The authors concluded that these results showed tachyphylaxis to the bronchoprotector properties of LABA as shown by the results to cold-air challenge but no tachyphylaxis to the bronchodilator responses as shown by the sustained improvement in FEV<sub>1</sub>.

*Research question 3c. What is the evidence on the association between genetic polymorphisms and asthma outcomes in children receiving LABA/ICS?*

- *There is limited and conflicting evidence on the association between genetic polymorphism and asthma outcomes in children treated with LABA/ICS.*
- *The observational studies identified provide some evidence that there may be an association between increased exacerbations and LABA/ICS exposure in children with the Arg 16 allele. The bias present in these studies makes conclusions about the impact of the medicines and phenotype unreliable but this is an area for further research*
- *In a small pragmatic RCT montelukast plus ICS was more effective than LABA/ICS in children with the Arg/Arg 16 genotype. Children with Arg/Gly genotype were not assessed and the possible association between response to medicine according to phenotype remains unclear.*

Two observational studies (38, 39) showed some evidence of an association between the Arg16 polymorphism and asthma outcomes in children receiving LABA/ICS (refer to table 2.6 and 2.7). While these two studies reported separate results for the LABA/ICS and ICS treatment groups, there was no direct comparison between treatment groups. Thus, it remains unclear whether the risk is worse in children treated with LABA/ICS compared to children treated with ICS alone. The results are somewhat contradictory and difficult to interpret. Basu et al (2009) reported an increased risk of asthma exacerbations per copy of the Arg16 allele in ICS and ICS/LABA-treated children. Zuurhout et al (2013) reported an increased risk of asthma exacerbations in children treated with LABA/ICS but not in children treated with ICS only. It is noted that information on asthma outcomes in these two studies was provided by the participants or their parents and therefore, the results are likely to be affected by recall bias. Furthermore, medicine exposure at the time of exacerbations was not assessed, thus conclusions about the impact of the medicines and phenotype cannot be reliably made.

**Table 2.6. Association of asthma exacerbations and Arg16 genotype in Basu et al 2009 (38)**

<b>Outcome</b>	<b>OR per copy of the Arg16 allele (95% CI, P value)</b>
Overall asthma exacerbations	1.30 (1.09 to 1.55, 0.003)
Oral steroid intake	1.27 (1.07 to 1.56, 0.02)
School absence caused by asthma exacerbations	1.29 (1.07 to 1.54, 0.007)
Hospital admission caused by asthma exacerbations	1.04 (0.82 to 1.34, 0.73)

Literature review part 2, p.29

**Table 2.7. Association of asthma exacerbations and Arg16 genotype in Zuurhout et al 2013 (39)**

<b>Outcome</b>	<b>Genotype 16</b>	<b>ICS only (n = 468)</b>		<b>LABA/ICS (n=129)</b>	
		<b>Odds ratio (95% CI)</b>	<b>P value</b>	<b>Odds ratio (95% CI)</b>	<b>P value</b>
<b>Any exacerbation</b>	Gly/Gly	1 (reference value)		1 (reference value)	

Outcome	Genotype 16	ICS only (n = 468)		LABA/ICS (n=129)	
		Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
	Gly/Arg	0.62 (0.33 to 1.17)	0.14	1.11 (0.18 to 6.99)	0.92
	Arg/Arg	0.43 (0.15 to 1.19)	0.11	12.13 (2.18 to 67.60)	0.004

Source: Literature review Part 2, p.30

One small prospective cohort study did not find an association between the Arg 16 polymorphism and the risk of asthma exacerbation in 98 children with severe asthma receiving LABA/ICS (40) Refer to table 2.8 below.

**Table 2.8. Rates of asthma exacerbations and Arg16 genotype in children on LABA/ICS in Giuburgia 2013. (40)**

Outcome	Arg/Arg n= 20	Arg/Gly n= 38	Gly/Gly n= 39	P value
Overall number of asthma exacerbations	40	88	80	
Asthma exacerbations <sup>1</sup>	2.2 (1.1 to 3.3)	2.4 (1.7 to 3.2)	2.3 (1.6 to 2.8)	0.20
Mild asthma exacerbations <sup>1</sup>	1 (0.5 to 1.4)	1.2 (0.7 to 1.6)	1.1 (0.7 to 1.4)	0.10
Severe asthma exacerbations <sup>1</sup>	2.2 (0.4 to 2)	1.2 (0.7 to 1.7)	1.2 (0.7 to 1.6)	0.30
Asthma-related hospital admissions	1	2	1	0.60

Source Literature Review Part 2, p.31

A pragmatic randomised controlled trial in 62 children with persistent asthma and the homozygous Arg16 genotype found greater efficacy of montelukast compared to salmeterol when added to ICS in terms of school absences (difference in score = -0.40, 95% CI -0.22,-0.58, p=0.005) but did not provide comparative data in children without homozygous Arg16 genotype (41).

## Section 3: ToR 2

### Medicines utilisation analysis

Review the DUSC report on utilisation of combination inhaled corticosteroid (ICS)/long-acting beta<sub>2</sub>-agonists (LABA) considered by PBAC and supplement this analysis with any additional data and clinical information sources available in Australia.

#### 3.1 Key findings for ToR 2

- *The use of FDC is higher than any other non-reliever asthma medicine.*
- *Fluticasone was the most commonly dispensed ICS inhaler in the 0 to 18 age group, with peak utilisation around five years of age.*
- *Fluticasone/salmeterol FDC was the most commonly dispensed FDC in the 0 to 18 age group.*
- *In excess of 90% of asthma preventer therapy is initiated by GPs.*
- *The DUSC analysis found that 83% of patients commencing a FDC did not receive an ICS in the prior 24 months. While the PMR analysis found 79% of patients initiated a FDC with neither ICS nor oral corticosteroids in the prior 24 months.*

#### **Stakeholder input from the Forum and submissions on Terms of Reference**

- There are reservations about the validity of the data interpretations presented in the DUSC analysis. In particular the analysis does not take into account the considerations of prescribers in practice (i.e. individual patient circumstances, needs and conditions).
- The published data on the numbers of children with asthma and asthma of differing severity has limited reliability. Comparisons of National estimates of prevalence of asthma (according to severity) to management of children presenting with symptoms makes interpretation of the utilisation data challenging.
- Some children present with symptoms of breathlessness from other causes and may be given a FDC.
- The diagnosis of asthma is difficult at first presentation. Children may not return for follow-up visits for a variety of reasons and there may not be the opportunity to review and change medications.
- There is no information in PBS data on the reason for prescribing.
- There is limited information or evidence in children. Much of the information presented to GP's is for adults.
- Cost is a significant factor for families, especially as one or more family members may have asthma.
- PBS restrictions require stabilisation on each component medicine which is not practical and not safe, as it increases the chance of LABA being taken as monotherapy.

#### 3.2 Published evidence

The Reference Group assisted with the interpretation of the utilisation reports. The Reference Group provided advice on assumptions used in the observational study of

Australian administrative pharmacy claim data and clinical and consumer context in interpretation of the results of the study.

### **3.2.1 Utilisation of PBS subsidised asthma medicines in Australia**

QUMPRC, an independent contractor, undertook an analysis of utilisation to supplement the original findings of the DUSC analysis. The supplemental analysis, *Utilisation of Medicines to Treat Asthma in Children Report* (PMR analysis), used pharmacy claim data collected by Medicare Australia and the analysis was undertaken using the date of supply of the prescription data. In addition supplementary data from Australian Bureau of Statistics (ABS) and The Family Medicine Research Centre, University of Sydney, GP prescribing dataset, Bettering the Evaluation and Care of Health (BEACH), was considered in the analyses.

There are a number of limitations of the pharmacy claim data. The data records supply of medicines but not the reason for the prescription. Therefore medicines subsidised for management of asthma could be prescribed for other obstructive airway conditions. In children this includes post viral wheeze, cough and bronchitis. Private prescriptions and over the counter medicine are not captured in PBS data, and prior to April 2012 only prescriptions priced over the PBS co-payment thresholds were captured. The dataset did not contain the lowest strengths of ICS and SABAs prior to April 2012. Of particular note for this analysis the dataset did not include a record of all people obtaining SABAs and some people receiving asthma medicines on discharge from public hospitals or through remote area Aboriginal Health Services.

### **3.2.2 DUSC analysis 2011**

The DUSC analysis was conducted in June 2011. In response to a request by the Paediatric Medicines Advisory Group (PMAG) the DUSC undertook a review of asthma preventer medicine utilisation in children. The DUSC analysis covered five calendar years of PBS data, from January 2006 to December 2010. Oral corticosteroids were excluded from this analysis. The rationale for excluding oral corticosteroids was that many children would be provided these if presenting for urgent medical assistance in a hospital setting rather than being prescribed and dispensed the medicine through the PBS, in addition oral corticosteroids are often used to treat conditions other than asthma.

The full DUSC analysis is appended at [Appendix A](#).

### **3.2.3 PMR analysis 2013**

The PMR analysis covers six years of data, from 1 July 2007 to 30 June 2013. This includes one year of available under co-payment data, from 1 July 2012 to 30 June 2013. It provides an estimate and description of the childhood PBS population (aged 0-18 years) using asthma medicines, the patterns of medicine use in children and compliance with Australian guidelines and the PBS restrictions.

The PMR analysis is comprised of four sections, each section uses a slightly different population in order to maximise use of available data, while ensuring the validity of specific findings.

The full PMR analysis is appended at [Appendix F](#).

### 3.3 Comparison of utilisation findings

The PMR analysis was able to corroborate the majority of the findings of the DUSC analysis. The key findings from the utilisation analyses are:

- The use of FDCs is higher than any other non-reliever asthma medicine. The four most used non-reliever medicines in children are fluticasone with salmeterol FDC, montelukast tablets, fluticasone inhaler, and budesonide with eformoterol FDC, other medicines had negligible comparative use.
- Some asthma medicines are being used in children younger than the product information recommends. Montelukast is also being used in older patients than recommended by the PBAC.
- Fluticasone was the most commonly dispensed ICS inhaler in the 0 to 18 age group, with peak utilisation around five years of age. There is very little use of other ICS products (budesonide, beclomethasone, ciclesonide) in this age group.
- LABA as a single agent inhaler has very limited use in children. This indicates that there is likely to be very little concomitant therapy of separate ICS and LABA inhalers.
- In excess of 90% of asthma preventer therapy is initiated by GPs. The analysis cannot determine what proportion of this was in consultation with a specialist.

**Table 3.1. Comparison of DUSC review and PMR Analysis**

	PMR Analysis	DUSC Analysis
Data	PBS (subsidised claim data) 1 July 2007 to 30 June 2013  PBS (complete claim data) 1 July 2012 to 31 June 2013  Subjects aged 0-18 years	PBS (subsidised claim data) 1 January 2006 to 31 December 2010.  Year of interest 2009  Subjects aged 4 - 14  Concession status for all supply of medicines
Initiated any asthma medicine (no prior asthma medicines, excl. relievers and oral corticosteroids, for 24 months)	(N=28,380 concession status in 2012)  58% single preventer  41.9% FDC	Not reported
Initiating FDC	79% (without ICS or oral corticosteroids in previous 24 months)	83% (without ICS in previous 24 months)
Treatment initiated by GPs	94%	93.4%
Initiating FDC, without prior ICS, and receiving only 1 supply in next 12 months	59% - 72% (concessional only)	60%
Initiating FDC, after prior ICS and receiving only 1 supply of FDC in next 12 months	49% - 61% (concessional only)	27.4%

Sources DUSC analysis Tables 7.4.8 and 7.4.12; PMR analysis Tables 3.3 and 3.4.

The DUSC analysis of 2009 PBS data found that 83% of all concession patients, aged between 4 and 14 years, who commenced their first supply of a FDC did not receive an ICS in the 24 months prior to commencing the FDC. In the PMR analysis using PBS data for 2012 79% of concession patients aged 0 to 18 years had initiated a FDC with neither ICS or oral corticosteroids in the prior 24 months. Although there are some differences in how the analysis was conducted both show that there is a significant majority of FDC prescribing which is not adhering to PBS restrictions nor best practice guideline management.

The DUSC report noted that a utilisation report for MSD reported 60% of children (concession status, 4-14 years) commencing a FDC, with no prior ICS therapy, filled only one prescription in 12 months. Only 27.4% of patients who had received ICS therapy prior to initiating a FDC filled one prescription in the following 12 months. A similar analysis in the PMR analysis showed that 59% to 72% (see Table 3.1) of children who initiated a FDC without a prior ICS or oral corticosteroid, filled only one FDC prescription in the 12 month period. Where the patient initiated a FDC with prior ICS or

oral corticosteroid use, 49% to 61% (see Table 3.1) received only one FDC prescription in the 12 month period. These findings lead to the conclusion that a patient is more likely to continue taking FDC if they had prior ICS or oral corticosteroid use than those who initiate FDC naïve to these medicines.

The PMR analysis found that in 2012, there were 28,380 children with concessional status aged 0 to 18 years who initiated to a preventer, LABA or FDC, after no prior dispensing of any of these medicines in the previous 24 months. Of these, 58% initiated a preventer, 41.9% initiated a FDC and 0.1% initiated a LABA. The DUSC analysis found similar proportions of dispensed medicines, however no raw numbers or percentages were reported.

The DUSC analysis concluded that there is likely to be a significant number of preventers dispensed to children who were not experiencing longer term asthma symptoms. This conclusion was based on the estimated prevalence of persistent asthma in children.

### **3.4 Findings of the PMR analysis**

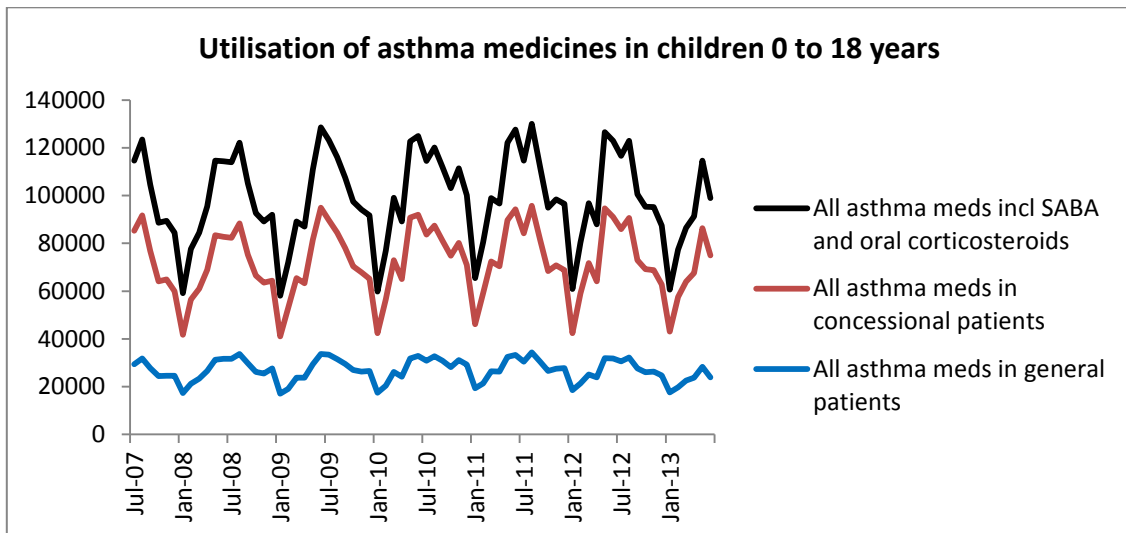
The overall utilisation of asthma medicines in children 0 – 18 years was stable over the observed years from July 2007 to June 2013.

- There were 480,664, or 9% of children aged 0 to 18 years who were dispensed an asthma medicine (excluding oral corticosteroids) between 1 July 2012 and 30 June 2013.
- Boys receive more prescriptions for asthma medicines than girls before the age of 16. During the late teenage years the trend is reversed with more girls treated with asthma medicines. This is consistent with the varying prevalence of the disease across age and gender.(6)
- In 2012, 94% of all therapy was initiated by GPs, according to the approved prescriber in the pharmacy claim data.
- The majority of dispensed asthma medicines is fluticasone with salmeterol FDC, followed by montelukast, fluticasone, and budesonide with eformoterol FDC. Other asthma medicines had negligible use in comparison (Figure 3.2).
- Fluticasone with salmeterol 125/25mcg and 50/25mcg (the two lower strength MDI) were the most commonly dispensed strengths of this FDC in children. The low-medium corticosteroid strengths of budesonide with eformoterol, 100/6mcg and 200/6mcg were the most commonly dispensed strengths of that FDC.
- Fluticasone was the most commonly dispensed ICS, with peak utilisation around five years of age. There was very limited use of other ICS.
- Montelukast use was highest in children 3 to 9 years old, while mast cell stabilisers / cromones had comparatively limited use.
- LABA as a single agent had very limited use in children, this indicates that there is likely to be very little concomitant therapy of separate ICS and LABA inhalers.

- In 2012, of the 13,365 children with concessional status aged 0 to 18 years who initiated a FDC (no FDC use in the prior 24 months): 79% had neither ICS nor oral corticosteroids; 12% had prior oral corticosteroid (no ICS); 5% had prior ICS; and 4% had both ICS and oral corticosteroid.

### 3.4.1 Utilisation July 2007 – June 2013

The overall numbers of prescriptions dispensed for asthma medicines in children 0 to 18 years is presented in Figure 3.1. The graph shows stable overall rate of prescription numbers across the years with some seasonal variation.

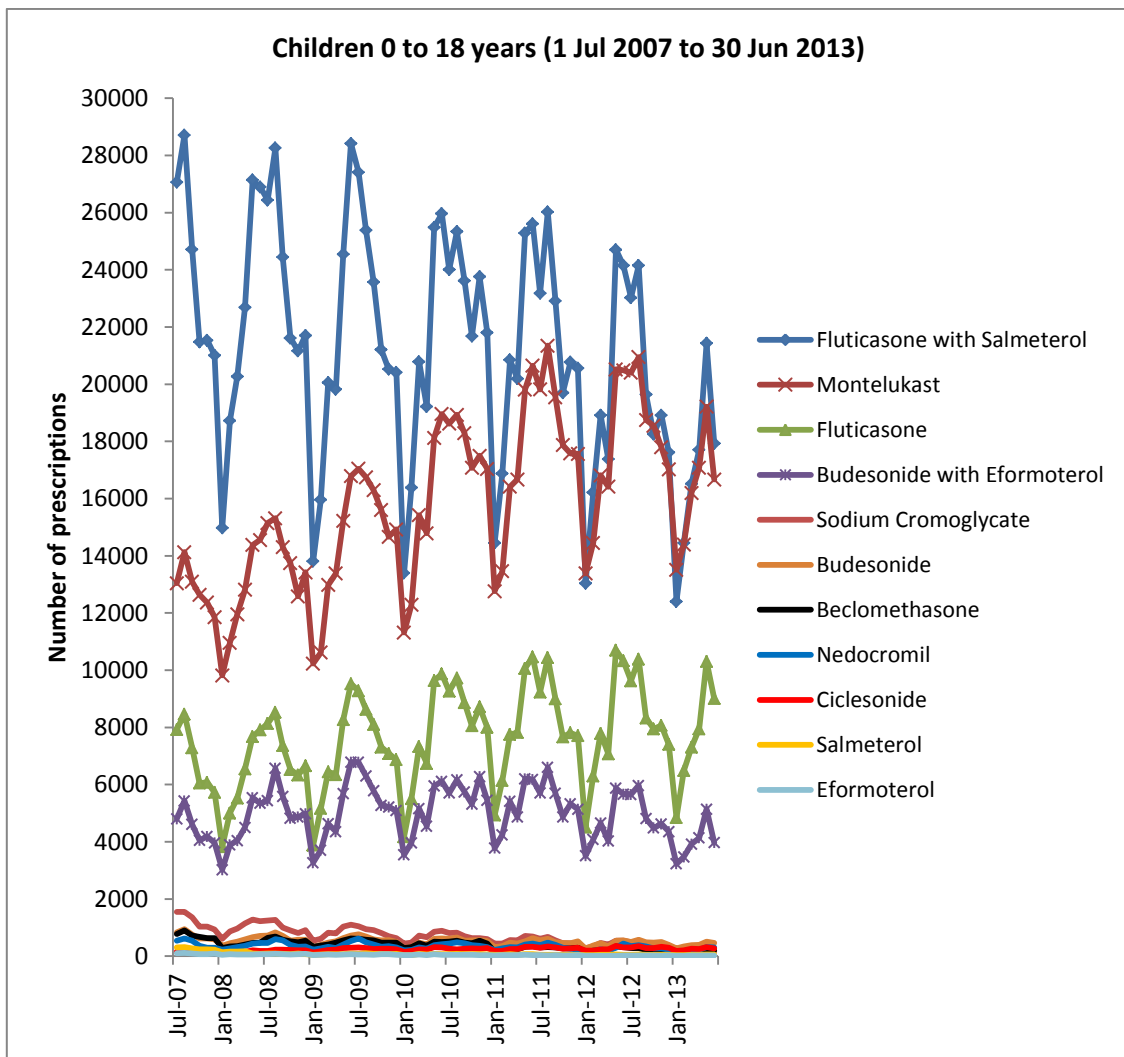


**Figure 3.1. PBS prescriptions for asthma medicines per month in children up to 18 years by concessional and general status, excluding under co-payment data.**

Source: PMR analysis Figure 1.

Figure 3.2. presents the monthly number of prescriptions dispensed for each individual preventer, LABA and FDC in children aged 0 to 18 years. The prescription numbers show a slight decrease in the use of FDCs with time, an initial upward increase in numbers for montelukast, and slightly increased prescriptions dispensed for fluticasone from the beginning of the period.

The reduction in fluticasone/salmeterol FDC is accompanied by only a small corresponding increase in montelukast and fluticasone. The absolute number of fluticasone prescriptions will be underreported as fluticasone 50mcg has been under co-payment for the entire period of data collection. Only PBS subsidised prescriptions linked to date of birth records are used for this analysis.



**Figure 3.2. Number of subsidised PBS prescriptions dispensed per month for preventers, LABAs and FDC for asthma in children aged 0 to 18 years. The PBS prescription data used in this graph excludes under co-payment data.**

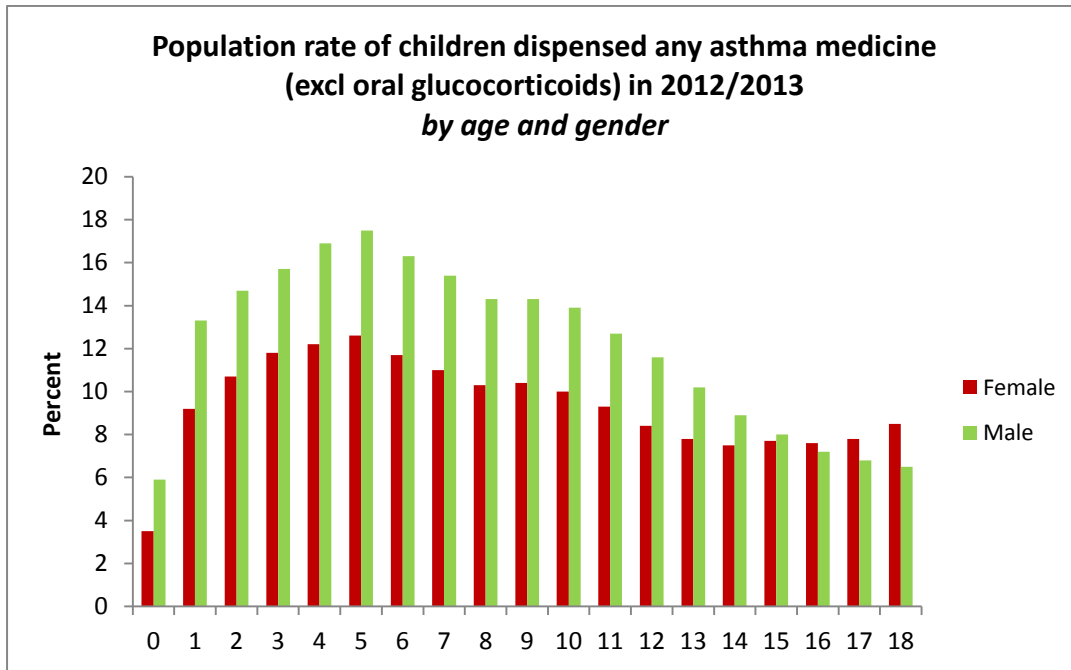
Source: PMR analysis Figure 2.

The DUSC analysis considered the long term trends of asthma medicines in terms of total estimated market across the 2006 to 2010 calendar years. As such the total usage of medicines used to treat asthma was able to be assessed; however the long term analysis did not account for differences in treatment between children and adults.

### 3.4.2 Current market utilisation July 2012 – June 2013

Overall, there were 480,664 children aged 0 to 18 years who were dispensed an asthma medicine (excluding oral corticosteroids) between 1 July 2012 and 30 June 2013. That is 9% of the estimated Australian resident population aged 0 to 18 years as reported by ABS at 30 June 2012.(42)

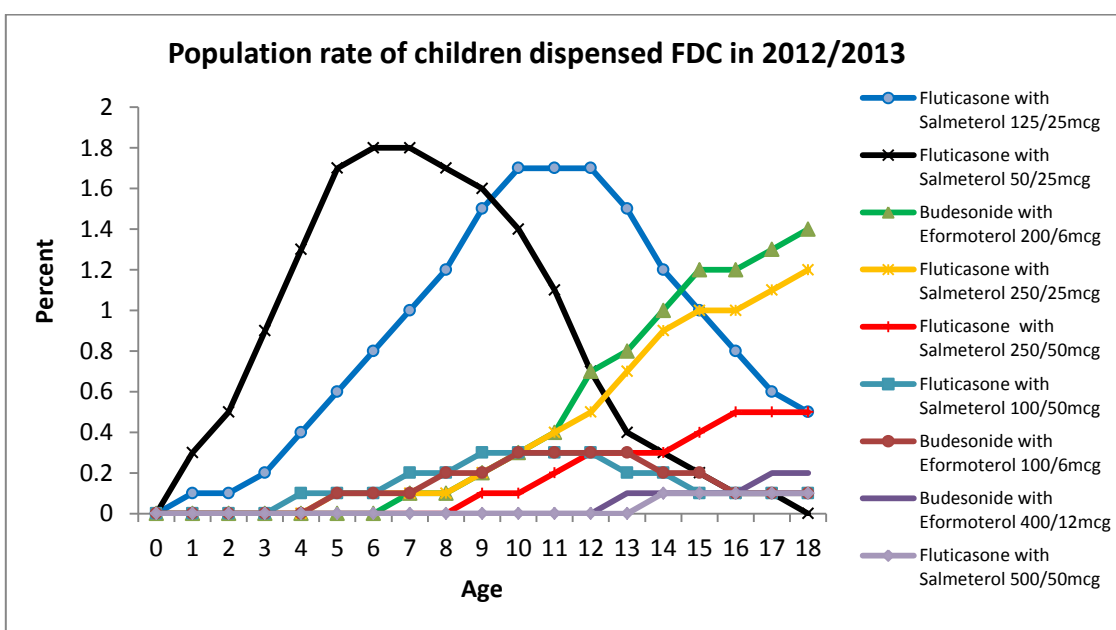
Boys receive more PBS prescriptions for asthma than girls before age 16 years (Figure 3.3.). This analysis includes all PBS prescriptions (general and concessional). During the late teenage years the trend is reversed as more girls received asthma medicines. This is consistent with the differing reported prevalence of the disease across age and gender.(6)



**Figure 3.3. Population rate of children dispensed any asthma medicine in 2012/2013 as proportion of estimated resident population at 30 June 2012 (42) (by age and gender).**  
 Source: PMR analysis Figure 13

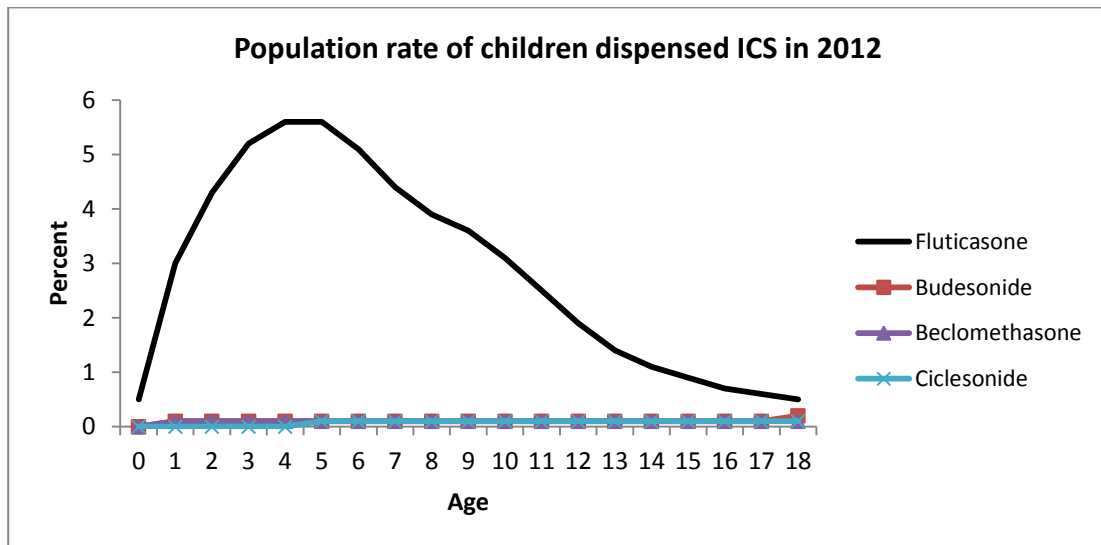
A small proportion of young children received FDCs. Fluticasone with salmeterol 125/25microgram and 50/25microgram were the most commonly dispensed FDC to children 14 years or less. Both these forms of FDC are metered dose inhalers suitable for use with a spacer. A larger proportion of children received single component fluticasone inhaler (Figure 3.4.).

In adolescent groups budesonide with eformoterol and the highest dose fluticasone with salmeterol (250/25microgram accuhaler) were most frequently supplied. This is a cross section analysis and does not indicate if people switched between doses.



**Figure 3.4. Age-specific population rates of children dispensed FDCs in 2012/2013**  
 Source: PMR analysis Figure 19. ABS population as at 30 June 2012 (42)

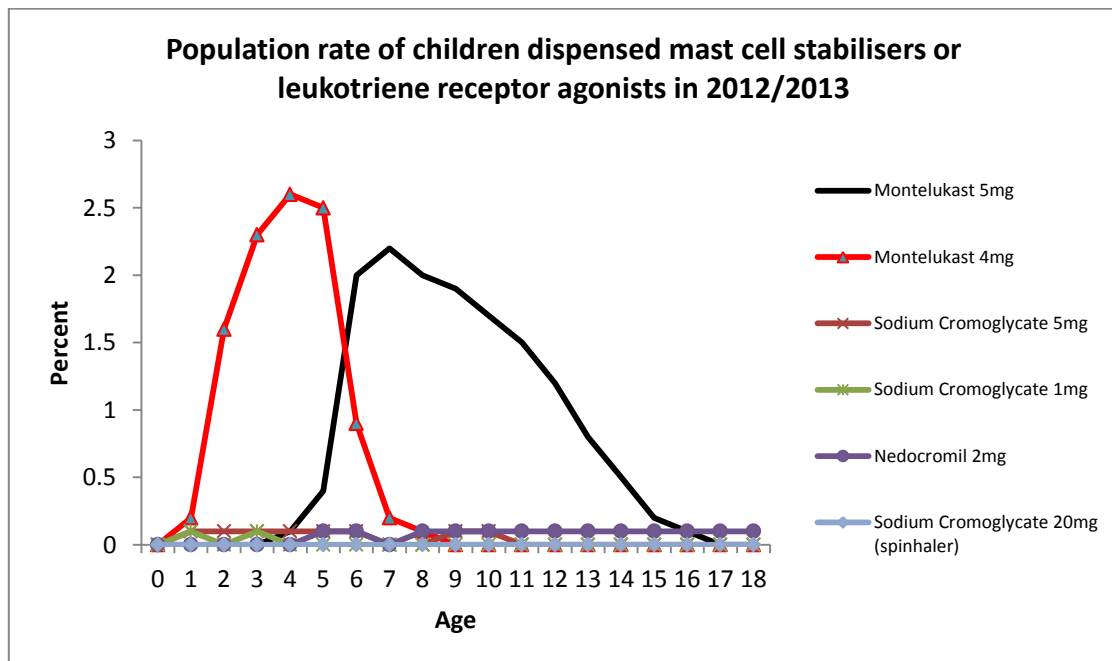
Fluticasone was the most commonly dispensed single component inhaled corticosteroid, with peak utilisation around five years of age (Figure 3.5.). There was very limited use of other ICSs



**Figure 3.5. Age specific population rates of children dispensed ICS in 2012/2013**

Source: PMR analysis Figure 20. ABS population as at 30 June 2012 (42)

Montelukast use was highest in children 3 to 9 years old. Mast cell stabilisers had comparatively limited use compared to ICS and FDCs.

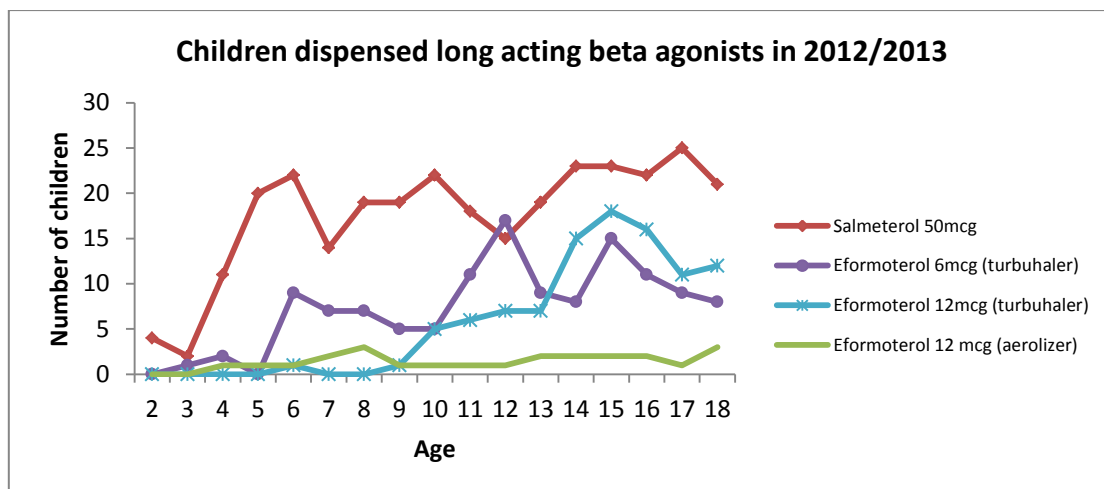


**Figure 3.6. Age specific ABS population rates (June 2012)of children dispensed mast cell stabilisers of leukotriene receptor agonists in 2012 (42)**

Source: PMR analysis Figure 23.

LABA as a single agent had very limited use in children. Population rates were not calculated because of the very low numbers. The very low numbers make any further

interpretation of this finding difficult. The analysis relies on entry of the correct family Medicare number. While this is checked during the quality assurance process there is likely to be a small error rate in the data collected.



**Figure 3.7. Number of children dispensed long-acting beta<sub>2</sub>-agonists by age and strength.**  
 Source: PMR analysis Figure 24.

The DUSC analysis considered both age and annual variance of PBS medicines used to treat asthma in the 2010 calendar year. All findings in the DUSC current market analysis were comparable to those found in the PMR current market analysis.

In addition to the current market analysis the DUSC analysis considered an estimate of preventer prevalence which was not duplicated in the PMR analysis. This prevalence analysis was not reproduced as it was considered that too many assumptions were required in the analysis and could potentially introduce error. However the analysis conducted by DUSC indicates that over 50% of children with asthma in 2007-08 had been supplied a preventer, which is more than double what would be expected from the epidemiological approach.

### 3.4.3 Medicines initiation analysis

In 2012, there were 260,340 children aged 0 to 18 years with constant concessional status who received at least one dispensing of asthma medicines or oral corticosteroid. Of these:

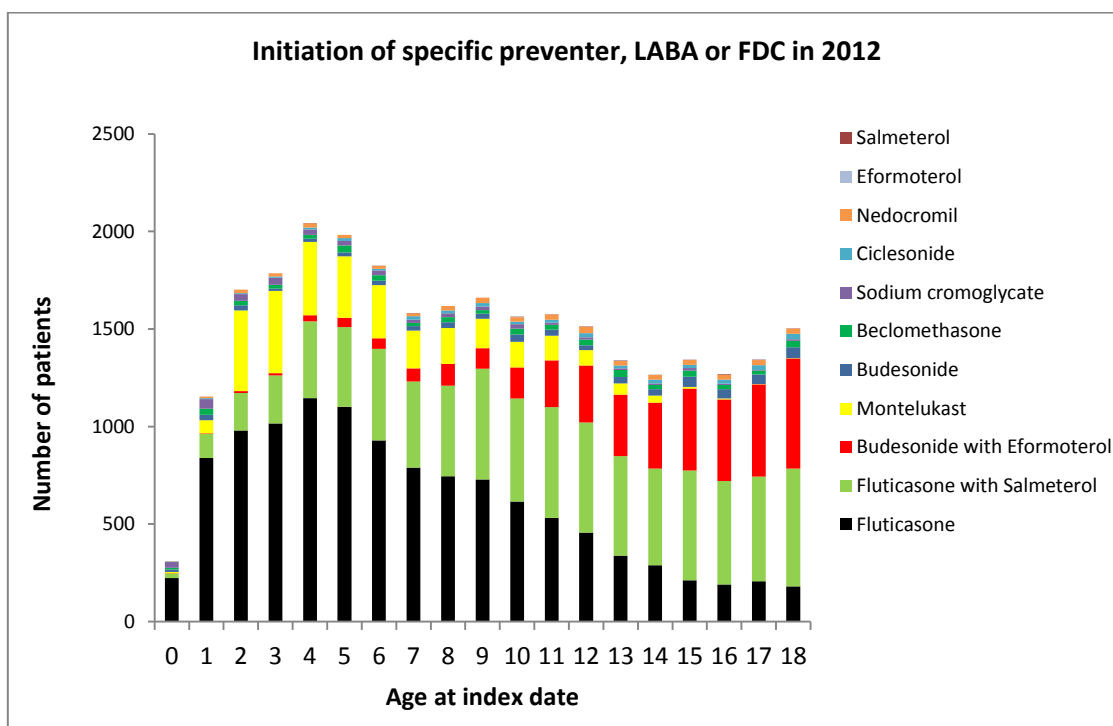
- 33.5% received relievers (with or without oral corticosteroids) but no preventers or FDC;
- 20.4% received preventers (with or without relievers or oral corticosteroids but no FDC); and
- 16.3% received at least one FDC (with or without relievers, preventers or oral corticosteroids).

The remaining 29.8% received just oral corticosteroids, a number of whom are likely to be treated for conditions other than asthma. There were 28,380 with concession status children aged 0 to 18 years who initiated a preventer, LABA or FDC, in 2012. The assumption of initiation to treatment was based on these children having no prior

dispensing of any of these medicines in the previous 24 months in the pharmacy claim dataset. Of these:

- 58% initiated a preventer (16,457);
- 41.9% initiated a FDC (11,897); and
- 0.1% initiated a LABA (26).

Initiation of preventers and FDC at the same time were excluded from the above calculations (N=222) as they made up only a small proportion of the total and would contribute multiple values to the initiation category.



**Figure 3.8. Initiating medicine for concessional children initiating preventer, LABA or FDC therapy in 2012.**

Source: PMR analysis Figure 25.

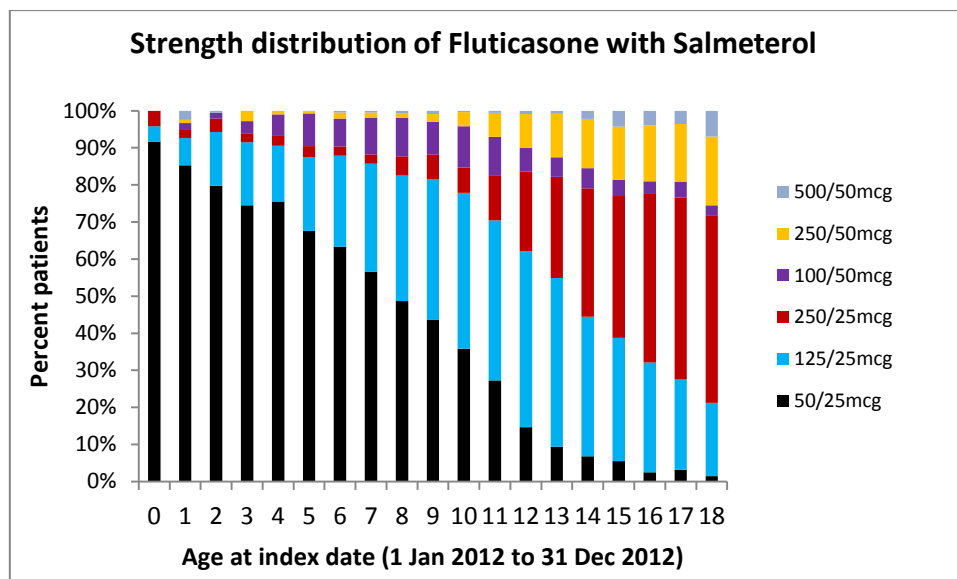
The majority of initiating preventer prescriptions in 2012 (94%) was by GPs. This is consistent with reports from the Australian Centre for Asthma Monitoring showing that GPs usually manage asthma without referral to a specialist. (12) The DUSC analysis found in 2009, that 93.4% of preventer therapy was initiated by GPs. These results show that GPs continue to manage the majority of children with respiratory illnesses.

### 3.4.4 FDC initiation analysis

13,365 children with concession status 0 to 18 years initiated a FDC in 2012, with no prior FDC in the last 24 months. Of these:

- 79% had neither ICS nor oral corticosteroid in the 24 months prior (10,587);
- 12% had prior oral corticosteroid (1580);
- 5% had prior ICS (686); and
- 4% had both ICS and oral corticosteroid (502).

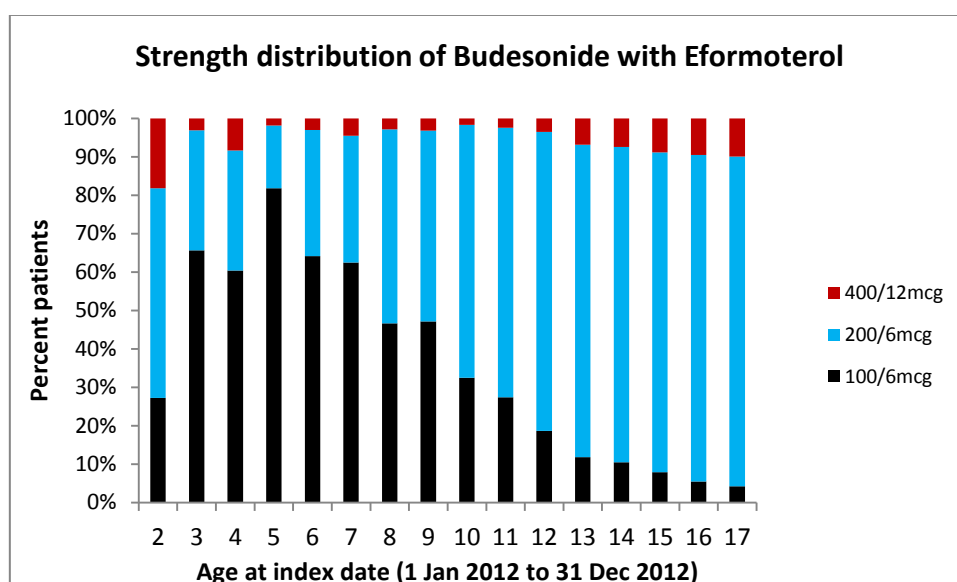
Fluticasone with salmeterol FDC (50/25mcg) was initiated for younger children as a metered dose inhaler, while slightly older children were initiated on 125/25mcg and 250/25mcg strengths.



**Figure 3.9. Initiation of fluticasone with salmeterol in concessional children in 2012 – by strength**

Source: PMR analysis Figure 28.

Analysis of budesonide with eformoterol initiation by strength shows that the majority of younger children who received the FDC, received the lowest corticosteroid dose (100/6microgram), while the 200/6 microgram formulation was received most commonly by older aged children.



**Figure 3.10. Initiation of budesonide with eformoterol in concessional children in 2012 – by strength**

Source: PMR analysis Figure 29.

The DUSC analysis found similar proportions of FDC initiators. However there were a few key differences between the analyses; the DUSC analysis uses an age group of 4 to 14 year olds and does not take into account the use of oral corticosteroids.

**Table 3.2 Concessional status patients between 4 and 14 years at index date who were supplied a FDC in 2009**

Prior Medicine Usage	Patients	% Patients	% of Initiators
No ICS in prior 24 months	12,947	37%	83%
ICS in prior 24 months	2,746	8%	17%
No Preventer in prior 24 months	12,192	35%	78%
Preventer in prior 24 months	3,501	10%	22%

Source: DUSC analysis page 23 (Medicare Australia R/PBS and PBS supplied script data.)

From the analysis above 83% of all concession status patients aged between 4 and 14 years in 2009 who commenced their first supply of a FDC did not receive an inhaled corticosteroid in the 24 months prior to commencing the FDC. When the analysis was expanded to include any preventer medication the percentage of patients dropped slightly to 78%.

### 3.4.5 Persistence analysis

In 2010, there were 243,296 children with concession status aged 0 to 16 years who had at least one asthma medicine (including oral corticosteroids) dispensed. Of these, 12,579 initiated a FDC, with no prior FDC in the last 24 months:

- 9,805 children had no prior preventer therapy; and
- 2,587 children had an ICS or oral corticosteroid in the previous 24 months.

We can infer that from the 12,579 FDC initiators in 2010, 78% (N=9,805) initiated directly on FDC without trialling ICS or oral corticosteroids, while just 20.5% (N=2,587) had ICS or oral corticosteroid prior to FDC initiation. The remaining 187 had only mast cell stabilisers, montelukast or LABA prior to FDC initiation (no ICS or oral corticosteroids) and were not analysed further.

An analysis of persistence showed that 59% of children less than 12 years of age and 72% of children aged between 12 and 17 Inclusive) (see Table 3.3) who initiated a FDC without a prior ICS or oral corticosteroid in 2010, filled only one FDC prescription in 12 months. In those who initiated a FDC with a history of corticosteroid dispensing, 49% to 61% (see Table 3.4) received only one FDC prescription in the 12 month follow-up.

Table 3.3 presents the proportion of FDC initiators who only filled one dispensing for FDC (the index one) in the next 12 months. The results confirm that over half of the children naïve to ICS or oral corticosteroids only filled one prescription for FDC in 12 months.

**Table 3.3. Proportion of children who only filled one prescription for FDC in FDC initiators naïve to ICS or oral corticosteroids**

FDC type	Strength	Number of children with index FDC dispensing		No further FDC dispensed in the next 12 months	
		<12 years	>=12 years	<12 years	>=12 years
Fluticasone with salmeterol	Fluticasone with 50mcg salmeterol (60 doses); (Accuhaler)	556	584	330 (59%)	357 (61%)
	Fluticasone with 25mcg salmeterol (120 doses); (MDI)	3939	1851	2590 (66%)	1234 (67%)
Budesonide with eformoterol	Budesonide with 6mcg or 12mcg eformoterol (all come in 120 doses); (Turbuhaler)	1062	1813	758 (71%)	1297 (72%)

Source: PMR analysis Table 7 (adapted).

In those initiators who had prior ICS or oral corticosteroid medicine supplied over half of the children only filled one prescription for FDC in the 12 months following (Table 3.4).

**Table 3.4. Proportion of children who only filled one prescription for FDC in FDC initiators not naïve to ICS or oral corticosteroids**

FDC type	Strength	Number of children with index FDC dispensing		No further FDC dispensed in the next 12 months	
		<12 years	>=12 years	<12 years	>=12 years
Fluticasone with salmeterol	Fluticasone with 50mcg salmeterol (60 doses); (Accuhaler)	158	79	77 (49%)	43 (54%)
	Fluticasone with 25mcg salmeterol (120 doses); (MDI)	1542	325	852 (55%)	192 (59%)
Budesonide with eformoterol	Budesonide with 6mcg or 12mcg eformoterol (all come in 120 doses); (Turbuhaler)	225	258	130 (58%)	158 (61%)

Source: PMR analysis Table 8 (adapted).

The DUSC analysis of prescriptions per patient per year show that 60% of children commencing a FDC, with no prior inhaled corticosteroid therapy only filled one prescription in 12 months. Where patients had received prior therapy the proportion who continued was much greater as only 27.4% filled one prescription in the following

12 months. These findings are in the same direction as those of the PMR analysis. The magnitude of the difference is greater in the DUSC analysis, however it was noted in the DUSC analysis that this data needs to be interpreted carefully as it under-represents true compliance with treatment regimens owing to limitations in the data.

## Section 4: ToR 3

### Clinical practice and clinical guidelines comparison

Identify areas of prescribing for childhood asthma in Australia where clinical practice is inconsistent with clinical guidelines; and if there is evidence that supports this practice.

#### 4.1 Key findings for ToR 3

- *Over 25% of FDC prescribing in children is below the age recommendations of the clinical guidelines.*
- *Even if all FDC initiation which could be consistent with clinical guidelines was, and PBS restrictions were not taken into account, there would still be over 6,000 children who initiated FDC treatment inconsistently with guidelines.*
- *49-72% of concessional children initiating to FDC only use one inhaler before discontinuing use, this is far more than might be expected if treatment is to be consistent with clinical guidelines.*
- *There are more prescriptions for FDC than there are for ICS, which is inconsistent with clinical guidelines as ICS are first line preventers and FDC are predominately second line preventers, which generally require a failed trial of ICS.*
- *There are significant areas of practice which would now be considered to be inconsistent with clinical guidelines.*

#### **Stakeholder input from the Forum and submissions on Terms of Reference**

- Treatment guidelines for asthma in children are not being adhered to by all prescribers as evidenced by an over utilisation of FDC in the treatment of children. This includes FDC being used as first line treatments and the use of these products to treat mild or intermittent asthma.
- There appears to be less awareness of paediatric management approaches for asthma than there is of adult management approaches; as such management techniques which are suitable for adult asthma are being applied in some cases when treating children.
- Prescribing behaviour is informed by guidelines however with social as well as clinical factors coming into the equation, on occasion; prescribers may choose to not follow these guidelines.
- In some cases GP's may feel pressured to resolve a child's illness immediately and as such GP prescribes what they consider to be the most effective treatment, focussing on quick management of symptoms rather than taking into consideration any longer term issues or guidelines.
- Some GPs may consider that prescribing medicines to stop symptoms is acceptable and as such may prescribe FDC in conditions other than asthma.
- Convenience of FDCs is considered important to parents and GPs.
- Health professionals do not want to see harm come to a child.
- Industry promotes the appropriate use of FDC in adults.

## 4.2 Introduction

The Australian Asthma Handbook 7<sup>th</sup> ed. 2014 (the Handbook) is produced by the National Asthma Council Australia (NAC), the first version was published in 1989 and it is the best practice standard for asthma management in Australia.(5)

In order to address this ToR the Handbook will be used as the reference document for clinical guidelines; although this edition was not in effect during the data collection period, it is now the best practice guide for treatment. In preparing the report the older guidelines (6<sup>th</sup> edition) were compared and found to be fundamentally similar in recommendations. As these guidelines were not active during the data period this section looks at prescribing practices which are inconsistent with the new guidelines, and if these prescribing practices were to continue they would be considered as not best practice treatment. This section does not make a judgement on whether these previous prescribing habits were appropriate or not.

### 4.2.1 Australian Asthma Handbook 7th ed. (2014)

The Handbook is a purpose built interactive website, and constitutes the best practice guidelines for asthma treatment in Australia, it can be found online at: <http://www.astmahandbook.org.au/>.

The Australian Asthma Handbook has been officially endorsed by the Royal Australian College of General Practitioners (RACGP), Australian Primary Health Care Nurses Association (APNA) and the Thoracic Society of Australia and New Zealand (TSANZ).

The Handbook was developed, predominately, for use by general practitioners, community pharmacists, asthma and respiratory educators, primary healthcare/practice nurses, and Aboriginal and Torres Strait Islander health workers and practitioners.(5)

The Handbook provides an evidence-based, practical guide to primary care health professionals on the most effective strategies for the diagnosis and management of asthma in adults and children.(5)

In children, initial treatment after making the diagnosis of asthma is guided by the pattern and severity of asthma symptoms. The aims of asthma management are to ensure that the child's asthma has been correctly diagnosed, and to enable the child to maintain a normal quality of life without interference from asthma or the side effects of asthma treatment.(5)

The stepped approach to adjusting asthma medication in children:

- All children will need a reliever, either SABA or low dose budesonide/formoterol (12 years and over and only if used appropriately as part of SMART).
- Some children will need a preventer of either a low dose ICS, montelukast, or cromone.

- Few children will need a stepped up preventer of either, high dose ICS, ICS/montelukast, or a FDC. Children in this category should be considered for referral to a specialist respiratory physician.

Under this stepped approach step up should only be considered if good control is not achieved at a lower level, and step down of treatment should be considered after three months if asthma has been stable and well controlled.(5)

When a person's asthma is not well controlled despite treatment, before considering dose escalation a prescriber should confirm the following:

- The diagnosis of asthma is correct;
- Current treatment is appropriate; and
- The patient is taking the medicine correctly and as prescribed.

For children already taking regular preventer treatment, adjustments in the treatment regimen are based on finding the lowest dose of medicines that will maintain good control of symptoms and prevent flare-ups.(5)

The Handbook differentiates prescribing on the basis of age, and provides several pathways to FDC use:

- Children five years or younger should not be prescribed a FDC at any point of the treatment pathway (this is also consistent with the GINA guidelines recommendations).
- For children six years and over a FDC can be used if their asthma is not adequately controlled on a low dose ICS.
- For children 12 years and over they may use a low dose budesonide + eformoterol FDC (50/3 and 100/3 MDI or 100/6 and 200/6 DPI), as part of a maintenance and reliever regime. With this regimen, SABA is not used a reliever.
- For children 14 years and over asthma management for adults will apply in most situations. In terms of FDCs this means that they can be considered as an alternative initiator to ICS, in patients who either have frequent day time symptoms and who have been woken due to asthma symptoms once in the last month, or in a new diagnosis of asthma where symptoms are severely uncontrolled or very troublesome.

The Handbook notes that unless there is a specified exception, prescribing recommendations follow TGA approved indications and PBS criteria.

### 4.3 Practice inconsistency with clinical guidelines

#### 4.3.1 FDC use outside of age recommendations

The PMR analysis found that:

- 25.7% (7,566) of all children prescribed budesonide/eformoterol FDC in the 2012/13 financial year were prescribed inconsistently with the age recommendation in the TGA approved product information.
- 28.7% (29,102) of all children prescribed fluticasone/salmeterol FDC were prescribed doses inconsistently with the age recommendation in the TGA approved product information. The NAC guidelines recommend FDC is for use in children six years and older however the product information for the lowest strength corticosteroid form of fluticasone/salmeterol FDC (50/25 MDI and 100/50 DPI), states children four and older can use either of the two formulations. When using the higher age recommendation in the guidelines an additional 15,310 FDC inhalers were prescribed inconsistently with clinical guidelines.
- Overall 71,887 FDC inhalers were prescribed inconsistently with the TGA approved age groups and 87,197 FDC inhalers prescribed inconsistently with clinical guidelines.

The clinical guidelines allow for the use of FDC in treatment algorithms for children six years and older, however they also stipulate that treatment, unless otherwise specified, should be conducted in line with TGA approved indications. Therefore over 25% of FDC prescribing is inconsistent with age recommendations in the clinical guidelines, as some higher dose FDCs are being used in age groups outside the TGA approved age indications.

#### 4.3.2 Initiation to FDC

Based upon the findings of the PMR analysis there are a substantial number of children initiating treatment using a FDC. As noted in Figure 3.8, in section 3.4.3, 11,897 concessional children initiated a FDC in 2012 without a prior preventer in the past 24 months. Of these 8,232 initiated to fluticasone/salmeterol FDC and the remaining 3,665 to budesonide/eformoterol FDC.

The NAC guidelines recommend children five years and under are not prescribed a FDC as there is a lack of evidence of safety and effectiveness in this group. Children six years and over can be prescribed a FDC if they have already trialled ICS. For children 12 years and over budesonide/eformoterol FDC can be used as both maintenance and reliever therapy, replacing an ICS and SABA, or if the child is over 14 and therefore can be considered in terms of the adult NAC guidelines.

Therefore all fluticasone/salmeterol FDC initiation, without prior preventer, in the 0–13 age group (5501 children) and all budesonide/eformoterol FDC initiation, without prior preventer, in the 0-11 age group (843 children) is inconsistent with the NAC guidelines. Assuming that initiation of fluticasone/salmeterol FDC for children in the 14-18 age

group (2731 children) follows the adult clinical guidelines, then this prescribing would be consistent with NAC guidelines. If it is assumed that all of the budesonide/eformoterol FDC initiation in the 12-18 age group (2,822 children) is used as part of a maintenance/reliever regime or in the 14-18 age group (2214 children) as part of the adult treatment guidelines it would consistent with NAC guidelines.

It should also be noted that in the clinical guidelines it is highlighted that when initiating an FDC, it may need to be prescribed as a private prescription if prescribing does not meet PBS restrictions. Given that all FDC restrictions require some sort of prior preventer use, the only recorded FDC initiating prescriptions which would be consistent with guidelines are those where a patient had received a relevant prior treatment in a tertiary institution, had received prior treatment on a private script or had been given a sample inhaler.

#### ***4.3.3 Once off use of FDC***

In the PMR persistence analysis an unexpectedly high level of once off use of FDCs was identified. In the 2010 concessional data 59-72% of children initiated to a FDC without first using ICS or oral corticosteroids, received only the one script in a 12 month period. Although lower, 49-61% of FDC initiators who had previously received ICS or oral corticosteroids still received only one FDC script in a 12 month period. This means that a majority of children starting a FDC receive only one script or one script occasionally.

Given the treatment pathways for prescribing FDC recommended in the NAC guidelines and the role of FDC as daily maintenance therapy there would be limited need to immediately discontinue treatment. According to the Handbook the majority of children will need to have failed to achieve adequate asthma control on low dose ICS before being prescribed a FDC and would continue FDC for at least 3 months. Therefore a majority of this prescribing would be inconsistent with the clinical guidelines, as the only reason to have a single FDC script in line with guidelines would be if the FDC was found to not be a suitable treatment.

#### ***4.3.4 High use of FDC***

In the 2012/13 financial year there were 275,825 FDC inhalers and 253,672 ICS inhalers dispensed to children aged 0-18 years. Of the FDC inhalers 53,758 were budesonide/eformoterol FDC inhalers.

Given the place of FDC in the NAC guidelines, based on evidence in randomised controlled trials in children who are not controlled on ICS, is predominately to manage more asthma in the few children who are poorly controlled on low doses of ICS,(5) the observed use of FDC and the pattern of use is significantly different to expected levels. A larger portion of the budesonide/eformoterol FDC use is likely to be in line with NAC guidelines due to use as a first line reliever therapy, however this would not include the 400/12 DPI or 200/6 MDI inhalers as these strengths are outside clinical guidelines for the maintenance/reliever regime.

#### 4.4 Explanation of inconsistencies with guidelines

In ToR 1 the literature review showed there is some evidence of a benefit to lung function, as measured by FEV<sub>1</sub>, when using a FDC over the same dose of ICS. In addition when comparing a FDC with twice the dose of ICS there is an increase in morning and evening PEF scores in the FDC group and evidence of decreased rate of growth in children using high doses of ICS (refer to section 2, and [Appendix E](#)). This evidence may support prescriber's choice of FDC over ICS for the treatment of asthma.

Although there is limited evidence on the benefits or risks of short term use of FDC there has been some anecdotal input to the Review which suggests that FDC may be being used for the short term management of severe respiratory symptoms, with immediate down titration to an ICS after the child has been stabilised. Although this treatment is inconsistent with guidelines and is not in line with current evidence, it could still potentially have clinical value.

It is possible that some clinical decision making is based upon the developmental stage of the child, i.e. a more developed child may be treated as an older child and therefore be put on medicines which are not indicated for use in their actual age group.

Through consultation and Reference Group discussion it has been noted that there is likely to be prescribing of these medicines to manage illnesses other than asthma, including but not limited to; post-viral wheeze and other non-specific cough.

A variety of stakeholders have raised the point that there is less awareness of paediatric asthma management guidelines than there is of adult asthma management guidelines. As such, when prescribers are treating paediatric asthma, they are utilising management techniques suitable for adult asthma. A range of reasons were given for this lack of knowledge, including the guidelines not being clear enough in delineating treatment between adults and children, and pharmaceutical representatives predominately providing information on the indication and use of FDC in adult populations.

There is a desire to alleviate the stress on the child and the family by quickly addressing breathlessness and wheeze associated with asthma. FDC are considered likely to resolve symptoms faster than ICS alone, and therefore can be used to allow children to return to day care or school sooner with a medicine that is administered before and after school. In addition cost may be an issue, particularly for families with multiple children with asthma. It may be more financially cost effective for the family to use a single preventer rather than having multiple preventer types or doses being prescribed, although this is advised against as sharing inhalers can spread viral and bacterial infections.

It was noted that some GP prescribing may be influenced by treatment at discharge from hospital. For example the child is discharged with an FDC inhaler and the GP is expected to continue providing prescriptions for this medicine.

## Section 5: ToR 4

### Healthcare professional and consumer education medication management

Identify and review recent (past five years) healthcare professional and consumer education in the area of medication management in children with asthma.

#### 5.1 Key findings for ToR 4

- *The Asthma Child and Adolescent Programme (ACAP) has provided Asthma first aid training to 72% of staff in schools and 48% of staff in preschools since 2010.(43)*
- *Parents and carers asking about their child's asthma accounted for over half (55%) of the 3487 calls in 2009–10,(44) and around a third of the 2621 calls in 2010–11(45) to the national 1800 ASTHMA phone line.*
- *The Triple A programme trained over 2000 senior students as peer leaders with the educational sessions they provide reaching more than 26,000 high school students from 35 schools across Australia.(46)*
- *One randomised control trial found that children with infrequent intermittent asthma were less likely use ICSs or LABAs if they were treated by a GP who had received asthma education by the Practitioner Asthma Communication Education (PACE) Australia programme.(47)*

#### **Stakeholder input from the Forum and submissions on Terms of Reference**

- Some patients are confused over what are preventer and reliever medications, despite the education work that has been done in this area.
- GPs are usually highly educated in relation to addressing general asthma but less so for paediatric asthma and are not as aware of the place of FDC in the treatment of asthma in children.
- Education programmes would be best offered to patients and their families at a time when they are most receptive to hearing and taking in the advice and information, usually during the follow-up phases and not during the acute phase.
- There is a lack of recent, paediatric specific education on the treatment of asthma, although general education on asthma with paediatric components is currently available. Specific paediatric courses should be developed for both health professionals and consumers.
- Home visiting programmes conducted by pharmacists and nurses have shown some promise but the evidence on these programmes has not yet been published.
- The needs of people from non-English speaking backgrounds need to be accounted for in communication about asthma management.
- Educational of health professionals needs to be complemented by consumer campaigns.

## 5.2 Introduction and Main Findings

The “*Post-Market Review of PBS Medicines used to treat asthma in children: a review of education and interventions to improve prescribing and quality use of asthma medicines in children*” literature review (PMR Interventions Review) was conducted by NPS MedicineWise, an independent, evidence-based and not-for-profit organisation that provides medicine information to consumers and health professionals. The PMR Interventions Review is split into two sections, one addressing each ToR 4 and 5. Section one, which covers ToR 4, reviews the past five years of active education activities dealing with medication management in children with asthma in Australia.

The full PMR Interventions Review is appended at [Appendix G](#).

The PMR Interventions Review identified 30 active educational activities, conducted in Australia between 2008 and 2013, that involve medication management in children. Of these, 19 are currently available and two will commence in 2014. These educational activities were put into one of three categories depending on the focus of the activity:

- Consumer focussed educational activities (12);
- Consumers and healthcare professional focussed educational activities (7); and
- Healthcare professional focussed educational activities (11).

The full list of programmes is appended in [Appendix H](#).

Educational activities with a consumer component were predominantly run by Asthma Australia and delivered by state and territory Asthma Foundations and targeted staff of schools, preschools and other children's services. The Australian National Asthma Council (NAC) was the most common provider of activities for healthcare professionals. The ongoing nature of many of the activities along with the introduction of legal requirements for education and expansion of existing programmes will ensure that education in this area continues.

## 5.3 Methodology

For ToR 4, only active educational programmes were considered for the report. An active educational activity was defined as the provision of education or training on asthma and its management that was delivered face-to-face, over the telephone or online. Educational approaches that involve the development of educational resources alone without an active dissemination strategy are considered inactive educational activities and are not included.

In addition, studies that only provided written materials or referred consumers to information on websites without any further interaction, were excluded. The majority of activities which were reviewed involved the provision of education alone, commonly in a workshop format, with a small number providing support and education.

### 5.3.1 Search strategy

The bibliographic databases MEDLINE, EMBASE, CINAHL and The Cochrane Library were searched using MeSH (Medical Subject Headings) and appropriate keywords such

as asthma, drug therapy, child and education. Searches were limited to active educational activities conducted within Australia from 2008 to September 2013 in a community setting. Searches for informally published literature were carried out through the websites of several Australian organisations that work with patients and health professionals involved in the management of asthma.

No restrictions were placed upon study type and both clinical trials and observational studies were eligible for inclusion. Studies relevant to ToR 4 identified during the searches for ToR 5 were also included (and vice versa).

### **5.3.2 Selection criteria**

Educational activities were included if they:

- specified they provided education on medicine use in children with asthma to Australian healthcare professionals or consumers (children and/or their carers); and
- actively provided an educational activity in a community setting between January 2008 and September 2013.

For educational activities which were part of clinical trials, the education component was required to have been performed within the last five years (2008 to 2013), regardless of the publication date of the study findings.

## **5.4 Consumer focussed educational activities**

Asthma Australia and the Asthma Foundations were identified as the dominant providers of educational activities directed at consumers over the past five years.(44, 48-56) The activities provided primarily involved the provision of emergency asthma management training to staff of schools, preschools and other children's services.

Programmes such as ACAP,(53) funded by the Commonwealth and coordinated by Asthma Australia, were found to be well established with 72% of staff in schools and 48% of staff in preschools receiving this training since 2010.(43) It is anticipated that the programme will continue to receive Commonwealth funding until 2016 and that it will be expanded to target children and parents in addition to school and preschool staff.(57) From January 2013, all child care centres were legally required to have at least one member of staff trained in emergency asthma management available at all times. This will be expected to increase the number of adults receiving training in this area.(58) A spike in the demand for this course has already been reported.(57)

The focus on emergency asthma management training for staff working with children is complemented by the national Asthma Friendly initiative. This initiative, which requires emergency asthma training as one of the criteria for accreditation, also promotes ongoing awareness of asthma first aid. It does so through the requirement for Asthma Emergency Kits to be available, Asthma First Aid posters to be displayed, and the need for an organisation's health and safety policies to explicitly include asthma.(59-61) In addition, work conducted as part of the Community Support Programme (CSP) provides

education to targeted community groups, which, is likely to benefit children indirectly.(56)

Broader asthma education is available to parents and carers via the national 1800 ASTHMA phone line and its predecessor the Asthma Information Line.(44, 45, 62) The service provides the opportunity to receive personalised information and support from a healthcare professional. Parents and carers asking about their child's asthma accounted for over half (55%) of the 3487 calls in 2009–10,(44) and around a third of the 2621 calls in 2010–11(45). These findings may highlight a demand for information from parents and carers.

While the above educational activities are available nationally, a number of local activities were also identified. The Community Asthma Programme servicing specific regions in Victoria continues to provide education and support to children with asthma and their families.(63, 64) Local support for children and their families was also provided in one educational activity involving swimming lessons attended by an asthma educator.(54) In contrast, children alone were the target audience of the Wimmera Asthma Camp,(55) the resources developed by Asthma Foundation NSW to assist teachers to incorporate asthma into the NSW school curriculum,(52) and the one off education provided to Victorian school students from Altona North's Early Learners school.(50) The Women's and Children's Hospital in Adelaide ran the Asthma In-Home programme for two years providing intensive one-on-one nurse-led asthma education for children who were newly diagnosed or attending ED frequently.

## **5.5 Consumers and healthcare professional focussed educational activities**

The seven educational activities identified were provided by a variety of organisations, (65-71) with Asthma Australia and the Asthma Foundations again linked with a number of these initiatives(66, 67, 69, 71).

Almost all of the activities were delivered in specific areas of Australia.(65, 66, 68, 70, 71) The *Taking action together project* was conducted in Sydney(68), the structured education and self-management pilot study was conducted in Western Australia(65) and both the *Regional Communities Breathe Better*(71) and the *Home Medicines Reviews for children with asthma* programmes(70) were conducted in areas of South Australia. In contrast, the Triple A programme has been undertaken nationally.(46, 69)

As reported for many of the consumer focussed educational activities, the Triple A programme targets the school setting, although, students are the target audience for this programme.(72, 73) Over 2000 senior students have been trained as peer leaders with the educational sessions they provide reaching more than 26,000 high school students from 35 schools across Australia.(46) Unlike other activities identified, this programme has begun to focus on schools with high levels of students from Aboriginal and Torres Strait Islander and refugee backgrounds.(66, 73) The Anti-Smoking Asthma Programme pilot study for high schools which is based on the Triple A programme also targeted Aboriginal and Torres Strait Islander and disadvantaged young people.(67)

## 5.6 Healthcare professional focussed activities

The NAC was found to provide the majority of healthcare focussed educational activities relevant to this ToR over the past five years. The NAC runs three workshops that cover the use of medicines in children with asthma as part of its *Asthma Best Practice for Professionals Programme*.(74-76) The PACE Australia programme is also provided by the NAC with funding from the Commonwealth.(77) Activities provided by other organisations included: an e-learning module(78); two asthma educator training courses (79, 80); and four one off lectures (three of which were supported by companies that manufacture pharmaceuticals).(81-83)

The educational activities identified, targeted GPs,(74, 77, 81-83) pharmacists,(74, 75, 77) healthcare professionals generally,(74, 79, 80) nurse practitioners,(78) practice nurses,(74, 76) GP interns(78), new prescribers in community care settings,(78) asthma and respiratory educators(74) and aboriginal health workers.(74) Of the 11 interventions identified six were available nationally.(74, 75, 77, 78, 81)

Information on the number of healthcare professionals reached by the educational activities identified was not found. It is also not clear how widely available and accessible the six national programmes are. The NAC report in their submission to the *Post-Market Review of PBS Medicines Used to Treat Asthma in Children* that they plan (in collaboration with the PACE group) to include the PACE workshops in the next iteration of their GP and Allied Healthcare professionals Asthma and Respiratory Education programme which was funded for roll-out in 2014.(84)

## 5.7 Overall Influence of education programmes on prescriber and patient behaviour

The extent to which the educational activities identified may have influenced the use of asthma medicines in children remains largely unknown as the impact on patient outcomes was only explored for three of the educational activities.(47, 63, 65, 85) Findings from activities that did evaluate impact on patient outcomes were mixed with the Community Asthma Programme model of care reporting a reduction in ED visits and an improvement in quality of life(63), while a pilot study of structured education and self-management reported no difference for these outcomes.(65) Only the PACE Australia programme explored the impact of the educational activity on appropriate medicine use in children.(47) The RCT found that children with infrequent intermittent asthma treated by intervention GPs were significantly less likely to use ICSs or LABAs.(47)

## **5.8 Issues Identified**

The primary issue found was that the reach and intensity of many of the activities identified was not reported, making it difficult to provide a comprehensive picture of education provided.

## Section 6: ToR 5

### Effectiveness of community setting interventions

Identify effective interventions that have resulted in improvement of prescribing and quality use of medicines in the context of childhood asthma using overseas or Australian literature.

#### 6.1 Key findings for ToR 5

- *A systematic literature review of interventions to improve prescribing and quality use of medicines in children with asthma identified that consumer education and behaviour interventions may have small benefits on healthcare utilisation, specifically ED and hospital visits. These findings are broadly supported by four other systematic reviews (86-89) but the evidence was generally of moderate to low strength.*
- *Very few healthcare professional intervention studies involving educational outreach visits, audit and feedback, reminders, and patient mediated interventions are available.*
- *In terms of healthcare professional interventions, little or no benefit was identified for multi component interventions; educational meetings had inconsistent impacts on improving prescribing; and patient mediated interventions had inconsistent impacts on healthcare utilisation.*
- *Healthcare professional reminders may slightly improve preventer use, but the evidence for this was of low strength.*
- *Overall, the literature review was unable to isolate intervention types that clearly and consistently improved prescribing, preventer use or healthcare utilisation.*

#### **Stakeholder input from the Forum and submissions on Terms of Reference**

- A multifaceted approach to paediatric specific asthma education is needed, involving a range of settings and stakeholders, including healthcare professionals and consumers. Schools and childcare settings were considered particularly important for childhood asthma education.
- Some healthcare professionals considered that professional education needs to involve clinical education in relation to diagnosis and type of asthma.
- Some stakeholders indicated that education programmes should be offered to patients and their families at a time when they are most receptive to hearing and taking in the advice and information, usually the follow-up phases and not during the acute phase.
- Some pharmacists considered that they could be more actively involved as part of the asthma primary care team for newly-diagnosed children potentially under a modified Pharmacy Asthma Management Service.
- Asthma care plans provide a useful form of communication between health care professionals, carers, school staff and others involved in a child's life. The way these are used currently may not promote maximum benefit.

## 6.2 Introduction and main findings of the literature review

NPS MedicineWise was commissioned by the Department to undertake a literature review of community setting interventions to improve prescribing and quality use of medicines in children with asthma, considering both Australian and international studies. The search was restricted to English language articles published between 2002 and September 2013.

Ninety-eight studies and fifteen systematic reviews investigating a diverse range of interventions were identified. Studies were categorised according to target population (consumer, healthcare professional, or both) and then by predominant intervention type. Key outcomes of importance for decision making were selected: use of preventers, clinic visits, emergency department (ED) visits and hospital visits. The overall quality of evidence was graded for these outcomes. Table 6.1. provides a summary of the strength of evidence in support of the interventions.

Overall, the review was unable to identify intervention types that clearly and consistently demonstrated improvements in the key outcomes of interest. The majority of studies were conducted overseas and focussed on consumers. Low numbers of studies for some intervention types, and the generally low to very low quality of evidence makes it difficult to draw conclusions regarding the effectiveness of interventions.

Consumer education and behaviour interventions may have slight benefits on healthcare utilisation, specifically ED and hospital visits. These findings are broadly supported by four other systematic reviews,(86-89) but the evidence was generally of moderate to low strength. Most healthcare professional interventions showed either inconsistent benefits or, little or no benefit, on prescribing and healthcare utilisation. Healthcare professional reminders may slightly improve preventer use, but the evidence for this was of low strength.

The full literature review is included at [Appendix G](#). This chapter provides a summary of the literature review methodology and results, with an emphasis on RCTs and intervention types that showed statistically significant benefits.

**Table 6.1. Summary of the strength of evidence in support of the interventions to improve the use of asthma medicines in children.**

<b>Intervention</b>	<b>Preventer use</b>	<b>Clinic visits</b>	<b>ED visits</b>	<b>Hospital visits</b>
<b>Consumer education</b>	Unable to draw conclusions <i>Strength: Very Low</i>	Little or no benefit <i>Strength: Low</i>	Slight benefit <i>Strength: Low</i>	Slight benefit <i>Strength: Low</i>
<b>Consumer behaviour</b>	Some benefit <i>Strength: Moderate</i>	Little or no benefit <i>Strength: Moderate</i>	Slight benefit <i>Strength: Moderate</i>	Slight benefit <i>Strength: Moderate</i>
<b>Consumer skills</b>	Unable to draw conclusions <i>Strength: Very Low</i>	Unable to draw conclusions <i>Strength: Very Low</i>	Unable to draw conclusions <i>Strength: Very Low</i>	Unable to draw conclusions <i>Strength: Very Low</i>
<b>Consumer support</b>	Some benefit <i>Strength: Moderate</i>	Little or no benefit <i>Strength: Moderate</i>	Little or no benefit <i>Strength: Low</i>	Little or no benefit <i>Strength: Moderate</i>
<b>Consumer &amp; healthcare professional</b>	Little or no benefit <i>Strength: Moderate</i>	Unable to draw conclusions <i>Strength: Very Low</i>	Slight benefit <i>Strength: Low</i>	Unable to draw conclusions <i>Strength: Very Low</i>
<b>Healthcare professional meetings</b>	Unable to draw conclusions <i>Strength: Very Low</i>	Little or no benefit <i>Strength: Low</i>	Slight benefit <i>Strength: Low</i>	Little or no benefit <i>Strength: Low</i>
<b>Healthcare professional multifaceted</b>	Little or no benefit <i>Strength: Low</i>	Little or no benefit <i>Strength: Low</i>	Little or no benefit <i>Strength: Low</i>	Little or no benefit <i>Strength: Low</i>
<b>Healthcare professional other</b>	Slight benefit using reminders <i>Strength: Low</i>	Little or no benefit for patient mediated <i>Strength: Moderate</i>	Some benefit for patient mediated <i>Strength: Moderate</i>	Little or no benefit for patient mediated <i>Strength: Moderate</i>

Notes:

Interventions classified according to taxonomy of consumer interventions developed by Lowe *et al.*(90) or the Cochrane Effective Practice and Organisation of Care (EPOC) taxonomy of healthcare professional interventions.(91)

Strength of evidence:

- High quality – Further research is unlikely to change our confidence in the estimate of effect.
- Moderate quality – Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low quality – Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very Low quality: We are very uncertain about the estimate.

### 6.3 Methodology used in this literature review

The bibliographic databases MEDLINE, EMBASE, CINAHL and The Cochrane Library were searched for relevant articles published in English between 2002 and September 2013. Grey literature was searched as for ToR 4 and the references of systematic reviews were checked for any additional eligible studies.

Studies were included if they involved children with asthma in a community setting; focussed on improving prescribing or quality use of medicines; and reported on outcomes such as medicines use, healthcare utilisation, changes in knowledge or

attitudes, or clinically relevant patient outcomes.(91) Studies identified were systematic reviews, randomised controlled trials (RCTs), controlled clinical trials (CCTs), controlled before and after studies (CBAs) and interrupted time series studies (ITSs).

Identified studies were categorised according to the target population (consumer, healthcare professional, or both) and then by predominant intervention type using the taxonomy of consumer interventions developed by Lowe *et al.*(90) or the EPOC taxonomy of healthcare professional interventions.(91) [Appendix I](#) describes the classification of interventions.

Systematic reviews were assessed using the AMSTAR tool.(92) The quality of other studies was assessed using the EPOC Review Group Data Collection Checklist.(91) Consistent with the Grading the Recommendations Assessment, Development and Evaluation (GRADE) guidelines, key outcomes of importance for decision making were selected and overall quality of evidence was graded as high, moderate, low, or very low for these outcomes.(93) The outcomes were: use of preventers, clinic visits, ED visits, and hospital visits. Synthesis of identified evidence was carried out using a narrative review according to intervention type, given the heterogeneity of the identified interventions.

Ninety-eight studies investigating a diverse range of interventions were identified, the majority of which were conducted overseas and focussed on consumers. A further 15 systematic reviews of adequate quality were also included.

## **6.4 Consumer focussed interventions providing education**

### **6.4.1 Key findings**

- Consumer education interventions were the most often studied.
- There is low quality evidence suggesting that asthma education for consumers may slightly decrease rates of ED and hospital visits.
- The narrative review of the evidence suggests more complex education is more likely to show some improvement. Basic asthma education appears to have a minimal impact on improving medicines use, Quality of Life (QoL) or healthcare utilisation.
- In terms of complex consumer education:
  - Home visits, and computer or web based asthma education interventions, do not appear to be highly successful in improving medicines or healthcare use.
  - The US school based programme (Open Airways for Schools) and Canadian school based programme (Roaring Adventures of Puff) have mixed success in improving health outcomes.
  - School based asthma clubs improved inhaler technique in one UK study.

#### **6.4.2 Small group education (basic intervention)**

Two studies investigated providing basic education to children and/or carers during small group sessions. The Canadian study reported a significant reduction in ED visits (0.45 vs 0.75,  $p=0.004$ ) and oral corticosteroid use (0.63 vs 0.85,  $p<0.001$ ) at 12 months.(94) The Spanish and Latin American study reported a significant drop in hospital visits at six months when children ( $-0.28$ , 95%CI  $-0.51$  to  $-0.05$ ), or children and caregivers ( $-0.25$ , 95%CI  $-0.49$  to  $-0.02$ ), received the education, but not when the caregivers alone received the education.(95)

#### **6.4.3 Home visits (complex intervention)**

In one Puerto Rican study, asthma educators visited children and families in their homes and followed them up with regular telephone calls, to provide education, identify and address barriers to appropriate medicine use and monitor healthcare system use. Control families received written educational flyers. The intervention reduced ED visits (1.13% vs 1.66%, IDR 0.63 [95% CI 0.41 to 0.95]) and hospital visits (0.41% vs 0.95%, IDR 0.32 [95% CI 0.15 to 0.72]), but made no difference to inhaler technique or overall caregiver QoL.(96)

#### **6.4.4 Open Airways for Schools (OAS) Programme (complex intervention)**

The '[Open Airways for Schools](#)' (OAS) programme offered by the American Lung Association is generally delivered in schools by teachers, school nurses or asthma educators over 4–6 45-minute sessions, including one session on using medicines appropriately. One US RCT compared the OAS programme combined with weekly health monitoring by nurses to usual care.(97) At 24 months, there was a decrease in ED visits (1.36 vs 1.59,  $p<0.001$ ) and hospitalisations (0.18 vs 0.45,  $p<0.05$ ). Two other RCTs in the US(98) and China(99), each with over 600 participants, did not show any difference in hospital or ED use between the intervention and control.

#### **6.4.5 Roaring Adventures of Puff (RAP) Programme (complex intervention)**

Three Canadian RCTs investigated the 'Roaring Adventures of Puff' (RAP) programme,(100) which is generally delivered in schools by nurses or asthma educators over six one-hour sessions, with one session on using medicines appropriately. The programme had no effect upon clinic or ED visits in two studies,(101, 102) while the average number of urgent clinic and ED visits was significantly lower in the intervention group in the third study (1.7 vs 2.5,  $p<0.01$ ).(103) Two of the studies reported on the impact on medicines use and found no difference in reliever use or ownership of an AAP between the intervention and control groups.(101, 102) One study reported an increase in the appropriate use of preventer medicines (63% vs 32%,  $p<0.001$ ),(101) and another study reported higher QoL scores (PAQLQ) (5.9 vs 4.9,  $p<0.05$ ),(102) in intervention children than controls.

#### **6.4.6 Other school based intervention studies**

One UK RCT evaluated a complex education programme delivered over eight sessions via primary school asthma clubs run by community nurses. This included general

asthma education and hands on demonstration of the use of inhalers. At 16 weeks, significantly more children in the intervention group had correct inhaler technique (56% vs 15%,  $p < 0.001$ ) or partially correct technique (84% vs 40%,  $p < 0.001$ ), than controls. There was no difference in QoL between the groups.(104)

## 6.5 Consumer focussed interventions supporting behaviour change

### 6.5.1 Key findings

- There is moderate quality evidence that asthma behaviour interventions lead to an increase in the use of preventers, and a slight decrease in ED and hospital visits.
- Electronic monitoring of medicines decreased ED visits in one study and increased preventer adherence in two studies, but adherence may not be sustained over time.
- Coaching interventions targeting caregivers had mixed success in reducing number of hospital visits, but improved parental QoL scores in one study.

### 6.5.2 Interventions targeting treatment behaviours

A small Australian study investigated the impact of measuring adherence using an electronic monitoring device and providing feedback on medicine use in children with poorly controlled asthma despite being prescribed preventers.(105) At four months, preventer adherence was significantly higher in the intervention compared to the control group (79% vs. 58%,  $p < 0.01$ ), while no significant differences were observed with use of reliever medicines.

A US RCT studied the efficacy of medication adherence feedback combined with asthma education compared to usual care. At 18 months, ED visits decreased faster for intervention children than controls (15% greater decrease in visits per six months,  $p < 0.02$ ), but there were no significant between group changes with respect to hospital visits. The intervention resulted in significant increases in the use of ICSs ( $p < 0.03$ ), which slowed during the 12-month follow-up by 9% per quarter ( $p < 0.03$ ). The intervention significantly reduced the use of oral corticosteroids over 18 months ( $p < 0.006$ ). (106)

### 6.5.3 Interventions targeting health promotion behaviours

Three US studies provided coaching based on the transtheoretical model of behaviour change to promote the adoption of positive health behaviours, such as administration of preventer and reliever medicines, use of an AAP, regular GP visits, and minimising exposure to allergens.(107-109) The coaches initially assessed parent's readiness to adopt the targeted behaviours followed by problem solving and change strategies to guide the adoption of key behaviours. In Fisher *et al.*, coaching reduced hospitalisations over two years (36.5% vs. 59.1%,  $p < 0.01$ ), (107) while Garbutt *et al.* (108) and Nelson *et al.* (109) reported no significant differences in hospitalisations, ED visits or acute clinic visits, but the intervention groups had more planned asthma monitoring visits. (108, 109) In Garbutt *et al.*, coaching significantly improved the proportion of patients who

reported having an AAP, but there was no significant difference in the use of preventer medicines.(108)

## **6.6 Consumer focussed interventions supporting the acquisition of skills and competencies**

### **6.6.1 Key findings**

- It is uncertain whether skills interventions for consumers lead to differences in rates of preventer use, clinic or ED visits, or hospitalisations because the quality of evidence is very low. The eight identified studies reported inconsistent results and many were classified as being at high risk of bias.
- Interventions with practical skills based training had mixed success in improving use of preventers and healthcare. One US school based programme improved inhaler technique.

### **6.6.2 Interventions with practical skills based component**

Four studies, three of which were school based, looked at asthma education interventions with an interactive, hands on, skills based component.(110-114) Horner *et al.* had educators deliver a seven step self-management intervention that incorporated education plus skills practice with MDIs, PFM and problem solving to increase self-efficacy of self-management. This study demonstrated a significant improvement in inhaler technique in intervention patients compared to controls (6.64 vs. 4.80,  $p < 0.001$ ). (113) Two other school based programmes found no significant differences in terms of spacer technique, (114) or use of preventers, healthcare utilisation or QoL, (110) between the intervention and usual care groups.

Butz *et al.* delivered a home based asthma self-management intervention over a 12-month period using trained community health nurses. The intervention included symptom recognition, home treatment of acute symptoms, appropriate asthma medicines and review/practice of nebuliser technique. The intervention resulted in significant decreases in ED visits (28% vs. 46%,  $p < 0.05$ ), hospitalisations (4% vs. 13%,  $p < 0.05$ ), and in the mean number of ICS prescriptions dispensed (2.47 vs. 3.30,  $p = 0.02$ ). No differences in having AAPs, or use of relievers or oral corticosteroid bursts, were found between groups.(111, 112)

### **6.6.3 Miscellaneous skills based interventions**

Chan *et al.* assessed whether in-home internet-based monitoring and skills training improved asthma outcomes in children. The intervention group received three in-person visits and three virtual visits via the internet. The virtual visits included video recording of the child's PFM and inhaler technique and electronic feedback by a case manager, and also provided asthma education. Control patients received all education and skills training via six in-person visits at an outpatient clinic with telephone follow up by case managers. Patients in the intervention group had significantly higher MDI +

spacer technique scores (94% vs. 89%,  $p < 0.05$ ). There were no differences between groups in medication use, healthcare utilisation, QoL or in dry powder inhaler technique.(115) Another study, found a significant improvement in QoL when inhaler technique education was provided via visual concept mapping (where concepts were instructed using shapes and diagrams) rather than face-to-face (0.3 vs. 0.1,  $p < 0.05$ ). (116)

## **6.7 Consumer focussed interventions providing support**

### **6.7.1 Key findings**

- There is moderate quality evidence that asthma support interventions for consumers lead to a slight increase in the use of preventers.
- An internet based asthma monitoring tool improved the use of preventers in one study, and a complex support intervention directed at families reported improvement in use of preventers and adherence to prescribed asthma medicines in another study.

### **6.7.2 Interactive asthma monitoring system based interventions**

Four studies assessed the effectiveness of interactive asthma monitoring systems designed to assist patients in managing their asthma.(117-120) Three studies found no differences between intervention and control groups in healthcare utilisation.(117, 118, 120) A Taiwanese study looked at an interactive, internet based asthma monitoring tool (Blue Angel for Asthma Kids). Intervention patients used an electronic asthma diary and recorded peak flow via a website and were instructed to follow subsequent instructions given by the computer and physicians (via email or telephone). Control children used paper asthma diaries. At 12 weeks, the internet based monitoring tool significantly improved use of preventers (63.2% vs. 42.1%,  $p < 0.05$ ), but had no effect upon inhaler technique.(119)

### **6.7.3 Case management interventions**

Six US studies involved case managers providing support to families through home visits, via telephone or both.(121-126). Only one study reported a change in medicines use, with a significant increase in the use of ICSs (70% vs. 38%,  $p < 0.05$ ) and adherence to medicines in the intervention group compared to control ( $3.1 \pm 1.2$  vs.  $2.1 \pm 1.4$ ,  $p < 0.001$ ). (121) One study reported significantly reduced clinic visits over a year (0.75 vs. 1.40,  $p = 0.0001$ ), (124) and another study reported a decrease in the number of hospitalisations at 12 months (0.11 vs 0.27,  $p = 0.05$ ). (122) None of the other studies reported any impact on healthcare utilisation.(122-126)

## 6.8 Consumer and healthcare professional focussed interventions

### 6.8.1 Key findings

- There is low quality evidence that consumer and healthcare professional interventions may lead to slightly fewer ED visits.
- An Australian study where GPs received academic detailing and children were actively reminded to attend GP visits for asthma care and education found improvements in reliever use and a reduction in unplanned clinic visits.
- A US study where GPs received academic detailing and children received asthma education decreased healthcare utilisation and improved QoL.

### 6.8.2 Consumers and GPs

In a 2000–01 Australian study, GPs were provided a one-on-one academic detailing session. The active recall GPs were asked to administer asthma care according to the 3+ Visit Plan and were sent reminders when a child's next visit was due. During the 3+ Visits children were provided with asthma education and had their medicines and device technique reviewed. The control arm was asked to provide usual care to their asthma patients. Children in the intervention group were significantly less likely to have seen their GP for an unplanned asthma visit, and significantly more likely to have seen their GP for at least one planned asthma visit. While there was no difference in the regular use of preventer between the intervention and control group, the intervention group were less likely to use relievers frequently (9% vs 30%,  $p=0.0001$ ). ED visits were similar in both groups.(127)

In a US study, teenagers were randomised to usual care or to an eight-week programme of group education on asthma management skills and individualised coaching sessions to identify needs and help students manage their medical visits. The primary health providers of the intervention students received academic detailing via telephone. After 12 months, there was no difference between groups in terms of preventer use, but there were significant reductions in clinic, ED and hospital visits in the intervention arm compared to the control arm.(128)

## 6.9 Healthcare professional focussed interventions involving educational meetings

### 6.9.1 Key findings

- There is low or very low quality evidence that group education meetings for healthcare professionals have little impact upon healthcare utilisation while the impact upon use of preventers is unclear.
- One study found that provision of education to community pharmacists could improve their ability to produce appropriate asthma plans for patients.

### **6.9.2 GP educational meetings**

Two studies evaluated the Practitioner Asthma Communication and Education (PACE) programme, which consists of GP interactive seminars on reviewing asthma guidelines, communication techniques using videos and case studies, protocol for patient communication, self-assessment and key asthma messages. In a US study, after 12 months, the PACE physicians were more confident in their ability to develop an asthma plan and their patients were less likely to attend the ED than those in the control arm.(129) In an Australian study, after 12 months, the GPs who had completed the programme were significantly more likely to ask patients to demonstrate inhaler technique, and their child patients with infrequent intermittent asthma were significantly less likely to use ICSs or LABAs.(47)

A Dutch study provided GPs with information on asthma guidelines, group training on asthma and inhalation technique, and individual treatment advice for children they were currently treating. The prescription rates for ICSs were significantly higher in the intervention group when compared to the group receiving guidelines alone (0.6 puffs per day vs 0.4 puffs per day).(130) In a New Zealand trial, intervention GPs who received group education on algorithms for treating chronic and acute asthma in children, showed significant drops in the rates of prescription of oral relievers when compared to the control GPs.(131) Two other studies showed that asthma education delivered to GPs by small group workshops was no more effective than guidelines(132, 133) or traditional lecture formats,(134) at increasing GP knowledge.

### **6.9.3 Pharmacist educational meetings**

A Canadian study trained community pharmacists in device and inhaler use, how to assess patients, introduce the concept of self-management and develop an asthma plan. Simulated patients assessed the pharmacists' ability to manage asthma in the pharmacy. The intervention pharmacists were more likely to produce an appropriate plan for patients than those in the control group.(135)

## **6.10 Other healthcare professional interventions**

### **6.10.1 Key findings**

- There is moderate quality evidence suggesting that patient mediated interventions for healthcare professionals lead to decreased rates of ED visits and little or no difference in rates of clinic visits and hospitalisations.
- There is low quality evidence suggesting that reminder interventions for healthcare professionals may slightly increase the rate of prescriptions for preventers. Clinical decision support based alerts and reminders increased preventer prescribing rates and use of AAPs by GPs in a single US study.

### **6.10.2 Patient mediated interventions**

Patient mediated interventions focussed on presenting providers with new clinical information collected directly from patients. Three US studies investigated the effectiveness of prompting or notifying providers via letters with information on patient-specific asthma symptoms, severity, medication and health service use together with guideline based treatment recommendations in improving asthma care.(136-138) At 12 months, only one study demonstrated a significant decrease in ED visits compared to the control group (0.87 vs.1.14,  $p=0.013$ ). (138) Another study found that compared to the control group, children in the intervention group were more likely to have asthma related preventive action taken at the visits (87% vs. 69%,  $p=0.002$ ), to obtain an AAP (50% vs. 24%,  $p<0.001$ ), to receive recommendations for a specific asthma follow up visit (54% vs. 37%,  $p=0.02$ ) and to have discussions regarding asthma (75% vs. 63%,  $p=0.05$ ). (136) No significant between group differences were found in any of the three studies with respect to change in medicines (new or altered dose), change in preventive medicines, discussions on compliance, clinic visits or hospital visits.(136-138)

### **6.10.3 Reminder interventions**

A US based RCT determined the impact of clinical decision support embedded in electronic health records on GP adherence to asthma guidelines. Healthcare providers in all participating practices received asthma education (modified PACE programme) as well as training in spirometry and devices. All practices had the same key asthma management tools available in the electronic health records, either passively in the control practices, or via decision support alerts and reminders in the intervention practices. At 12 months, the intervention resulted in significant increases in the prescription rate for preventers (7% vs. 1%,  $p=0.006$ ) and use of AAPs (14% vs. 11%,  $p=0.03$ ). (139)

## **6.11 Comparisons with systematic reviews**

### **6.11.1 Key findings**

This review found that consumer education interventions may have some impact on healthcare utilisation but the evidence to support these conclusions was of low or very low quality. These findings are similar to those of two Cochrane reviews (published in 2009 and 2011) on education and a 2007 Agency for Healthcare Research and Quality (AHRQ) report.(86-88) A 2003 Cochrane review concluded consumer education improved ED visits.(89, 140) There was no overlap in the studies between the 2003 Cochrane review and this review.

This review's finding that group education meetings for healthcare professionals may have little impact on healthcare utilisation is echoed by a 2013 AHRQ report which concluded that education based healthcare professional interventions were likely to show no benefit.(141) The findings of this review differed from the 2013 AHRQ report in that the AHRQ found some low to moderate evidence to support the use of decision

support tools, feedback and audit, and clinical pharmacy support in increasing the adherence of healthcare providers to asthma guidelines. However, often these results relied heavily on less rigorous study designs and the authors acknowledged that studies of a higher quality were less likely to find differences in outcomes.(141)

### **6.11.2 Cochrane reviews**

Boyd et al. (2009) identified 38 RCTs of asthma education for children who had attended the ED for asthma (n = 7843). This review reported a significantly reduced risk of subsequent ED visits (RR 0.73, 95% CI 0.65–0.81), hospital admissions (RR 0.79, 95% CI 0.69–0.92) and unscheduled doctor visits (RR 0.68, 95% CI 0.57–0.81) compared with control. However, the nature and delivery of education varied so much that the authors were unable to identify the characteristics associated with a successful outcome.

An older Cochrane review including 32 trials published prior to 1998, examined the efficacy of asthma self-management education on health outcomes in 3706 children. Education programmes were associated with a modest reduction in ED visits of 0.21 fewer visits (95% CI -0.33 to -0.09). There was no improvement in clinic visits or hospitalisations.(89, 140)

### **6.11.3 AHRQ reports**

A 2013 AHRQ report investigated the effect of interventions designed to improve healthcare providers' adherence to asthma guidelines. The review identified 68 randomised and non-randomised studies. The authors pointed out that evidence that was of higher quality (i.e. RCTs) was less likely to find differences in outcomes. The authors concluded that there was:

- Moderate strength of evidence for the effectiveness of decision support interventions to increase prescribing of asthma controller medicines by healthcare providers, mainly from non-randomised studies.
- Moderate strength of evidence to support feedback and audit interventions as an effective means to increase prescribing of asthma controller medications. Most feedback and audit interventions were multifaceted, limiting the ability to discern whether the feedback and audit component was effective in increasing controller medication prescribing by practitioners.
- Moderate strength of evidence that clinical pharmacy support interventions increase prescribing of asthma controller medications.
- Moderate strength of evidence supporting the effectiveness of decision support interventions to reduce ED visits or hospitalisations, mostly from non-randomised studies.(141)

A 2007 AHRQ report looked in part at the impact of self-monitoring, self-management or consumer education interventions for children with asthma. It included 69 studies, largely RCTs but also non-randomised trials and controlled before and after studies published up until 2004. Multivariate analyses were performed when more than 15 studies reported on the same outcome to identify factors that could potentially explain

why interventions may or may not have worked. This found that interventions targeting parents or caregivers were more likely to be associated with improvements in clinical outcomes.(87)

#### **6.11.4 Other reviews**

A medium quality review of school based asthma education identified 24 randomised and non-randomised studies (n = 9030). Among the 8–10 studies that measured the effect of an intervention on consumer asthma knowledge and asthma self-management, the majority reported significant improvements.(142)

A review of the effectiveness of psycho-educational interventions identified 35 studies in children. Pooling results from nine of these studies found psycho-educational interventions reduced hospital admissions (RR 0.64, 95% CI 0.46 to 0.89), but there was no significant impact on ED visits.(143)

A review into interactive computerised asthma patient education programmes (computer games, web-based education and personal interactive communication) identified nine RCTs. It concluded that while interactive computer education programmes may improve patient asthma knowledge and symptoms, their effect on clinical outcomes was mixed.(144)

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## **Appendix A – DUSC analysis 2011**

For details of this report please email the post market review secretariat  
[PBSPostmarket@health.gov.au](mailto:PBSPostmarket@health.gov.au)

## Appendix B – Reference Group Members

<b>Member</b>	<b>Type of Membership</b>	<b>Area of Expertise</b>
Professor Andrew McLachlan (Chair)	Individual – Technical	Pharmacy
Professor Peter van Asperen	Individual – Technical	Paediatric Respiratory Physician
Dr Sean Beggs	Individual – Technical	Paediatrician
Mr Mark Brooke	Representative - Organisational Interests	Asthma Australia
Associate. Professor Kingsley Coulthard	Individual – Technical	Pharmacy
Dr Suzanne Davey	Representative - Organisational Interests	Australian Medical Association
Professor Davina Gherzi	Representative - Organisational Interests	National Health and Medical Research Council
Dr Kerry Hancock	Representative - Organisational Interests	National Asthma Council
Ms Debra Kay	Consumer advocate	Consumer’s Health Forum
Dr Steven Rudolphy	Individual – Technical	General Practitioner
Dr Helen Toyne	Individual – Technical	General Practitioner
Dr Lynn Weekes	Representative - Organisational Interests	NPS: MedicineWise

## Appendix C – PBS Subsidised Medicines

### *Preventers – Inhaled Corticosteroids\**

<b>Beclomethasone ATC Code: R03BA01</b>						
<b>Item Code</b>	<b>Form</b>	<b>Dose</b>	<b>Max. qty</b>	<b>No. rpts</b>	<b>DPMQ</b>	<b>Restriction</b>
<b>8406K</b>	Oral pressurised inhalation	50 micrograms per dose (200 doses)	1	5	\$19.50	<b><i>Unrestricted</i></b>
<b>8407L</b>	Oral pressurised inhalation	100 micrograms per dose (200 doses)	1	5	\$33.67	<b><i>Unrestricted</i></b>
<b>8408M</b>	Oral pressurised inhalation in breath actuated device	50 micrograms per dose (200 doses)	1	5	\$28.08	<b><i>Restricted Benefit</i></b> <ul style="list-style-type: none"> <li>• Patients unable to achieve coordinated use of other metered dose inhalers containing this drug</li> </ul>
<b>8409N</b>	Oral pressurised inhalation in breath actuated device	100 micrograms per dose (200 doses)	1	5	\$39.34	<b><i>Restricted Benefit</i></b> <ul style="list-style-type: none"> <li>• Patients unable to achieve coordinated use of other metered dose inhalers containing this drug</li> </ul>
<b>Budesonide ATC Code: R03BA02</b>						
<b>Item Code</b>	<b>Form</b>	<b>Dose</b>	<b>Max. qty</b>	<b>No. rpts</b>	<b>DPMQ</b>	<b>Restriction</b>
<b>2065Q</b>	Nebuliser suspension single dose unites	500 microgram per 2 mL inhalation: solution, 30 x 2 mL ampoules	1	5	\$38.07	<b><i>Authority Required (STREAMLINED)</i></b> <ul style="list-style-type: none"> <li>• <b>1351</b> Severe chronic asthma in patients who require long-term steroid therapy and who are unable to use other forms of inhaled steroid therapy</li> </ul>
<b>2066R</b>	Nebuliser suspension single dose units	1 milligram per 2 mL inhalation: solution, 30 x 2 mL	1	5	\$49.21	<b><i>Authority Required (STREAMLINED)</i></b> <ul style="list-style-type: none"> <li>• <b>1351</b> Severe chronic asthma in patients who require long-term steroid therapy and who are unable to use other forms of inhaled steroid therapy</li> </ul>
<b>2070Y</b>	Powder for oral inhalation in breath actuated device	100 micrograms per dose (200 doses)	1	5	\$23.55	<b><i>Unrestricted</i></b>

<b>Budesonide ATC Code: R03BA02</b>						
<b>Item Code</b>	<b>Form</b>	<b>Dose</b>	<b>Max. qty</b>	<b>No. rpts</b>	<b>DPMQ</b>	<b>Restriction</b>
<b>2071B</b>	Powder for oral inhalation in breath actuated device	200 micrograms per dose (200 doses)	1	5	\$31.29	<b><i>Unrestricted</i></b>
<b>2072C</b>	Powder for oral inhalation in breath actuated device	400 micrograms per dose (200 doses)	1	5	\$46.05	<b><i>Unrestricted</i></b>
<b>Fluticasone ATC Code: R03BA05</b>						
<b>Item Code</b>	<b>Form</b>	<b>Dose</b>	<b>Max. qty</b>	<b>No. rpts</b>	<b>DPMQ</b>	<b>Restriction</b>
<b>8147T</b>	Powder for oral inhalation in breath actuated device	100 micrograms per dose (60 doses)	1	5	\$17.30	<b><i>Unrestricted</i></b>
<b>8148W</b>	Powder for oral inhalation in breath actuated device	250 micrograms per dose (60 doses)	1	5	\$30.87	<b><i>Unrestricted</i></b>
<b>8149X</b>	Powder for oral inhalation in breath actuated device	500 micrograms per dose (60 doses)	1	5	\$49.93	<b><i>Unrestricted</i></b>
<b>8345F</b>	Oral pressurised inhalation	125 micrograms per dose (120 doses)	1	5	\$30.87	<b><i>Unrestricted</i></b>
<b>8346G</b>	Oral pressurised inhalation	250 micrograms per dose (120 doses)	1	1	\$49.93	<b><i>Unrestricted</i></b>
<b>8516F</b>	Oral pressurised inhalation	50 micrograms per dose (120 doses)	1	5	\$17.30	<b><i>Unrestricted</i></b>
<b>Ciclesonide ATC Code: R03BA08</b>						
<b>Item Code</b>	<b>Form</b>	<b>Dose</b>	<b>Max. qty</b>	<b>No. rpts</b>	<b>DPMQ</b>	<b>Restriction</b>
<b>8853Y</b>	Oral pressurised inhalation	80 micrograms per dose (120 doses)	1	5	\$26.36	<b><i>Unrestricted</i></b>
<b>8854B</b>	Oral pressurised inhalation	160 micrograms per dose (120 doses)	1	5	\$42.46	<b><i>Unrestricted</i></b>

**Mast Cell Stabilisers\***

<b>Sodium Cromoglycate ATC Code: R03BC01</b>						
<b>Item Code</b>	<b>Form</b>	<b>Dose</b>	<b>Max. qty</b>	<b>No. rpts</b>	<b>DPMQ</b>	<b>Restriction</b>
<b>2878L</b>	Capsule containing powder for oral inhalation	20 milligram per capsule	100	5	\$31.62	<b><i>Unrestricted</i></b>
<b>8334P</b>	Oral pressurised inhalation	5 milligram per dose (112 doses),	1	5	\$38.52	<b><i>Unrestricted</i></b>
<b>8767K</b>	Oral pressurised inhalation	1 milligram per dose (200 doses),	1	5	\$33.71	<b><i>Unrestricted</i></b>
<b>Nedocromil ATC Code: R03BC03</b>						
<b>Item Code</b>	<b>Form</b>	<b>Dose</b>	<b>Max. qty</b>	<b>No. rpts</b>	<b>DPMQ</b>	<b>Restriction</b>
<b>8365G</b>	Oral pressurised inhalation	2 milligram per dose (112 doses)	1	5	\$37.90	<b><i>Unrestricted</i></b>

**Long-Acting Beta<sub>2</sub>-Agonists\***

<b>Salmeterol ATC Code: R03AC12</b>						
<b>Item Code</b>	<b>Form</b>	<b>Dose</b>	<b>Max. qty</b>	<b>No. rpts</b>	<b>DPMQ</b>	<b>Restriction</b>
<b>8141L</b>	Powder for oral inhalation in breath actuated device	50 micrograms per dose (60 doses)	1	5	\$37.54	<p><b>Restricted Benefit</b></p> <ul style="list-style-type: none"> <li>• Patients with frequent episodes of asthma who are currently receiving treatment with oral corticosteroids</li> <li>• Patients with frequent episodes of asthma who are currently receiving treatment with optimal doses of inhaled corticosteroids</li> </ul>
<b>Eformoterol ATC Code: R03AC13</b>						
<b>Item Code</b>	<b>Form</b>	<b>Dose</b>	<b>Max. qty</b>	<b>No. rpts</b>	<b>DPMQ</b>	<b>Restriction</b>
<b>8136F</b>	Capsule containing powder for oral inhalation	12 micrograms (60 capsules)	60	5	\$37.54	<p><b>Restricted Benefit</b></p> <ul style="list-style-type: none"> <li>• Patients with frequent episodes of asthma who are currently receiving treatment with oral corticosteroids</li> <li>• Patients with frequent episodes of asthma who are currently receiving treatment with optimal doses of inhaled corticosteroids</li> </ul>
<b>8239P</b>	Powder for oral inhalation in breath actuated device	6 micrograms per dose (60 doses)	1	5	\$26.59	<p><b>Restricted Benefit</b></p> <ul style="list-style-type: none"> <li>• Patients with frequent episodes of asthma who are currently receiving treatment with oral corticosteroids</li> <li>• Patients with frequent episodes of asthma who are currently receiving treatment with optimal doses of inhaled corticosteroids</li> </ul>
<b>8240Q</b>	Powder for oral inhalation in breath actuated device	12 micrograms per dose (60 doses)	1	5	\$36.65	<p><b>Restricted Benefit</b></p> <ul style="list-style-type: none"> <li>• Patients with frequent episodes of asthma who are currently receiving treatment with oral corticosteroids</li> <li>• Patients with frequent episodes of asthma who are currently receiving treatment with optimal doses of inhaled corticosteroids</li> </ul>

*Leukotriene Receptor Antagonist\**

Montelukast ATC Code: R03DC03						
Item Code	Form	Dose	Max. qty	No. rpts	DPMQ	Restriction
8627C	Chewable tablet	4 milligram	28	5	\$42.21	<p><b>Authority Required (STREAMLINED)</b></p> <ul style="list-style-type: none"> <li>• <b>2617</b> First-line preventer medication, as the single preventer agent for children aged 2 to 5 years with frequent intermittent or mild persistent asthma, as an alternative to sodium cromoglycate or nedocromil sodium</li> </ul> <p><b>Note</b> No applications for increased maximum quantities and/or repeats will be authorised. Montelukast sodium is not PBS-subsidised for use in a child aged 2 to 5 years with moderate to severe asthma. It is not intended as an alternative for a child aged 2 to 5 years who requires a corticosteroid as a preventer medication. Montelukast sodium is not subsidised in a child aged 2 to 5 years for use in combination with other preventer medications. PBS subsidy for montelukast sodium will therefore cease for a child aged 2 to 5 years who requires a preventer medication in addition to montelukast sodium.</p>
8628D	Chewable tablet	5 milligram	28	5	\$40.23	<p><b>Authority Required (STREAMLINED)</b></p> <ul style="list-style-type: none"> <li>• <b>2618</b> First-line preventer medication, as the single preventer agent for children aged 6 to 14 years with frequent intermittent or mild persistent asthma, as an alternative to sodium cromoglycate or nedocromil sodium</li> <li>• <b>3217</b> Prevention of exercise-induced asthma, as an alternative to adding salmeterol xinafoate or eformoterol fumarate, in a child aged 6 to 14 years whose asthma is otherwise well controlled while receiving optimal dose inhaled corticosteroid, but who requires short-acting beta<sub>2</sub>-agonist 3 or more times per week for prevention or relief of residual exercise-related symptoms</li> </ul> <p><b>Note</b> No applications for increased maximum quantities and/or repeats will be authorised. Montelukast sodium is not PBS-subsidised for use in a patient aged 15 years or older, or for use in addition to a long-acting beta<sub>2</sub>-agonist in any age group, or for use as a single second line preventer, as an alternative to corticosteroids, in a child aged 6 to 14 years with moderate to severe asthma.</p>

*Fixed dose combinations* \*,\*\*

<b>Salmeterol with Fluticasone ATC Code: R03AK06</b>						
<b>Item Code</b>	<b>Form</b>	<b>Dose</b>	<b>Max. qty</b>	<b>No. rpts</b>	<b>DPMQ</b>	<b>Restriction</b>
<b>8517G</b>	Oral pressurised inhalation	50 micrograms +25 micrograms per dose (120 doses),	1	5	\$47.41	<p><b>Restricted Benefit</b></p> <ul style="list-style-type: none"> <li> <p><b>Asthma</b>  <b>Clinical criteria:</b>                      Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids,                      AND                      Patient must have been stabilised on concomitant inhaled salmeterol xinafoate and fluticasone propionate if aged less than 12 years.</p> </li> </ul>
<b>8518H</b>	Oral pressurised inhalation	125 micrograms +25 micrograms per dose (120 doses),	1	5	\$59.52	<p><b>Restricted Benefit</b></p> <ul style="list-style-type: none"> <li> <p><b>Asthma</b>  <b>Clinical criteria:</b>                      Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids,                      AND                      Patient must have been stabilised on concomitant inhaled salmeterol xinafoate and fluticasone propionate if aged less than 12 years.</p> </li> </ul>
<b>8519J</b>	Oral pressurised inhalation	250 micrograms +25 micrograms per dose (120 doses),	1	5	\$78.65	<p><b>Restricted Benefit</b></p> <ul style="list-style-type: none"> <li> <p><b>Asthma</b>  <b>Clinical criteria:</b>                      Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids'                      AND                      Patient must have been stabilised on concomitant inhaled salmeterol</p> </li> </ul>

<b>Salmeterol with Fluticasone ATC Code: R03AK06</b>						
<b>Item Code</b>	<b>Form</b>	<b>Dose</b>	<b>Max. qty</b>	<b>No. rpts</b>	<b>DPMQ</b>	<b>Restriction</b>
						<p>xinafoate and fluticasone propionate if aged less than 12 years.</p> <ul style="list-style-type: none"> <li>• <b>Chronic obstructive pulmonary disease (COPD)</b>  <b>Clinical criteria:</b>  Patient must have a forced expiratory volume in 1 second (FEV<sub>1</sub>) less than 50% of predicted normal prior to therapy,  AND  Patient must have a history of repeated exacerbations with significant symptoms despite regular beta<sub>2</sub>-agonist bronchodilator therapy,  AND  The treatment must be for symptomatic treatment.</li> </ul> <p><b>Note</b>  Seretide is not indicated for the initiation of bronchodilator therapy in COPD.</p>
<b>8430Q</b>	Powder for oral inhalation in breath actuated device	100 micrograms +50 micrograms per dose (60 doses)	1	5	\$47.41	<p><b>Restricted Benefit</b></p> <ul style="list-style-type: none"> <li>• <b>Asthma</b>  <b>Clinical criteria:</b>  Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids,  AND  Patient must have been stabilised on concomitant inhaled salmeterol xinafoate and fluticasone propionate if aged less than 12 years.</li> </ul>
<b>8431R</b>	Powder for oral inhalation in breath actuated device	250 micrograms +50 micrograms per dose (60 doses)	1	5	\$59.52	<p><b>Restricted Benefit</b></p> <ul style="list-style-type: none"> <li>• <b>Asthma</b>  <b>Clinical criteria:</b>  Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids,</li> </ul>

Salmeterol with Fluticasone ATC Code: R03AK06						
Item Code	Form	Dose	Max. qty	No. rpts	DPMQ	Restriction
						AND Patient must have been stabilised on concomitant inhaled salmeterol xinafoate and fluticasone propionate if aged less than 12 years.
8432T	Powder for oral inhalation in breath actuated device	500 micrograms +50 micrograms per dose (60 doses)	1	5	\$78.65	<p><b>Restricted Benefit</b></p> <ul style="list-style-type: none"> <li> <p><b>Asthma</b>  <b>Clinical criteria:</b>  Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids'  AND  Patient must have been stabilised on concomitant inhaled salmeterol xinafoate and fluticasone propionate if aged less than 12 years.</p> </li> <li> <p><b>Chronic obstructive pulmonary disease (COPD)</b>  <b>Clinical criteria:</b>  Patient must have a forced expiratory volume in 1 second (FEV<sub>1</sub>) less than 50% of predicted normal prior to therapy,  AND  Patient must have a history of repeated exacerbations with significant symptoms despite regular beta<sub>2</sub>-agonist bronchodilator therapy,  AND  The treatment must be for symptomatic treatment.</p> </li> </ul> <p><b>Note</b>  Seretide is not indicated for the initiation of bronchodilator therapy in COPD.</p>

<b>Eformoterol with Budesonide ATC Code: R03AK07</b>						
<b>Item Code</b>	<b>Form</b>	<b>Dose</b>	<b>Max. qty</b>	<b>No. rpts</b>	<b>DPMQ</b>	<b>Restriction</b>
<b>10024N</b>	Oral pressurised inhalation	50 micrograms +3 micrograms per dose (120 doses)	2	5	\$54.67	<p><b>Restricted Benefit</b></p> <ul style="list-style-type: none"> <li>• <b>Asthma</b> <b>Clinical criteria:</b> <ul style="list-style-type: none"> <li>○ Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids; OR</li> <li>○ Patient must have experienced frequent asthma symptoms while receiving treatment with oral or inhaled corticosteroids and require single maintenance and reliever therapy; OR</li> <li>○ Patient must have experienced frequent asthma symptoms while receiving treatment with a combination of an inhaled corticosteroid and long-acting beta<sub>2</sub> agonist.</li> </ul> </li> <li><b>Population criteria:</b> Patient must be aged 12 years or over.</li> </ul>
<b>10015D</b>	Oral pressurised inhalation	100 micrograms +3 micrograms per dose (120 doses)	2	5	\$58.97	<p><b>Restricted Benefit</b></p> <ul style="list-style-type: none"> <li>• <b>Asthma</b> <b>Clinical criteria:</b> <ul style="list-style-type: none"> <li>○ Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids; OR</li> <li>○ Patient must have experienced frequent asthma symptoms while receiving treatment with oral or inhaled corticosteroids and require single maintenance and reliever therapy; OR</li> <li>○ Patient must have experienced frequent asthma symptoms while receiving treatment with a combination of an inhaled corticosteroid and long-acting beta<sub>2</sub> agonist.</li> </ul> </li> <li><b>Population criteria:</b> Patient must be aged 12 years or over.</li> </ul>
<b>10018G</b>	Oral pressurised inhalation	200 micrograms +6 micrograms per dose (120 doses)	2	5	\$90.75	<p><b>Restricted Benefit</b></p> <ul style="list-style-type: none"> <li>• <b>Asthma</b> <b>Clinical criteria:</b></li> </ul>

Eformoterol with Budesonide ATC Code: R03AK07						
Item Code	Form	Dose	Max. qty	No. rpts	DPMQ	Restriction
						<p>Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids.</p> <p><b>Population criteria:</b> Patient must be aged 12 years or over.</p> <ul style="list-style-type: none"> <li>• <b>Chronic obstructive pulmonary disease (COPD)</b> <b>Clinical criteria:</b> Patient must have a forced expiratory volume in 1 second (FEV<sub>1</sub>) less than 50% of predicted normal prior to therapy, AND Patient must have a history of repeated exacerbations with significant symptoms despite regular beta<sub>2</sub>-agonist bronchodilator therapy.</li> </ul> <p><b>Note</b> Unlike Symbicort Turbuhaler 200/6, Symbicort Rapihaler 200/6 is not recommended nor PBS-subsidised for use as 'maintenance and reliever' therapy as the approved Product Information does not specify such use. Budesonide with eformoterol fumarate dihydrate is not indicated for the initiation of bronchodilator therapy in COPD.</p>
8796Y	Powder for oral inhalation in breath actuated device	100 micrograms +6 micrograms per dose (120 doses)	1	5	\$54.68	<p><b>Restricted Benefit</b></p> <ul style="list-style-type: none"> <li>• <b>Asthma</b> <b>Clinical criteria:</b> Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids; OR Patient must have experienced frequent asthma symptoms while receiving treatment with oral or inhaled corticosteroids and require single maintenance and reliever therapy; OR Patient must have experienced frequent asthma symptoms while receiving treatment with a combination of an inhaled corticosteroid</li> </ul>

<b>Eformoterol with Budesonide ATC Code: R03AK07</b>						
<b>Item Code</b>	<b>Form</b>	<b>Dose</b>	<b>Max. qty</b>	<b>No. rpts</b>	<b>DPMQ</b>	<b>Restriction</b>
						and long-acting beta <sub>2</sub> agonist and require single maintenance and reliever therapy. <b>Population criteria:</b> Patient must be aged 12 years or over.
<b>8625Y</b>	Powder for oral inhalation in breath actuated device	200 micrograms +6 micrograms per dose (120 doses)	1	5	\$58.98	<b>Restricted Benefit</b>  <ul style="list-style-type: none"> <li>• <b>Asthma</b> <b>Clinical criteria:</b> Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids; OR Patient must have experienced frequent asthma symptoms while receiving treatment with oral or inhaled corticosteroids and require single maintenance and reliever therapy; OR Patient must have experienced frequent asthma symptoms while receiving treatment with a combination of an inhaled corticosteroid and long-acting beta<sub>2</sub> agonist and require single maintenance and reliever therapy. <b>Population criteria:</b> Patient must be aged 12 years or over.</li> </ul>
<b>8750M</b>	Powder for oral inhalation in breath actuated device	400 micrograms +12 micrograms per dose (120 doses)	1	5	\$90.76	<b>Restricted Benefit</b>  <ul style="list-style-type: none"> <li>• <b>Asthma</b> <b>Clinical criteria:</b> Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids. <b>Population criteria:</b> Patient must be aged 12 years or over.</li> <li>• <b>Chronic obstructive pulmonary disease (COPD)</b> <b>Clinical criteria:</b> Patient must have a forced expiratory volume in 1 second (FEV<sub>1</sub>) less</li> </ul>

<b>Eformoterol with Budesonide ATC Code: R03AK07</b>						
<b>Item Code</b>	<b>Form</b>	<b>Dose</b>	<b>Max. qty</b>	<b>No. rpts</b>	<b>DPMQ</b>	<b>Restriction</b>
						<p>than 50% of predicted normal prior to therapy, AND Patient must have a history of repeated exacerbations with significant symptoms despite regular beta<sub>2</sub>-agonist bronchodilator therapy, AND The treatment must be for symptomatic treatment.</p> <p><b>Note</b> Symbicort 400/12 is not recommended nor PBS-subsidised for use as 'maintenance and reliever' therapy. Budesonide with eformoterol fumarate dihydrate is not indicated for the initiation of bronchodilator therapy in COPD.</p>

<b>Eformoterol with Fluticasone ATC Code: R03AK11</b>						
<b>Item Code</b>	<b>Form</b>	<b>Dose</b>	<b>Max. qty</b>	<b>No. rpts</b>	<b>DPMQ</b>	<b>Restriction</b>
<b>2827T</b>	Oral pressurised inhalation	50 micrograms + 5 micrograms per dose (120 doses)	1	5	\$45.83	<p><b>Restricted Benefit</b></p> <ul style="list-style-type: none"> <li><b>Asthma Clinical criteria:</b> Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids.</li> <li><b>Population criteria:</b> Patient must be aged 12 years or over.</li> </ul> <p><b>Note</b> Flutiform is not recommended nor PBS-subsidised for use as 'maintenance and reliever' therapy. Flutiform is not indicated or PBS-subsidised for bronchodilator therapy in COPD.</p>

<b>Eformoterol with Fluticasone ATC Code: R03AK11</b>						
<b>Item Code</b>	<b>Form</b>	<b>Dose</b>	<b>Max. qty</b>	<b>No. rpts</b>	<b>DPMQ</b>	<b>Restriction</b>
<b>10007Q</b>	Oral pressurised inhalation	125 micrograms + 5 micrograms per dose (120 doses)	1	5	\$56.58	<p><b>Restricted Benefit</b></p> <ul style="list-style-type: none"> <li><b>Asthma</b> <b>Clinical criteria:</b> Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids. <b>Population criteria:</b> Patient must be aged 12 years or over.</li> </ul> <p><b>Note</b> Flutiform is not recommended nor PBS-subsidised for use as 'maintenance and reliever' therapy. Flutiform is not indicated or PBS-subsidised for bronchodilator therapy in COPD.</p>
<b>10008R</b>	Oral pressurised inhalation	250 micrograms + 10 micrograms per dose (120 doses)	1	5	\$78.65	<p><b>Restricted Benefit</b></p> <ul style="list-style-type: none"> <li><b>Asthma</b> <b>Clinical criteria:</b> Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids. <b>Population criteria:</b> Patient must be aged 12 years or over.</li> </ul> <p><b>Note</b> Flutiform is not recommended nor PBS-subsidised for use as 'maintenance and reliever' therapy. Flutiform is not indicated or PBS-subsidised for bronchodilator therapy in COPD.</p>

\*Table of PBS listed medicines correct as at March 2014.

\*\*Both Fluticasone Furoate/Vilanterol Trifenatate and Mometasone/eformoterol FDCs have been recommended by PBAC but are not yet listed.

## Appendix D - Recommendations from international clinical guidelines on use of preventers

Country	Guidelines	Date	Recommendations
United Kingdom	British guideline on the management of asthma (14)	2012	<p>The British guideline recommends a stepwise approach with ICS as the recommended preventer drug for adults and children (step 2). LTRA and cromones are presented as a less effective preventer therapy in all age groups.</p> <p>As add-on therapy in in children &gt; 12 years and adults taking ICS at doses 200-800 mcg BDP/day and in children 5-12 years taking ICS at doses of 400 mcg BDP/day (step 3), it recommends as first choice the addition of LABA. In children &lt;5 years, it recommends LTRA.</p> <p>Use of a single combination inhaler (SMART, budesonide/formoterol) as a rescue medication and a preventer therapy is considered at step 2 or step 3 only in selected adult patients who are poorly controlled</p>
Canada	<p>Canadian Thoracic Society Asthma Management Continuum – 2010 Consensus Summary for children six years of age and over, and adults (15)</p> <p>Canadian Thoracic Society 2012 guideline update (145)</p>	<p>2010</p> <p>2012</p>	<p>The 2010 Canadian Thoracic Society guideline recommends in adults and children 6 years of age and over:</p> <p>step 2: low dose ICS (alternative LTRA);</p> <p>The 2012 Canadian Thoracic Society guideline update states that**:</p> <ul style="list-style-type: none"> <li>- In adults with asthma not achieving control despite adherence to a low dose of ICS, the addition of a LABA is recommended. Alternative options include adding an LTRA or increasing to a medium dose of ICS (251-500 mcg BDP/day).</li> <li>- In children (6-11 years), with asthma not achieving control despite adherence to a low dose of ICS, increasing to a medium dose of ICS is recommended.</li> <li>- In children (6-11 years) not achieving asthma control on a medium dose of ICS, the addition of a LABA or LTRA is suggested.</li> </ul>
International (GINA*)	Global strategy for asthma management and prevention (146)	2012	<p>In adults and children &gt;5 years, the GINA guideline recommends a stepwise approach**:</p> <p>step 2: low dose ICS (alternative LTRA);</p> <p>step 3: low dose ICS plus LABA in adults (alternative medium ICS dose);            medium dose ICS in children &gt;5 years (alternative a low dose ICS plus LABA);            another alternative is to combine low dose ICS plus LTRA;</p> <p>step 4: medium or high dose (on a trial basis) ICS plus LABA in adults (alternative add on LTRA);</p> <p>The SMART approach is briefly mentioned as an alternative.</p>

Country	Guidelines	Date	Recommendations
International (GINA*)	Global strategy for asthma management and prevention in children 5 years and younger (147)	2009	In children < 5 years the GINA guideline recommends a stepwise approach**: step 2: low dose ICS; step 3: double low-dose ICS (alternative add LTRA).

GINA: Global Initiative for Asthma Guidelines have been developed from a collaboration between the National Heart, Lung, and Blood Institute, National Institutes of Health, USA, and the World Health Organization).

\*\* Low ICS dose is defined as  $\leq 200$  mcg BDP (beclomethasone dipropionate equivalent) /day in children 5 to 12 years old, and  $\leq 250$  mcg BDP/day in adults and children > 12 years

Medium ICS dose is defined as 201-400 mcg BDP / day in children 5 to 12 years old, and 250-500 mcg BDP/day in adults and children > 12 years;

High dose is defined as >400 mcg BDP / day in children 5 to 12 years old, and > 500 mcg BDP/day in adults and children > 12 years

## **Appendix E – Efficacy and safety of long-acting beta<sub>2</sub>-agonists and inhaled corticosteroids for asthma in children**

For details of this report please email the post market review secretariat  
[PBSpstmarket@health.gov.au](mailto:PBSpstmarket@health.gov.au)

## **Appendix F – PMR analysis 2013**

For details of this report please email the post market review secretariat  
[PBSpotmarket@health.gov.au](mailto:PBSpotmarket@health.gov.au)

## **Appendix G – PMR Interventions Review**

For details of this report please email the post market review secretariat  
[PBSpotmarket@health.gov.au](mailto:PBSpotmarket@health.gov.au)

## Appendix H - Educational Activities

Intervention	Provider	Further information
Asthma First Aid and Management face to face training	Asthma Australia	<a href="#">Asthma Australia website</a>
Asthma First Aid and Management face to face training for child care services	Asthma Australia	<a href="#">Asthma Australia</a> <a href="#">Asthma Friendly Child care Training in the Northern Territory</a>
Emergency Asthma Management training	Asthma Australia	<a href="#">Asthma Australia website</a>
The Asthma Friendly Initiative	Asthma Australia	<a href="#">Asthma Australia website</a>
Community Support Program	Asthma Australia	<a href="#">Asthma Australia website</a>
The Asthma Information Line and the 1800 ASTHMA National Phone Line	Asthma Foundation NSW and Asthma Australia.	The Asthma Information Line is discussed in the Asthma Foundation NSW annual reports <a href="#">2009-2010</a> and <a href="#">2010-2011</a> . The 1800 ASTHMA phone line is discussed in the <a href="#">Asthma Foundation NSW 2012-2013 annual report</a> .
Community Asthma Program	Royal Children's Hospital	<a href="#">Royal Children's Hospital website</a> <a href="#">The Dianella Community Health Inc. website</a>
Wimmera Asthma Camp	Asthma Australia	<a href="#">Asthma Australia Website</a>
Swim Program in the Northern Territory	Asthma Australia and ConocoPhillips	<a href="#">Asthma Australia website</a>
Strategy for incorporating asthma into the school curriculum	Asthma Foundation NSW	<a href="#">Asthma Foundation NSW</a>
Early Learners workshop on asthma	Asthma Australia	<a href="#">Asthma Australia website</a>
The Triple A program	Asthma Australia	<a href="#">Asthma Australia</a>
Triple A program in Darwin	Asthma Australia	<a href="#">The Thoracic Society of Australia and New Zealand</a>
Taking Action Together for Asthma Project	Part of a study funded by a grant from the University of Sydney	<a href="#">Instructional Design and Assessment: An Interprofessional Learning Module on Asthma Health Promotion</a>
Anti-Smoking Asthma Program for high schools	Asthma Australia and Asthma Foundation NSW	<a href="#">Asthma Australia</a>

<b>Intervention</b>	<b>Provider</b>	<b>Further information</b>
Regional Communities Breathe Better Program.	Asthma Australia and <a href="#">ElectraNet</a>	<a href="#">Asthma Australia website</a>
Patient asthma education and completion of an AAP.	Part of a study coordinated by researchers in Western Australia	<a href="#">Impact of structured education and self management on rural asthma outcomes</a>
Home Medicines Reviews for children with asthma presenting to the Women's and Children's Hospital in Adelaide	Women's and Children's Hospital in Adelaide staff in combination with Adelaide Northern Division of General Practice and Adelaide Western General Practice Network	<a href="#">National Medicines Symposium 2010 Medicines in People's Lives Final Program and Abstract Book</a>
PACE Australia	National Asthma Council Australia	<a href="#">National Asthma Council website</a>
The Asthma and Respiratory Management Seminar for Practice Nurses	National Asthma Council Australia	<a href="#">National Asthma Council Australia</a>
Primary care asthma update workshop	National Asthma Council Australia	<a href="#">National Asthma Council Australia</a>
Asthma update for pharmacists	National Asthma Council Australia	<a href="#">National Asthma Council Australia</a>
Asthma Educator training	Asthma Australia	<a href="#">Asthma Australia website</a>
Asthma Educator's Course	Lung Health Promotion Centre	<a href="#">Inner East Melbourne Medicare Local website</a>
The Medicinewise Practitioner	NPS Medicinewise	The <a href="#">NPS Medicinewise</a> website
The Twilight Update Series: Achieving Better Asthma Control in Children	The Royal Australian College of General Practitioners	<a href="#">The Royal Australian College of General Practitioners website</a>
Chronic cough, asthma and the snoring child	The Royal Children's Hospital with Northern Melbourne Medicare Local. Supported by CSL	<a href="#">The Royal Children's Hospital with Northern Melbourne</a>
Experts on air weekend educational meeting series	GlaxoSmithKline	<a href="#">GlaxoSmithKline</a>
Appropriate management of paediatric asthma	GlaxoSmithKline	<a href="#">GlaxoSmithKline</a>
Asthma In-Home program	Adelaide Women's and Children's Hospital	Coulthard K, et al. Australian Pharmacist 2011;30:450-51.

Source: *PMR Interventions Review pages 98 and 99*

## Appendix I - Classification of interventions

### ***Consumer interventions:***

- Education — providing information or education
- Communication — facilitating communication and/or decision making
- Skills — acquiring skills and competencies
- Behaviour — supporting behaviour change
- Support — helping consumers cope with and manage their health
- Risk — minimising risks or harms
- Quality — improving quality, coordination or integration of care
- Participation — involving consumers in decision making processes at a system level.

### ***Healthcare professional interventions:***

- Education — distribution of educational materials
- Meetings — healthcare providers participate in conferences, lectures, workshops or traineeships
- Consensus — local consensus process to determine the best way to approach practice
- Educational outreach visits — use of a trained person to meet with a provider to give information with the intent of changing practice
- Opinion — local opinion leaders
- Patient mediated — new clinical information (not previously available) collected directly from patients and given to the provider
- Audit and feedback — providing summaries of clinical performance of healthcare over a specified period of time
- Reminders — provision of information designed or intended to prompt a healthcare professional to perform or avoid some action.

### ***Consumer and healthcare professional interventions:***

- Interventions that targeted both consumers and healthcare professional