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Respiratory Research Review™

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Issue 125 – 2016

In this issue:

Abbreviations used in this issue

COPD = chronic obstructive pulmonary disease
CV = cardiovascular
FEV = forced expiratory volume
FVC = forced vital capacity
HR = hazard ratio
ICS = inhaled corticosteroid
LABA = long-acting β-agonist
LAMA = long-acting antimuscarinic agent
L/RV = left/right ventricular
OR = odds ratio
RCT = randomised controlled trial

Welcome to issue 125 of Respiratory Research Review.

'Smoking cessation and pulmonary rehabilitation are the king and queen of COPD management', summarised my esteemed colleague A/Prof Jim Reid during a discussion about COPD management. Following PHARMAC's announcement to fund more medications to manage COPD, this is an important statement. While no new classes of medications are available to treat COPD, the magnitude of change in treating our patients with COPD will be similar to PHARMAC announcing that they are funding two more β-blockers, three more angiotensin antagonists, two more statins and three combinations of both. It would have hardly startled anybody – nor should the increased number of medications within the same class confuse us in managing our patients with COPD.

'Smoking, not COPD, as the disease' (click here) and 'Don't wait for COPD to treat tobacco use' (click here) are the editorials of our opinion leaders. Some of you may have followed the debate about the increase of plain tobacco packaging around the world or may have seen the Lancet announcement 'Turkmenistan bans tobacco sales'. All this may help us to stay focussed in our NZ debate to encourage smoking cessation, although the evidence whether e-cigarettes are helpful and distracting isn't quite out as yet. NZ ought to maintain its goal to become smoke-free in 2025.

The evidence for pulmonary rehabilitation is overwhelming with a number needed to treat of two (Lancet editorial). According to the 2015 PHARMAC report (page 36), NZ spent more than $50 million on combination product inhalers. In contrast, many rehabilitation or respiratory relief courses still rely in 'gold coin donations'. The evidence base for rehabilitation is strong, and it is summarised in the combined ERS/ATS policy statement: 'Enhancing implementation, use and delivery of pulmonary rehabilitation'.

A trial randomising more than 16,000 patients with COPD for treatment with vilanterol/fluticasone furoate did not reduce mortality. This shouldn't actually surprise us, because a beautifully performed network analysis based on more than 130,000 patients in 208 RCTs found no effect of any inhaler medication on mortality compared with placebo. This links back to the statement above that most COPD medications, either alone or in combination, improve symptoms, but that they are not significantly better than placebo in improving mortality.

In my opinion, the new inhaler only provides marginal improvements, like once daily use, a choice of devices and an easier combination of medication, for our patients with COPD. The WISDOM study (Respiratory Research Review, issue 107) introduces a new concept to COPD care by withdrawing steroids in patients on triple therapy for COPD. We have now the observation from the Quebec health insurance database, that the discontinuation of ICS use in COPD is associated with a reduction in the risk of serious pneumonia in COPD (click here). Confidence in treatment without steroids may also be gained from the FLAME study, showing that a LAMA/LABA combination (glycopyrronium/indacaterol) was superior to a LABA/ICS combination (salmeterol/fluticasone) in preventing COPD exacerbations.

Finally, this research review is mainly addressing issues relevant for colleagues in general practice, who are likely to have the greatest impact when treating patients in primary care by addressing smoking cessation, rehabilitation and symptomatic treatment. However, I would like to draw attention to three publications relevant for hospital-based doctors: i) the guidelines of the TSANZ on acute oxygen use in adults: 'Swimming between the flags'; ii) the new BTS/ICS guidelines for ventilator management of acute hypercapnic respiratory failure in adults; and iii) ERS perspective on 'Treatable traits: towards precision medicine of chronic airways disease'. If you only have time to click on one link in this review, make it the 'treatable traits'.

We hope you enjoy this selection and are looking forward to questions and comments.

Kind regards

Professor Lutz Beckert
lutzbeckert@researchreview.co.nz

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*LAMA = Long-acting muscarinic antagonist, LABA = Long-acting beta$_2$-agonist; TAPS DA1637IG/16MA/UCV/0029/16

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A qualitative analysis of Māori and Pacific smokers' views on informed choice and smoking

Authors: Gifford H et al.

Summary: Qualitative in-depth interviews were used to explore the ways in which 20 Māori and Pacific smokers aged 18–26 years interpreted 'informed choice' in relation to smoking in this NZ research. An informed-choice framework was used to analyse the data with a thematic analysis approach. None of the participants met more than the framework's initial two criteria, and few regarded themselves as well informed. Most participants reflected on their unthinking uptake and subsequent addiction, and were able to identify environmental factors that facilitated uptake. Despite this context, most participants agreed they made informed choices to smoke.

Comment: NZ is being recognised for its vision to become smoke-free by 2025. Much of this impetus stems from Māori political leaders like Tau Henare and Tariana Turia, who recognised smoking was not part of Māori kaupapa and led the parliamentary 'Inquiry into the tobacco industry in Aotearoa and the consequences of tobacco use for Māori' (hyperlink). The enquiry found the smoking prevalence in Māori (38%) was more than twice that of NZ Europeans (15%). This article explores some of the cultural and socioeconomic influences that influence young Māori and Pacific adults' decision making. **Bottom line: government legislation can assist smoking cessation together with contextual factors relevant to Māori and Pacific communities.**

Reference: BMJ Open 2016;6:e011415
Abstract

E-cigarettes and smoking cessation in real-world and clinical settings

Authors: Kalkhoran S & Glantz SA

Summary: This was a systematic review and meta-analysis of 38 studies reporting on the association between e-cigarette use and cigarette smoking cessation among adults, with 20 studies with control groups (15 cohort studies, three cross-sectional studies and two clinical trials) included in a random effects meta-analysis and sensitivity analyses. Compared with study participants who did not use e-cigarettes, those who did were significantly less likely to quit cigarette smoking (OR 0.72 [95% CI 0.57, 0.91]), and the associations did not differ significantly between studies of all smokers using e-cigarettes versus those only enrolling smokers interested in stopping (ORs 0.63 vs. 0.86 [p=0.94]). No other study characteristics had a significant impact on the overall effect size (p≥0.77).

Comment: Two RCTs, including one from NZ (Respiratory Research Review, issue 95), suggested that e-cigarettes as part of a smoking cessation programme may assist quitting. A meta-analysis on the RCT and cohort studies showed conflicting results, which led these authors to explore the role of e-cigarettes further. They included 38 studies exploring the use of e-cigarettes in the 'real word', outside smoking cessation trials; this included adults who wished to use nicotine in smoke-free areas and college students using e-cigarettes as an introductory device to cigarettes. **Bottom line: outside formal smoking cessation programmes, the use of e-cigarettes was associated with a 28% lower chance of quitting.**

Reference: Lancet Respir Med 2016;4(2):116–28
Abstract

Time spent reading this publication has been approved for CME for Royal New Zealand College of General Practitioners (RNZCGP) General Practice Educational Programme Stage 2 (GPEP2) and the Maintenance of Professional Standards (MOPS) purposes, provided that a Learning Reflection Form is completed. Please **CLICK HERE** to download your CPD MOPS Learning Reflection Form. One form per review read would be required.

Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please **CLICK HERE**.

Independent commentary by Professor Lutz Beckert.

Professor Lutz Beckert is the Head of Department of Medicine of the University of Otago, Christchurch. He is also a Respiratory Physician at Canterbury District Health Board.

FOR FULL BIO CLICK HERE

Health-care provider screening and advice for smoking cessation among smokers with and without COPD

Authors: Schauer GL et al.

Summary: This US study assessed the prevalence of clinician-delivered 5A strategies (ask, advise, assess, assist, arrange) in adult smokers with and without COPD; 20,021 adult past-year cigarette smokers surveyed in the 2009–2010 National Adult Tobacco Survey reported whether or not they had been a recipient of a 5A strategy in the past year. Compared with smokers without COPD, those with COPD were more likely to report being asked about tobacco use (95.4% vs. 85.8%), advised to quit (87.5% vs. 59.4%), assessed for readiness to quit (63.8% vs. 37.9%), offered assistance to quit (58.6% vs. 34.0%) and offered follow-up (14.9% vs. 5.2%).

Comment: These authors from the US report on data obtained from more than 20,000 adult smokers; the results are probably relevant to NZ. A total of 95% of smokers with COPD were asked about smoking. A total of 88% of patients with COPD were advised to quit smoking, but only 60% of patients without COPD were given the same advice. However, only 34% of patients without COPD were offered assistance to quit and only 5% were offered follow-up. **Bottom line: the Ask, Brief Advice and Cessation framework is relevant to all health professionals – we need to be better at giving cessation support using the MoH and PHARMAC framework.**

Reference: Chest 2016;149(3):676–84
Abstract

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Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT)

Authors: Vestbo J et al., on behalf of the SUMMIT Investigators

Summary: Patients aged 40–80 years with COPD, postbronchodilator FEV_1 50–70% of predicted, postbronchodilator FEV_1-FVC ratio ≤0.70, a smoking history of ≥10 pack-years, a modified Medical Research Council dyspnoea scale score ≥2, and a history or an increased risk of CV disease were randomised to receive inhaled fluticasone furoate 100µg (n=4135), vilanterol 25µg (n=4118), fluticasone furoate 100µg plus vilanterol 2µg (n=4121) or placebo (n=4111) once daily. There were no significant reductions in all-cause mortality (primary outcome) between the three active treatment groups compared with the placebo group (respective HRs 0.91 [95% CI 0.77, 1.08], 0.96 [0.81, 1.14] and 0.88 [0.74, 1.04]). Findings for secondary outcomes, which should be interpreted cautiously, included reduced rates of decline in FEV_1 in the combination and fluticasone furoate groups versus placebo (differences 8 mL/year for both), but not vilanterol (difference –2 mL/year). There were no differences between the active treatments and placebo for composite CV events, but all treatments were associated with reduced rates of moderate and severe exacerbations. There were no significant differences among the groups for pneumonia or adverse cardiac events.

Comment: Does anybody remember the TORCH study, which set out to show that salmeterol/fluticasone improved survival in COPD; however, it turned out to show no effect? It must be a sense of déjà vu for the sponsor of this massive study including more than 16,000 patients in more than 1000 study centres. The data are reassuring in that the therapy does no harm, improves symptoms and reduces exacerbations. It will certainly show us many insights on COPD management in the future. **Bottom line: in patients with moderate COPD and heightened CV risk, treatment with fluticasone furoate and vilanterol did not improve mortality or CV events.**

Reference: Lancet 2016;387(10,030):1817–26
Abstract

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Comparative safety and effectiveness of long-acting inhaled agents for treating chronic obstructive pulmonary disease

Authors: Tricco AC et al.

Summary: This was a systematic review and network meta-analysis of 208 RCTs (n=134,692) comparing LAMAs, LABAs or ICSs alone or in combination against placebo in patients with COPD. Compared with placebo, 32 treatments were found to be effective for preventing moderate-to-severe exacerbations in 20 RCTs (n=26,141), with the combination of tiotropium, budesonide and formoterol being the most effective at 99.2% on the SUCRA (Surface Under the Cumulative Ranking) curve. The combination of fluticasone and salmeterol was more effective than placebo, formoterol and fluticasone alone for reducing mortality in 88 RCTs (n=97,526), and was the most effective at 71% on the SUCRA curve. For CV-related mortality, data from 37 RCTs (n=55,156) showed that: i) salmeterol was safer than placebo, tiotropium and tiotropium soft mist inhaler; ii) fluticasone was safer than tiotropium soft mist inhaler; and iii) salmeterol/fluticasone was safer than tiotropium and tiotropium soft mist inhaler; triamcinolone acetonide was the most harmful with a SUCRA value of 81%. Compared with placebo, fluticasone and fluticasone plus salmeterol were found to be associated with increased risk of pneumonia in 54 RCTs (n=61,551), with fluticasone plus salmeterol the most harmful (SUCRA value 89%). There were no significant differences among agents for arrhythmia.

Comment: One of the features of a statistical tool of a network meta-analysis is that it allows conclusions to be drawn on the effect of treatments against placebo, even if the report was against another treatment. In this amazing analysis, Andrea Tricco and colleagues included more than 100,000 participants from more than 200 RCTs to compare safety and effectiveness of long-acting inhaled agents in the treatment of COPD. They found many trials of poor quality and at risk of bias. **Bottom line: most treatments reduced the risk of exacerbations, but none improved mortality compared with placebo.**

Reference: BMJ Open 2015;5:e009183
Abstract

Discontinuation of inhaled corticosteroids in COPD and the risk reduction of pneumonia

Authors: Suissa S et al.

Summary: This Canadian study evaluated the impact of ICS discontinuation on the risk of pneumonia in patients with COPD. The cohort comprised 103,386 patients with COPD who were treated with ICSs during 1990–2005 and followed until 2007 or until a serious pneumonia event occurred. A nested case-control analysis of the cohort estimated the rate ratio of serious pneumonia associated with ICS discontinuation compared with continued use. Serious pneumonia events occurred in 14,020 participants during 4.9 years of follow-up. ICS discontinuation was associated with a 37% decrease in the rate of serious pneumonia. The risk reduction was rapidly evident, increasing from 20% in the first month to 50% by the fourth month after discontinuation. The risk reduction was greater with fluticasone than with budesonide (42% vs. 13%).

Comment: This study is reporting on more than 100,000 patients from Quebec health insurance databases. These authors start with the observation that approximately 80% of all patients with COPD are prescribed ICSs against suggestions from guidelines. They compared 100,000 users of ICSs, who had 14,000 admissions to hospital with pneumonia, with 130,000 controls of whom 70% had stopped ICSs. This sort of epidemiological data is not easy to translate into clinical practice; still the authors come up with an impressive **bottom line: cessation of ICSs in COPD led to a 37% reduction in the incidence of pneumonia, which reaches 50% by the fourth month of discontinuation.**

Reference: Chest 2015;148(5):1177–83
Abstract

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Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD

Authors: Wedzicha JA et al., for the FLAME Investigators

Summary: Patients with COPD and with ≥1 exacerbation during the prior year were randomised to receive inhaled indacaterol 110µg plus glycopyrronium 50µg once daily (LABA/LAMA; n=1680) or salmeterol 50µg plus fluticasone 500µg twice daily (LABA/ICS; n=1682) in this noninferiority trial. Indacaterol plus glycopyrronium was not only noninferior but also superior to salmeterol plus fluticasone for the primary outcome of annual COPD exacerbations (3.59 vs. 4.03; rate ratio 0.89 [95% CI 0.83, 0.96]), including moderate or severe exacerbations (0.98 vs. 1.19; 0.83 [0.75, 0.91]), with also longer times to first exacerbation (71 vs. 51 days; HR 0.84 [0.78, 0.91]), first moderate or severe exacerbation (HR 0.78 [0.70, 0.86]) and first severe exacerbation (0.81 [0.66, 1.00]). Baseline blood eosinophil count did not modify the effect on COPD exacerbation rate. Adverse events and mortality were similar between the two groups, except for a lower incidence of pneumonia with the LABA/LAMA combination than with the LABA/ICS combination (3.2% vs. 4.8% [p=0.02]).

Comment: This European study has several surprising outcomes: i) although the authors specifically targeted patients with an exacerbation of COPD, they found the LAMA/LABA combination was superior to the LABA/ICS combination; and ii) treatment with LAMA/LABA, i.e. indacaterol/glycopyrronium, reduced the rate of exacerbations, extended the time to first exacerbation, increased the trough FEV_1, decreased the risk of pneumonia and improved quality of life measurements. **Bottom line: the FLAME study provides support for using LAMA/LABA in GOLD groups band D. We should follow the guidelines and can stop using ICSs in patients who don't qualify for ICS use.**

Reference: N Engl J Med 2016;374(23):2222–34
Abstract

Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids

Authors: Watz H et al.

Summary: These authors conducted a *post hoc* analysis of COPD exacerbations according to blood eosinophil count subgroups in WISDOM trial participants who received tiotropium 18µg, salmeterol 100µg and fluticasone propionate 1000µg daily for 6 weeks and were then randomised 1:1 to receive continued or reduced ICS over 12 weeks. Compared with participants who continued ICS treatment, those in the withdrawal group had an increased risk of moderate or severe exacerbations as eosinophil count cutoff increased (respective rate ratios 1.22 [95% CI 1.02, 1.48], 1.63 [1.19, 2.24] and 1.82 [1.20, 2.76] for ≥2%, ≥4% and ≥5% of total white blood cell count), with a significant treatment-by-subgroup interaction for the 4% and 5% cutoffs only. The results were similar for eosinophil cutoffs of 300 and 400 cells/µL, and mutually exclusive subgroups.

Comment: In the FLAME study, a blood eosinophil marker of ≥2% did not identify patients who respond to a LABA/ICS regimen. Henrik Watz and colleagues present the *post hoc* analysis of the WISDOM trial, which demonstrated one can withdraw ICSs without an increased risk of exacerbations. The authors report that a blood eosinophil count ≥4% or 300 cells/uL may identify patients in whom it may be detrimental to withdraw ICSs. I agree with the authors rather than the editorial's **bottom line: this finding needs to be confirmed in a prospective study before it can be considered in clinical practice.**

Reference: Lancet Respir Med 2016;4(5):390–8
Abstract

Lung deflation and cardiovascular structure and function in chronic obstructive pulmonary disease

Authors: Stone IS et al.

Summary: Forty-five patients with COPD with hyperinflated lungs received 7–14 days of fluticasone furoate 100µg plus vilanterol 25µg and placebo in a randomised crossover design with a ≥7-day washout. Compared with placebo, the ICS/LABA combination was associated with a significant increase in change from baseline RV end-diastolic volume index (primary outcome) of 5.8 mL/m^2, a significant reduction in residual volume of 429mL, and significant increases in LV end-diastolic and left atrial end-systolic volumes of 3.63 and 2.33 mL/m^2 (p=0.002). A *post hoc* analysis showed that RV stroke volume increased by 4.87 mL/m^2 (p=0.003), while RV ejection fraction did not change. LV adaptation was similar; left atrial ejection fraction increased significantly by 3.17%. There was no change in intrinsic myocardial function. Pulmonary main and left artery pulsatility increased significantly by 2.9% and 2.67%, respectively. Safety of the ICS/LABA combination was similar to placebo.

Comment: This is a rather complex proof-of-concept study to which Henrik Watz wrote a most learned editorial, which I recommend reading. The partially GSK-based team use cardiac MRI scans in patients with hyperinflation to demonstrate an increase in the RV end-diastolic volume of about 7.5% (6 mL/m^2) after treatment with vilanterol/fluticasone furoate. This corresponded with a reduction in hyperinflation and an increase in RV stroke volume. **Bottom line: bronchodilator therapy deflated the lung and counteracted treatable underfilling of the heart in COPD patients with hyperinflated lungs.**

Reference: Am J Respir Crit Care Med 2016;193(7):717–26
Abstract

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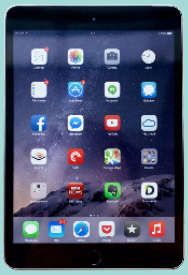

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β-blockers are associated with a reduction in COPD exacerbations

Authors: Bhatt SP et al., for the COPDGene Investigators

Summary: This study investigated whether β-blockers reduced the frequency of acute exacerbations in 3464 patients with GOLD stage 2–4 COPD who were participating in a prospective follow-up of the COPDGene cohort. Total and severe exacerbation rates were compared between groups categorised according to β-blocker use. β-blocker use was associated with significantly lower rates of total and severe exacerbations during follow-up of median 2.1 years (respective incidence risk ratios 0.73 [95% CI 0.60, 0.90] and 0.67 [0.48, 0.93]), and these rates were also lower among participants with GOLD stage 3–4 disease and on home oxygen (0.33 [0.19, 0.58] and 0.35 [0.16, 0.76]), with the greatest reduction seen for GOLD stage B. β-blocker use had no effect on all-cause mortality.

Comment: It is probably one of our most hotly debated paradoxes in respiratory medicine, that therapy with LABA/LAMAs improves symptoms but not survival in patients with COPD, while therapy with β-blockers may reduce exacerbations and possibly improves survival. Here the authors of the American based COPDGene study prospectively followed almost 3500 patients with COPD for about 2 years. The use of β-blockers was associated with a significantly lower rate of severe exacerbations, particularly in the GOLD B group. **Bottom line: while we are awaiting prospective studies, you may enjoy the remarkable summary of our local colleagues on 'cardiac dysfunction during exacerbation of COPD'.**

Reference: Thorax 2016;71(1):8–14
Abstract

Endobronchial valves for emphysema without interlobar collateral ventilation

Authors: Klooster K et al.

Summary: Patients with severe emphysema without collateral ventilation were randomised to receive bronchoscopic endobronchial valve treatment (n=34) or standard medical care (controls; n=34). Compared with controls, endobronchial valve treatment was associated with greater 6-month increases in FEV_1 by 140mL, FVC by 347mL and 6-minute walk distance by 74m ($p<0.01$ for all), but with significantly more serious adverse events (23 vs. 5 [$p<0.001$]), including one death in the endobronchial valve group, pneumothorax in 18% and events requiring valve replacement (12%) or removal (15%).

Comment: The use of endobronchial valves for the medical treatment of hyperinflation in patients with severe emphysema is coming of age; all major journals have published positive reports in 2016. This Dutch group had previously reported some improvement after valve placement. A subgroup analysis helped them in designing a trial to include patients with an intact intralobular fissure, a surrogate marker for absence of interlobar collateral ventilations. In this group FEV_1 improved by 140mL, FVC by 350mL and 6-minute walk distance by 74m. Serious adverse events included pneumothoraces and valve replacement or removal. **Bottom line: endobronchial valve placement in patients with severe emphysema improves lung function and exercise capacity.**

Reference: N Engl J Med 2015;373(24):2325–35
Abstract

Association of psychological disorders with 30-day readmission rates in patients with COPD

Authors: Singh G et al.

Summary: This study examined the impact of psychological disorders on early readmission rates in 80,088 US Medicare beneficiaries diagnosed with COPD during 2001–2011. There were 135,498 hospitalisations for COPD during the study period. Of these, 22.3% of patients had ≥1 psychological disorder. Multivariate analyses showed that the likelihood of 30-day readmission was higher in COPD patients with coexisting depression (OR 1.34 [1.29, 1.39]), anxiety (1.43 [1.37, 1.50]), psychosis (1.18 [1.10, 1.27]), alcohol abuse (1.30 [1.15, 1.47]) or drug abuse (1.29 [1.11, 1.50]) compared with patients without psychological disorders.

Comment: After exploring the physiological relationship between the heart and lungs, these authors explored the role of psychological disorders and readmission in 80,000 COPD patients. They report that patients with psychological-like anxiety, depression, alcohol abuse or drug abuse are younger, more likely to be female, have a longer length of stay and were more likely to be discharged to a care facility. Pulmonary rehabilitation has been shown to reduce anxiety and depression; however, the uptake is low in this group. **Bottom line: we need prospective studies to explore if the treatment of anxiety and depression reduces the rates of exacerbations and hospitalisation in these patients.**

Reference: Chest 2016;149(4):905–15
Abstract

Symbicort® Turbuhaler® 100/6 (budesonide 100 mcg and eformoterol fumarate 6 mcg per metered dose) or **Symbicort® Turbuhaler® 200/6** (budesonide 200 mcg and eformoterol fumarate 6 mcg per metered dose) or **Symbicort® Turbuhaler® 400/12** (budesonide 400 mcg and eformoterol fumarate 12 mcg per metered dose). Symbicort 400/12 is not approved for use in the Symbicort SMART regime. **Approved indication:** For the regular treatment of asthma where use of combination inhaled corticosteroid and long acting beta-agonist is appropriate using either Symbicort Maintenance and Reliever Therapy (SMART) or Symbicort maintenance therapy. **Contraindications & Precautions:** Hypersensitivity to budesonide, eformoterol or inhaled lactose. Treatment with Symbicort should not be initiated to treat a severe exacerbation. Care required for HPA axis suppression, when co-administering with inhibitors of CYP3A4 (e.g. ketoconazole, beta-blockers) or in patients with tuberculosis, severe cardiovascular disorders, diabetes, untreated hypokalaemia or thyrotoxicosis, pregnancy and lactation. **Common side effects** include headache, palpitations, tremor, oral candidiasis, mild throat irritation, coughing and hoarseness. Before prescribing please refer to the full product data sheet available at www.medsafe.govt.nz 21 May 2015. Symbicort is a fully funded Prescription Medicine. Special authority criteria and a prescription charge will apply. Please refer to the Pharmaceutical Schedule. Symbicort® and Turbuhaler® are trademarks of the AstraZeneca Group. AstraZeneca Limited, P299 Private Bag 92175, Auckland 1142. Telephone (09) 306 5650 or Facsimile (09) 306 5651. FEBRUARY 2016 essence AZ7377 DA1606GF 427,249.022

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