NHS
NPC
National Prescribing Centre
VOLUME 19 NUMBER 2

Current issues in the drug treatment of asthma

SUMMARY

Inhaled corticosteroids (ICSs):

- Regular standard dose ICSs (200–800 micrograms/day of beclometasone equivalent in adults, 200–400 micrograms/day in children) are the recommended first line preventer drug at step 2 of the BTS/SIGN guideline for adults and children for achieving overall treatment goals.
- ICSs are safe and effective for most patients with asthma, although the risk of systemic side effects is greater when higher doses are used. The dose of ICS should be titrated to the lowest dose at which effective control of asthma is maintained. Reviewing patients and stepping down are key elements of the BTS/SIGN guideline.

Long-acting beta2 agonists (LABAs):

- LABAs remain the preferred add-on therapy at step 3 of the BTS/SIGN guideline, for a significant minority of adults and children aged 5 and over, with stable asthma that is not adequately controlled on regular standard dose ICSs alone.
- A small but significant increase in serious adverse events and asthma mortality has been observed with LABAs in some meta-analyses. This appears to be substantially reduced, but perhaps not abolished when LABAs are used concurrently with an ICS.
- Advice on the use of LABAs from the Commission on Human Medicines should be followed.

Stepping down:

- Stepping down asthma treatment is important, but this recommendation appears to be sub-optimally implemented, leaving some patients over-treated. Prescribing of ICS/LABA combination inhalers has increased by almost 95% in the past 5 years, which may suggest some people are being stepped up to step 3, but not stepped back down again when asthma control has been achieved.

Budesonide/formoterol SMART® dosing:

- The use of a budesonide/formoterol (Symbicort®) combination inhaler as both maintenance and reliever therapy (SMART®) is an alternative option for a minority of adult patients, who are poorly controlled at step 3.

The dose of ICS should be titrated to the lowest dose at which effective control of asthma is maintained

Introduction

This *Bulletin* discusses three current issues in the drug treatment of asthma: safety of high dose inhaled corticosteroids (ICSs); safety of long-acting beta2 agonists (LABAs); and the use of budesonide/formoterol as maintenance and reliever therapy (Symbicort SMART®). For further details on the management of asthma, see the new British Guideline on the Management of Asthma,[1] published jointly by the British Thoracic Society (BTS) and the Scottish Intercollegiate Guidelines Network (SIGN), in May 2008. A range of educational materials on asthma (e.g. case studies, quiz, data focussed commentary) is also available on the respiratory floor of NPCi.

What are the safety issues with inhaled corticosteroids?

ICSs are the recommended first line preventer drug at step 2 of the BTS/SIGN guideline for adults and children for achieving overall treatment goals.[1] In adults, a reasonable starting dose is 400 micrograms/day of beclometasone (BDP) equivalent (see **Panel 1, page 2**) and, in children, 200 micrograms/day. The dose of ICS should be titrated to the lowest dose at which effective control of asthma is maintained.[1]

As with all effective medicines, the benefits of ICSs must be balanced against their potential risks. These range from unpleasant local effects, such as oral candidiasis and dysphonia, to less common systemic side-effects, such as adrenal suppression and osteoporosis.[3] Although local side-effects can occur in 1 or 2 of every 100 patients using ICSs at standard doses, the risk is greater when higher doses are used.[4] For most patients, dose escalation to high doses produces on average little additional clinical benefit.[4,5]

All ICSs exhibit dose-related systemic side-effects, although these are less frequent than with comparable doses of oral corticosteroids.[6] A meta-analysis of 27 studies found that

This publication was correct at the time of preparation: September 2008

This MeReC Publication is produced by the NHS for the NHS

marked adrenal suppression occurs with doses >1500 micrograms/day (>750 micrograms/day for fluticasone), although there is a considerable degree of inter-patient susceptibility.[6] The Committee on Safety of Medicines (CSM) have issued warnings about the use of high dose ICSs, particularly in relation to fluticasone.[7–9] Further details of the relevant key studies can be found on the asthma floor of NPCi.

In children, high doses of ICSs ≥400 micrgos/day (≥200 micrograms/day for fluticasone) may be associated with systemic side effects.

Is the risk greater in children?

In children, high doses of ICSs ≥400 micrograms/day (≥200 micrograms/day for fluticasone) may be associated with systemic side effects, including growth failure and adrenal suppression.[1] The dose of ICS required to put a child at risk of clinical adrenal insufficiency is unknown, but this is likely to occur at ≥800 micrograms/day (≥400 micrograms/day for fluticasone).[1] The majority of cases of clinical adrenal insufficiency have related to fluticasone and although rare, this adverse effect is serious and potentially life threatening.[10]

Children treated with ≥800 micrograms/day (≥400 micrograms/day for fluticasone) should be under the care of a specialist paediatrician for the duration of high dose treatment and their asthma management plan should include specific advice about steroid replacement during severe intercurrent illness.[1] For children under 5 years of age, referral to a specialist paediatrician should be considered at lower ICS doses.[1]

What is happening in practice?

The majority of children requiring regular preventative treatment can be managed at step 2 of the BTS/SIGN guideline, with regular standard dose (200–400 micrograms/day) ICS.[11] Only a small proportion (around 5–10% of children with asthma) are likely to need additional treatment.[11]

High doses (>400 micrograms/day, up to a maximum of 800 micrograms/day) are only recommended in children aged 5 to 12 years at step 4 of the BTS/SIGN guideline. That is, where adding in a LABA, or alternative add-on therapy to standard dose ICS has failed to control asthma adequately.[1]

A UK observational study of GP prescribing of ICSs conducted in July 2003, involving more than 4000 children under 12 years of age, found that high dose prescribing (>400 micrograms/day) occurred in 5.6% (95% confidence interval [CI] 4.3% to 6.9%) of the under-5s and 10% (95%CI 9.0% to 11.0%) of the 5 to 11 year olds.[12] Of these children, 63.6% of the under-5s and 46.7% of the 5 to 11 year olds were not co-prescribed any of the add-on therapies, as recommended by BTS/SIGN. Of further concern was that very high ICS doses >800 micrograms/day were prescribed to 3.9% (95%CI 2.6% to 5.2%) of the under-5s and 4.9% (95%CI 4.2% to 5.6%) of the 5 to 11 year olds.[12]

There are approximately 1.1 million children receiving treatment for asthma in the UK.[13] Although precise figures are not available, we estimate that 30% of these children are taking an ICS.[11,14] Based on the observational study described above,[12] the number of children in the UK taking a dose of ICS >400 micrograms/day, potentially putting them at risk of systemic side effects, may be as high as 25,000. In addition, up to 12,000 children may be sub-optimally managed on >400 micrograms/day of ICS with no add-on therapy. And of greater concern, as many as

The majority of cases of clinical adrenal insufficiency have related to fluticasone.

Panel 1: Beclometasone equivalent doses

All doses of ICSs used in this *Bulletin* refer to beclometasone (BDP) given via CFC-metered dose inhaler, or BDP equivalent doses unless otherwise stated. The table below compares the approximate dosing equivalence of the ICSs. For example, fluticasone provides equal clinical activity to beclometasone and budesonide at ***half*** the dosage[1]

ICS	Equivalent doses
Beclometasone equivalent (CFC-MDI)	400 micrograms
Budesonide	400 micrograms
Fluticasone	200 micrograms
Mometasone▼	200[1]/400[2] micrograms‡
Ciclesonide▼	160[2] micrograms‡
Clenil®▼ (BDP CFC-free)	400 micrograms
Qvar® (BDP CFC-free)	200 micrograms

‡ Ciclesonide▼ and mometasone▼ are newer ICSs and their dose equivalence and safety profiles are not well established.[1]

15,000 children may be taking >800 micrograms/day of ICS — a dose which potentially puts them at risk of clinical adrenal insufficiency.

Preliminary results of an analysis of the GPRD database indicates that the use of high dose ICSs has reduced between 2000 and 2007 in UK children with asthma (Personal Communication, MHRA). We will report those findings as a MeReC Stop Press blog when they are available.

Is stepping down possible in practice?
The stepwise management of asthma aims to achieve early control and maintain control by stepping up treatment as needed and stepping down when control is achieved. The BTS/SIGN guideline recognises that although stepping down is important, it is often not implemented, leaving some patients over-treated[1] and unnecessarily exposed to systemic adverse effects. Evidence suggests that stepping down the ICS dose can be achieved without compromising asthma control,[15] but it is unclear as to what extent this happens in clinical practice. See the BTS/SIGN guideline for recommendations on stepping down.

Prescribers are reminded that:

- all patients on ICSs, particularly children taking high doses >400 micrograms/day (>200 micrograms/day for fluticasone) should be reviewed regularly and titrated down to the lowest dose at which effective control is maintained[1]
- children treated with ≥800 micrograms/day (≥400 micrograms/day for fluticasone) should be under the care of a specialist paediatrician for the duration of high dose treatment.[1] For children under 5 years of age, referral should be considered at lower ICS doses.

What about the safety of long-acting beta2 agonists?

LABAs are the preferred add-on therapy to ICSs for adults and children aged 5 and older, uncontrolled on regular standard dose ICS alone, at step 3 of the BTS/SIGN guideline.[1] Addition of a LABA to ICS can lead to improvements in lung function, symptoms and decreased exacerbations.[1,16] However, before initiating any new drug, compliance and inhaler technique should be checked and trigger factors eliminated were possible.[1]

In 2003, the CSM (now the Commission on Human Medicines, [CHM]) considered an interim analysis of the SMART (Salmeterol Multicenter Asthma Research Trial) randomised controlled trial (RCT)[17] and reminded prescribers that for the maintenance treatment of asthma, the LABAs **salmeterol and formoterol should be prescribed only in conjunction with an ICS**.[18]

What are the safety concerns with LABAs?
A Cochrane systematic review of 34 RCTs (n=62,630) of patients with chronic asthma including the largest RCT SMART (n=26,355) has assessed the risk of mortality and non-fatal serious adverse events with the LABA salmeterol, compared with placebo or regular short-acting beta2 agonist.[16] The main findings are shown in **Table 1**.

For the maintenance treatment of asthma, the LABAs salmeterol and formoterol should be prescribed only in conjunction with an ICS.

Another large (n=33,826) meta-analysis of 19 RCTs of LABAs in asthma also found that LABA use increased the risk of hospitalisations for asthma exacerbation (not reported in SMART; 1.72% vs. 0.60%; OR 2.6; 95%CI 1.6 to 4.3); and life-threatening asthma exacerbations, which included asthma deaths (0.32% vs. 0.17%; OR 1.8; 95%CI 1.1 to 2.9), compared with placebo.[19]

Are inhaled corticosteroids protective of these adverse effects?
In patients not taking an ICS at baseline, the Cochrane review found a significant increase in the risk of asthma-related death (0.12% vs. 0%; OR 9.52; 95%CI 1.24 to 73.09) with regular salmeterol, compared with either regular salbutamol or placebo, indicating a clear increased risk of asthma death when salmeterol was not used with an ICS.[16] For those who were taking an ICS at baseline, the increase in asthma mortality was not statistically significant (0.07% vs. 0.05%; OR 1.52; 95%CI 0.51 to 4.49).[16] However, the confidence interval is too wide to rule out an increase in asthma mortality in this group.[16]

A recent meta-analysis of data from RCTs conducted by GlaxoSmithKline has suggested that salmeterol does not increase the risk of serious asthma-related

Table 1: Main findings from the Cochrane review[16]

Outcome	Number of trials/patients N/n	Absolute risk salmeterol vs. placebo	Odds ratio (OR) salmeterol vs. placebo (95%CI)
All cause mortality	14/30,254	0.29% vs. 0.22%	1.33 (0.85 to 2.10)
Non-fatal serious adverse events	18/31,529	3.98% vs. 3.53%	1.14 (1.01 to 1.28)
Asthma mortality	1/26,355	0.099% vs. 0.023%	4.34 (1.24 to 15.22)

adverse events when added to an ICS.[20] However, as with all meta-analyses there were many limitations to this study, and the results are discussed further in the MeReC Rapid Review blog.

Current evidence suggests the small increase in asthma mortality observed with salmeterol appears to be substantially reduced, but perhaps not abolished, when salmeterol is used concurrently with an ICS.[16]

What do these findings mean in clinical practice?
For patients not well controlled on standard dose ICSs alone, adding-in a LABA can give symptomatic benefit but some meta-analyses of RCTs[1,16] have found a small absolute increase in serious adverse events and asthma related mortality. As LABAs are commonly prescribed these findings are important, but they were largely driven by the SMART RCT in which only 47% of patients were using ICSs at the start of the study.[17] A large population based case control study found no evidence of increased mortality with medium to long term use of LABAs,[21] but this is a less reliable form of evidence than RCTs.

Prescribers should follow CHM advice when prescribing salmeterol or formoterol for chronic asthma.

From analysis of prescribing data, we estimate that approximately 500,000 people in England are taking a LABA for asthma. Applying the risk increase found in the Cochrane review to this level of population usage, if all were given regular salmeterol for 28 weeks, there may be 2,500 additional non-fatal serious adverse events, compared with placebo. This is probably an over-estimate and is likely to be reduced if all were taking concomitant ICSs.

Is a review of clinical practice required?
In England, there were 335,000 items of ICS/LABA combination inhalers prescribed in May 2008, compared with 172,000 in June 2003.[22] In contrast, monocomponent LABA inhalers have reduced from 200,000 items in June 2003, to 135,000 in May 2008.[22] A significant proportion, but by no means all of this prescribing will be for patients with chronic obstructive pulmonary disease, and it would appear that increasing numbers of patients with asthma are being treated at BTS/SIGN step 3 or above.

This apparent increase in ICS/LABA prescribing may reflect better treatment for previously under-treated patients. Alternatively, it may also reflect patients being stepped up from step 2 to achieve control of their asthma, but not being stepped back down again, as recommended by BTS/SIGN.

Prescribers are reminded that:
- LABAs remain the first choice add-on therapy to ICSs, but only for those patients uncontrolled on regular standard dose ICS alone after ICS compliance and inhaler technique have been optimised[1]
- in asthma, LABAs should be prescribed in **conjunction with an ICS**; advice from the CHM should be followed (see **Panel 2**)

Panel 2: CHM advice on salmeterol and formoterol for chronic asthma[23]

In the management of chronic asthma, formoterol and salmeterol should:
- be added only if regular use of standard-dose ICS has failed to control asthma adequately
- not be initiated in patients with rapidly deteriorating asthma
- be introduced at a low dose and the effect properly monitored before considering dose increase
- be discontinued in the absence of benefit
- be reviewed as appropriate: stepping down therapy should be considered when good long-term asthma control has been achieved

Patients should report any deterioration in symptoms following initiation of treatment with a LABA

What is budesonide/formoterol (Symbicort®) SMART® dosing?

Budesonide/formoterol SMART® (Symbicort for Maintenance And Reliever Therapy) dosing is a new approach to the management of moderate to severe asthma, and should not be confused with the SMART RCT discussed earlier. It involves the use of a single budesonide/formoterol combination inhaler as both maintenance and reliever treatment for adults aged ≥18 years.

Is there evidence to support its use?
There is evidence that budesonide/formoterol SMART® dosing may be more effective at reducing **exacerbation rates** in people with **moderate to severe** asthma symptoms compared with conventional methods.[24–26] See **Table 2** for a summary of the evidence and recommendations.

The key trials with budesonide/formoterol SMART® dosing included patients who were not typical of most people managed in primary care:
- all were at step 3 or 4 of BTS/SIGN and had experienced one or more severe exacerbation in the previous 12 months[24–27]
- in trials comparing SMART® with fixed dose budesonide/formoterol or higher dose ICS, the majority of patients had their maintenance ICS dose reduced[24,25]
- at study entry, the majority were using their reliever inhaler on ≥5 of the previous 7 days (i.e. their asthma was uncontrolled)[25–27]

Participants using typically >10 reliever inhalations in any one day were excluded.[24–26]

There have been no systematic reviews evaluating budesonide/formoterol SMART® dosing.

Where does SMART® fit in the management of asthma?

Budesonide/formoterol SMART® dosing does not fit within the conventional BTS/SIGN stepped approach. It is an alternative **option** for **adults** at **step 3 who are poorly controlled**.[1] This refers to patients who have previously stepped up from regular ICS alone (step 2) to regular ICS plus LABA (step 3), and whose asthma is still poorly controlled. Further research on budesonide/formoterol SMART® dosing is particularly needed in people:

- who overuse reliever therapy,[28] owing to the potential for inadvertent use of high doses of ICSs
- who are unable/fail to recognise worsening asthma symptoms.[29]

Budesonide/formoterol SMART® dosing is an alternative to increasing the ICS dose up to 2000 micrograms/day (step 4).[30]

Table 2: Summary of the evidence and recommendations for budesonide/formoterol SMART® dosing using the principles of good prescribing[31]

Maximising effectiveness	**Budesonide/formoterol SMART® dosing is an option for adult patients at step 3 who are poorly controlled.[1]** • In key trials, SMART® dosing reduced the relative rate of severe asthma exacerbations compared with fixed dosing of ICS/LABA by 28–47%, in patients already at step 3 or 4[24,26] • The absolute reduction in severe exacerbations with SMART® dosing when compared with fixed dose fluticasone/salmeterol was 0.07 exacerbations/patient/6-months.[26] Alternatively, the number needed to treat (NNT) for 6 months to prevent one serious asthma exacerbation was 14 • When compared with high dose ICS (1000 micrograms/day fluticasone, equivalent to 2000 micrograms/day BDP) plus LABA (step 4), there was no significant difference in the time to first severe exacerbation with SMART® dosing (risk ratio 0.82; 95%CI 0.63 to 1.05)[27] • For other important measures of asthma control, overall there were no clinically meaningful differences between SMART® and conventional dosing of ICS/LABA[26,27]
Minimising risks	**Current evidence is limited to company sponsored clinical trials, and its place in routine practice is not well established.** • SMART® may decrease the ICS burden for some patients,[26,27] but there is the potential to use very high doses of ICS (>2000 micrograms/day), although overuse did not appear to be a problem in trials[28] • The majority of trials were conducted in uncontrolled patients, so those with good asthma control should not be switched to SMART®[28,29]
Minimising costs	**There is currently little information on the cost-effectiveness of SMART® dosing, compared with guideline-based treatment.** • SMART® dosing is only an option for the 100/6 or 200/6 micrograms strengths of Symbicort® Turbohaler £33.00* for 100/6 (120 doses)[32] £38.00* for 200/6 (120 doses)[32]
Respecting patient choices	**Some people with poor symptom control on ICS/LABA may benefit from SMART® dosing as an alternative to increasing their maintenance doses.** • Fewer than 5% of patients with asthma are uncontrolled on combination therapy i.e. at step 4 or above.[14] Therefore, SMART® dosing is only an option for a minority of patients • Some patients may prefer a trial of SMART®, rather than using high dose ICSs • Before initiating SMART®, careful patient education is required[1] • SMART® is not suitable for people who overuse relievers or who find it difficult to recognise worsening asthma symptoms[29]

* Prices based on Drug Tariff, August 2008

References

1. Scottish Intercollegiate Guidelines Network/British Thoracic Society: British Guideline on the Management of Asthma, 2008. Accessed from http://www.sign.ac.uk/guidelines/fulltext/101/index.html on 18/08/08
2. Global Initiative for Asthma (GINA). GINA Report, Global Strategy for Asthma Management and Prevention, updated 2007. Accessed from http://www.ginasthma.com/Guidelineitem.asp??l1=2&l2=1&intId=60 on 19/08/08
3. National Institute for Health and Clinical Excellence (NICE). Technology appraisal guidance 138: Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over, March 2008. Accessed from http://www.nice.org.uk/guidance/index.jsp?action=download&o=40099 on 18/08/08
4. Powell H, Gibson PG. Inhaled corticosteroid doses in asthma: an evidence-based approach. Med J Aust 2003;178:223–5
5. National Prescribing Centre. Chronic Asthma. MeReC Briefing 2002;18:1–5. Accessed from http://www.npc.co.uk/MeReC_Briefings/2001/briefing_no_18.pdf on 18/08/08
6. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy. A systematic review and meta-analysis. Arch Intern Med 1999;159:941–55. Accessed from http://archinte.ama-assn.org/cgi/content/full/159/9/941 on 08/08/08
7. Committee on Safety of Medicines. Reminder: Fluticasone propionate (Flixotide): use of high doses (>500 micrograms/twice daily). Current Problems in Pharmacovigilance 2001;27:10. Accessed from http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/CON007455 on 18/08/08
8. Committee on Safety of Medicines. Inhaled corticosteroids and adrenal suppression in children. Current Problems in Pharmacovigilance 2002;28:7. Accessed from http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/CON007451 on 18/08/08
9. Committee on Safety of Medicines. Inhaled corticosteroids and adrenal suppression in children. Current Problems in Pharmacovigilance 2006;31:5. Accessed from http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/CON2023859 on 18/08/08
10. Todd GRG, Acerini CL, Ross-Russell R, et al. Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. Arch Dis Child 2002;87:457–61. Accessed from http://adc.bmj.com/cgi/content/full/87/6/457 on 18/08/08
11. Cohen S, Taitz J, Jaffe A. Paediatric prescribing of asthma drugs in the UK: are we sticking to the guideline? Arch Dis Child 2007;92:847–9. Accessed from http://adc.bmj.com/cgi/content/full/92/10/847 on 08.08.08
12. Thomas M, Turner S, Leather D, et al. High-dose inhaled corticosteroid use in childhood asthma: an observational study of GP prescribing. Br J Gen Pract 2006;56:788–90. Accessed from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1920720 on 18/08/08
13. Asthma UK (2006) What is asthma? Accessed from http://www.asthma.org.uk/all_about_asthma/asthma_basics/ on 18/08/08
14. Walsh LJ, Wong CA, Cooper S, et al. Morbidity from asthma in relation to regular treatment: a community based study. Thorax 1999;54:296–300. Accessed from http://thorax.bmj.com/cgi/content/full/54/4/296?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&andorexactfulltext=and&searchid=1&FIRSTINDEX=0&sortspec=relevance&volume=54&firstpage=296&resourcetype=HWCIT on 08/08/08
15. Hawkins G, McMahon AD, Twaddle S, et al. Stepping down inhaled corticosteroids in asthma: randomised controlled trial. BMJ 2003;326:1115, doi:10.1136/bmj.326.7399.1115. Accessed from http://www.bmj.com/cgi/content/full/326/7399/1115 on 18/08/08
16. Cates CJ, Cates MJ. Regular treatment with salmeterol for chronic asthma: serious adverse events. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD006363. DOI: 10.1002/14651858.CD006363.pub2. Accessed from http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD006363/frame.html on 18/08/08
17. Nelson HS, Weiss ST, Bleecker ER, et al. The Salmeterol Multicenter Asthma Research Trial. A comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006;129:15–26. Accessed from http://www.chestjournal.org/cgi/content/full/129/1/15?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=1&andorexacttitle=and&andorexacttitleabs=and&andorexactfulltext=and&searchid=1&FIRSTINDEX=0&sortspec=relevance&volume=129&firstpage=15&resourcetype=HWCIT on 18/08/08
18. Committee on Safety of Medicines. Salmeterol (Serevent) and formoterol (Oxis) in asthma management. Current Problems in Pharmacovigilance 2003;29:5. Accessed from http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/CON007449 on 18/08/08
19. Salpeter SR, Buckley NS, Ormiston TM, et al. Meta-analysis: effect of long-acting â-agonists on severe asthma exacerbations and asthma-related deaths. Ann Intern Med. 2006;144:904–12. Accessed from http://www.annals.org/cgi/content/full/144/12/904 on 18/08/08
20. Bateman E, Nelson H, Bousquet J, et al. Meta-analysis: Effects of adding salmeterol to inhaled corticosteroids on serious asthma-related events. Ann Intern Med 2008;149:33–42. Accessed from http://www.annals.org/cgi/content/full/149/1/33 on 18/08/08
21. Anderson HR, Ayres JG, Sturdy PM, et al. Bronchodilator treatment and deaths from asthma: case-control study. BMJ 2005;330;117; doi:10.1136/bmj.38316.729907.8F. Accessed from http://www.bmj.com/cgi/content/full/330/7483/117 on 18/08/08
22. Personal Communication. Prescription Pricing Division, NHS Business Services Authority. ePACT data. Accessed from http://www.epact.ppa.nhs.uk/index.htm on 07/08/08
23. Medicines and Healthcare products Regulatory Agency/Commission on Human Medicines. Asthma: long-acting â2 agonists, last updated February 7th 2008. Accessed from http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/Asthma/index.htm on 18/08/08
24. O'Byrne PM, Bisgaard H, Godard PP, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med 2005;171:129–36. Accessed from http://ajrccm.atsjournals.org/cgi/content/full/171/2/129 on 24/06/08
25. Rabe KF, Atienza T, Magyar P, et al. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. Lancet 2006;368:744–53. Accessed from http://www.thelancet.com/journals/lancet/article/PIIS0140673606692842/fulltext on 18/08/08
26. Kuna P, Peters MJ, Manjra AI, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. Int J Clin Pract 2007;61:725–36. Accessed from http://www.blackwell-synergy.com/doi/full/10.1111/j.1742-1241.2007.01338.x?prevSearch=%28%28author%3A%28Kuna%29%29%29 on 18/08/08
27. Bousquet J, Boulet L-P, Peters MJ, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high dose salmeterol/fluticasone. Respir Med 2007;101:2437–46. Accessed from http://www.resmedjournal.com/article/S0954-6111(07)00317-4/abstract on 18/08/08.
28. CKS. Asthma (clinical topic). Clinical Knowledge Summaries, 2007. Accessed from http://www.cks.library.nhs.uk/asthma on 18/08/08
29. National Prescribing Service. Budesonide with eformoterol dry powder inhaler (Symbicort Turbuhaler) maintenance and reliever regimen for asthma. NPS Rational Assessment of Drugs and Research (RADAR), July 2007. Accessed from http://www.npsradar.org.au/site.php?page=1&content=/npsradar/content/budesonide_with_eformoterol.html on 18/08/08
30. National Prescribing Centre. Revised British Asthma Guideline from SIGN and BTS. MeReC Stop Press blog, May 12th 2008. Accessed from http://www.npci.org.uk/blog/?p=114 on 18/08/08
31. Barber N. What constitutes good prescribing? BMJ 1995;310:923–5. Accessed from http://www.bmj.com/cgi/content/full/310/6984/923?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=good+prescribing+barber&searchid=1&FIRSTINDEX=0&resourcetype=HWCIT on 18/08/08
32. Prescription Pricing Division (PPD). NHS Business Services Authority. NHS Electronic Drug Tariff, June 2008. Accessed from http://www.ppa.org.uk/edt/August_2008/mindex.htm on 20/08/08

The National Institute for Health and Clinical Excellence (NICE) is associated with MeReC Publications published by the NPC through a funding contract. This arrangement provides NICE with the ability to secure value for money in the use of NHS funds invested in its work and enables it to influence topic selection, methodology and dissemination practice. NICE considers the work of this organisation to be of value to the NHS in England and Wales and recommends that it be used to inform decisions on service organisation and delivery. This publication represents the views of the authors and not necessarily those of the Institute.

NPC materials may be downloaded / copied freely by people employed by the NHS in England for purposes that support NHS activities in England. Any person not employed by the NHS, or who is working for the NHS outside England, who wishes to download / copy NPC materials for purposes other than their personal use should seek permission first from the NPC. Email: copyright@npc.nhs.uk **Copyright 2008**
National Prescribing Centre, The Infirmary, 70 Pembroke Place, Liverpool, L69 3GF Tel: 0151 794 8146 Fax: 0151 794 8139 www.npc.co.uk www.npc.nhs.uk