ADIS DRUG EVALUATION

Drugs 2007; 67 (16): 2383-2405
0012-6667/07/0016-2383/$49.95/0

Salmeterol/Fluticasone Propionate

A Review of its Use in the Treatment of Chronic Obstructive Pulmonary Disease

Gillian M. Keating and *Paul L. McCormack*

Wolters Kluwer Health | Adis, Auckland, New Zealand, an editorial office of Wolters Kluwer Health, Conshohocken, Pennsylvania, USA

Various sections of the manuscript reviewed by:

J. Bourbeau, Respiratory Epidemiology and Clinical Research Unit, McGill University Health Center, Montreal, Quebec, Canada; ***M. Cazzola***, Unit of Respiratory Diseases, Department of Internal Medicine, University of Rome 'Tor Vergata', Rome, Italy; ***N.A. Hanania***, Section of Pulmonary and Critical Care Medicine, Asthma Clinical Research Center, Baylor College of Medicine, Houston, Texas, USA; ***P.K. Jeffery***, Lung Pathology, Royal Brompton Hospital, London, England; ***P. Santus***, Institute of Lung Disease, Respiratory Unit, San Paolo Hospital, University of Milan, Milan, Italy; ***E.F.M. Wouters***, Department of Respiratory Medicine, University Hospital Maastricht, Maastricht, The Netherlands.

Data Selection

Sources: Medical literature published in any language since 1980 on 'salmeterol/fluticasone', identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE, EMBASE and AdisBase search terms were 'salmeterol/fluticasone' and ('chronic obstructive pulmonary disease' or 'COPD'). Searches were last updated 15 October 2007.

Selection: Studies in patients with chronic obstructive pulmonary disease who received salmeterol/fluticasone propionate. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Salmeterol, fluticasone propionate, chronic obstructive pulmonary disease, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

Contents

Summary

Abstract

Salmeterol/fluticasone propionate (Seretide®, Advair®, Viani®) administered using a multidose dry powder inhaler (Diskus®, Accuhaler®) is approved for use in the treatment of chronic obstructive pulmonary disease (COPD) in numerous countries.

Salmeterol/fluticasone propionate administered twice daily via dry powder inhaler is effective and generally well tolerated in patients with COPD. Although not associated with a statistically significant reduction in mortality versus placebo in the TORCH study ($p = 0.052$), salmeterol/fluticasone propionate reduced the rate of decline in lung function over the 3 years of the trial and was associated with lower exacerbation rates than the component monotherapies or placebo; other trials revealed clinically significant improvements in health status and dyspnoea scores with salmeterol/fluticasone propionate. Results of the INSPIRE trial suggest that salmeterol/fluticasone propionate is associated with a significantly lower mortality rate than tiotropium bromide monotherapy in patients with COPD; the two treatments had similar effects in terms of exacerbation rates and lung function. Thus, salmeterol/fluticasone propionate is an important option in the treatment of patients with COPD who are appropriate candidates for combination therapy with a long-acting bronchodilator and an inhaled corticosteroid.

Pharmacological Properties

Salmeterol is a highly selective β_2-adrenoceptor agonist with, among other effects, long-acting bronchodilator activity, and fluticasone propionate is a corticosteroid with anti-inflammatory activity. Together, they appear to have additive, or even synergistic, effects. In patients with COPD, salmeterol/fluticasone propionate demonstrated beneficial effects on airway inflammation; fluticasone propionate alone may also have a beneficial effect on systemic inflammation in this patient group. The systemic effects of salmeterol/fluticasone propionate are similar to those of the individual agents, with no evidence of systemic pharmacodynamic interaction.

The pharmacokinetics of the salmeterol/fluticasone propionate combination product are similar to those of its individual components. Both salmeterol and fluticasone propionate are lipophilic and act locally in the lung, so plasma concentrations are not predictive of therapeutic effect. Hepatic clearance is predominantly responsible for the clearance of both salmeterol and fluticasone propionate, meaning that patients with hepatic disease who receive salmeterol/fluticasone propionate should be closely monitored and caution is recommended

when salmeterol/fluticasone propionate is co-administered with potent cytochrome P450 3A4 inhibitors.

Therapeutic Efficacy

A number of well designed trials have compared the efficacy of salmeterol/fluticasone propionate 50μg/250μg or 50μg/500μg administered twice daily via dry powder inhaler with that of various comparators in patients with COPD.

Several randomised, double-blind, multicentre studies of 24 weeks to 3 years' duration have compared twice-daily salmeterol/fluticasone propionate 50μg/250μg or 50μg/500μg with the component monotherapies and/or placebo in patients with COPD. Results of the 3-year TORCH study did not reveal a statistically significant difference in mortality between salmeterol/fluticasone propionate and either placebo or salmeterol alone, although there was a significantly lower probability of death with salmeterol/fluticasone propionate than with fluticasone propionate alone. In two studies comparing salmeterol/fluticasone propionate with the component monotherapies, including the TORCH study, significantly fewer moderate to severe exacerbations occurred with salmeterol/fluticasone propionate than with the component monotherapies. The results of the 3-year TORCH study suggest that long-term therapy with salmeterol/fluticasone propionate in COPD reduced the rate of decline in lung function. In all studies, lung function improved to a significantly greater extent with salmeterol/fluticasone propionate than with component monotherapies or placebo. In addition, some trials revealed clinically significant improvements in health status and dyspnoea scores with salmeterol/fluticasone propionate.

Twice-daily salmeterol/fluticasone propionate 50μg/500μg had a similar effect to once-daily tiotropium bromide 18μg in terms of healthcare utilisation and symptom-based exacerbation rates and lung function in patients with severe COPD, according to the results of the 2-year, randomised, double-blind, multicentre INSPIRE trial. However, the relative probability of all-cause mortality was significantly lower with salmeterol/fluticasone propionate than with tiotropium bromide.

Twice-daily salmeterol/fluticasone propionate 50μg/250μg was more effective than four-times-daily salbutamol/ipratropium bromide 206μg/36μg, administered via metered-dose inhaler, in the treatment of COPD, according to the results of two randomised, double-blind, multicentre, 8-week studies. The change from baseline in morning predose forced expiratory volume in 1 second (FEV_1) significantly favoured patients receiving salmeterol/fluticasone propionate in both studies, as did the 6-hour area under the FEV_1 curve, morning peak expiratory flow (PEF), the percentage of symptom-free nights, the transitional dyspnoea index focal score and the overall combined daytime symptom score.

There was no significant difference between patients receiving salmeterol/fluticasone propionate 50μg/500μg twice daily or fluticasone propionate 500μg plus oral sustained-release theophylline, both administered twice daily, in the change from baseline in FEV_1 after 4 months of treatment in a randomised nonblind study in patients with COPD. However, the reductions from baseline in the visual analogue scale score for dyspnoea and rescue medication use significantly favoured salmeterol/fluticasone propionate.

Administering twice-daily salmeterol/fluticasone propionate 50μg/500μg in combination with once-daily tiotropium bromide 18μg did not confer additional benefit to patients with COPD in terms of exacerbation rates (vs once-daily tiotropium bromide 18μg alone), although some benefits were seen in terms of hospitalisation rates (vs once-daily tiotropium bromide 18μg alone), lung function

(vs twice-daily salmeterol/fluticasone propionate 50μg/500μg alone or once-daily tiotropium bromide 18μg alone) and health status (vs once-daily tiotropium bromide 18μg alone), according to the results of three randomised, double-blind trials.

Withdrawing fluticasone propionate resulted in a significant, albeit small, decline in FEV_1 in patients with COPD who had been receiving salmeterol/fluticasone propionate 50μg/500μg twice daily for 3 months according to the results of a randomised, double-blind, multicentre trial. Moreover, significantly greater reductions from baseline in FEV_1 : forced vital capacity and PEF were seen with salmeterol alone versus salmeterol/fluticasone propionate, although results were mixed in terms of other endpoints.

Tolerability

In general, adverse events occurring with salmeterol/fluticasone propionate were those that would be expected with the component drugs. In the TORCH study, the most commonly occurring adverse events in salmeterol/fluticasone propionate recipients included COPD exacerbation, upper respiratory tract infection, nasopharyngitis, pneumonia, candidiasis, bronchitis, headache, back pain, sinusitis, cough and hypertension.

In the TORCH and INSPIRE studies, there were no significant between-group differences in fracture incidence. An additional safety analysis conducted in a subgroup of patients from the TORCH trial revealed that there were no significant between-group differences in the change from baseline in bone mineral density of the hip or lumbar spine. In the TORCH study, there was no significant difference between patients receiving salmeterol/fluticasone propionate, salmeterol alone, fluticasone propionate alone or placebo in the incidence of eye disorders, including the development of cataracts. The incidence of pneumonia was significantly higher with salmeterol/fluticasone propionate or fluticasone propionate alone than with placebo in the TORCH study, and with salmeterol/fluticasone propionate than with tiotropium bromide in the INSPIRE study.

Pharmacoeconomic Considerations

Salmeterol/fluticasone propionate was a cost-effective option in the treatment of COPD, according to the results of a pharmacoeconomic analysis conducted in conjunction with the TORCH study; the analysis was conducted from the perspective of the UK National Health Service. The incremental cost-effectiveness ratio (ICER) for salmeterol/fluticasone propionate versus placebo was £17 000 (95% CI 8100, 41 700) per quality-adjusted life-year (QALY) gained (year of costing not stated). Results of a modelling study conducted from the perspective of the Canadian Ministry of Health also found salmeterol/fluticasone propionate to be a potentially cost-effective option in the treatment of patients with poorly reversible COPD and frequent exacerbations. The ICER for salmeterol/fluticasone propionate versus placebo was $Can74 887 per QALY gained (2002 values).

1. Introduction

Chronic obstructive pulmonary disease (COPD) poses a significant global health problem,[1] with ≈2.7 million deaths attributed to COPD in 2000.[2] Smoking is the most common cause of COPD in developed countries, although there are various other risk factors such as air pollution and occupational exposure.[1]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as a disease characterised by airflow limitation that is not fully reversible, that is usually progressive and that is associated with an abnormal inflammatory response of the lung to noxious particles or gases.[3] COPD involves both small airway disease (obstructive bronchiolitis) and destruction of the parenchyma

(emphysema); the relative contribution of these two components varies between patients.[3] Mucociliary dysfunction is also a feature of COPD.[4,5]

Although they share some similarities (e.g. airflow limitation and airway inflammation) and can sometimes be difficult to differentiate, COPD and asthma are disparate conditions.[3,6] Unlike COPD, the airflow limitation experienced by patients with asthma is usually fully reversible with bronchodilators.[6] In addition, airway inflammation in COPD is characterised by the presence of neutrophils, CD8+ T cells and macrophages, whereas the predominant inflammatory cells seen in asthma are eosinophils, mast cells and CD4+ T cells.[6]

Salmeterol/fluticasone propionate (Seretide®, Advair®, Viani®)[1] administered using a multidose dry powder inhaler (Diskus®, Accuhaler®) is approved for use in both the treatment of COPD and asthma in numerous countries. This article reviews the pharmacological properties of salmeterol/fluticasone propionate, as well as its clinical efficacy and tolerability in the management of COPD.

2. Pharmacodynamic Properties

This section provides a brief overview of the pharmacodynamic properties of salmeterol and fluticasone propionate. Two randomised, double-blind studies included healthy volunteers (n = 28[7] and 33[8]) who received salmeterol/fluticasone propionate via a dry powder inhaler[7] or salmeterol via a nasal aerosol spray.[8] Several randomised studies were conducted in patients with COPD (n = 12–140); studies were of double-blind[9-13] or single-blind[14-16] design. Where specified, patients had mild to moderate,[12] moderate to severe[9,10,15,16] or severe[14] COPD with an forced expiratory volume in 1 second (FEV_1) : forced vital capacity (FVC) of ≤0.7[9,11,13,15] or <0.75[12] and received salmeterol/fluticasone propionate or its individual components administered via dry powder inhaler[10,11,15] or metered-dose inhaler.[9,13,14,16]

2.1 Mechanism of Action

Salmeterol is a long-acting β_2-adrenoceptor agonist.[17] It is selective for β_2-adrenoceptors, with almost no affinity for β_1-adrenoceptors or α-adrenoceptors.[18] Salmeterol is at least 50 times more selective for β_2-adrenoceptors than salbutamol (albuterol).[17] Binding of salmeterol to the β_2-adrenoceptor results in activation of intracellular adenyl cyclase, which catalyses the conversion of adenosine triphosphate to cyclic adenosine monophosphate (cAMP).[17,19] Increased cAMP levels lead to bronchial smooth muscle relaxation.[19] Other actions of salmeterol that may be of relevance to COPD include reduction of cytokine secretion,[20,21] inhibition of antigen-induced increases in vascular permeability,[22] improved mucociliary clearance[8] and improved ciliary beat frequency.[23,24]

Fluticasone propionate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity that is largely mediated via glucocorticoid receptors.[6,17,25] *In vitro* studies show fluticasone propionate to be a human glucocorticoid receptor agonist with an affinity 18 times greater than dexamethasone, almost two times greater than the active metabolite of beclometasone (beclometasone-17-monopropionate), and two to three times greater than budesonide.[17,26,27]

As well as having complementary modes of action when administered together, salmeterol and fluticasone propionate also appear to have additive, and even synergistic, effects.[21,28-30] Molecular mechanisms that may explain this include protection against the downregulation of β_2-adrenoceptors by corticosteroids[31-33] and the ligand-independent activation of the glucocorticoid receptor by salmeterol.[34,35] Moreover, enhanced glucocorticoid receptor translocation into the nucleus was observed when salmeterol and fluticasone propionate were co-administered,[36] suggesting that salmeterol may amplify the anti-inflammatory effects of fluticasone propionate.[25]

2.2 Pulmonary Effects

A clinically significant (15%) increase in FEV_1 was reported 10 minutes after administration of salmeterol 50μg in patients with COPD; formoterol 24μg had an onset of action of 11 minutes.[16] The increase from baseline in FEV_1 was significantly ($p = 0.0001$) greater with budesonide/formoterol

1 The use of trade names is for product identification purposes only and does not imply endorsement.

160μg/4.5μg than with salmeterol/fluticasone propionate 25μg/250μg, 5 minutes after administration of a single dose to patients with COPD.[9]

In patients with COPD, peak bronchodilation (i.e. mean maximum improvement in FEV_1) occurred ≤2 hours after administration of a single dose of salmeterol 25–75μg[13,14] and 5 hours after administration of a single dose of salmeterol/fluticasone propionate 50μg/250μg.[15] The increase from baseline in FEV_1 was significantly ($p < 0.05$) greater after a single dose of budesonide/formoterol 400μg/12μg than after a single dose of salmeterol/fluticasone propionate 50μg/250μg at 120 and 360 minutes, with no significant between-group difference seen at 240, 480, 600 or 720 minutes.[15] Salmeterol had a prolonged duration of action, with bronchodilation lasting for at least 12 hours.[14,15]

In terms of repeat administration, results of the TRISTAN (Trial of Inhaled Steroids and Long-Acting β_2 Agonists) study revealed that salmeterol/fluticasone propionate 50μg/500μg twice daily significantly improved peak expiratory flow (PEF) after 1 day and breathlessness after 2 days of treatment (both $p < 0.001$ vs placebo).[37] Results of this and other longer-term studies examining the effects of salmeterol/fluticasone propionate on lung function are discussed in section 4.

Salmeterol and fluticasone propionate have also been shown to have other beneficial effects on the airways.[8,23,38,39] Salmeterol significantly improved mucociliary clearance in the nasal cavity of healthy volunteers ($p = 0.0001$ vs placebo), most probably as a result of increased ciliary beat activity,[8] and significantly reduced ($p < 0.05$) the pyocyanin-induced slowing of ciliary beat frequency *in vitro*.[23] Salmeterol also protected human adenoid epithelium from *Haemophilus influenzae*-induced damage,[38] and salmeterol plus fluticasone propionate had a synergistic effect in terms of preserving ciliated cells in human nasal turbinate tissue infected with *Pseudomonas aeruginosa*[39] in *in vitro* studies.

2.3 Anti-Inflammatory Effects

As mentioned previously, airway inflammation in COPD is characterised by the presence of neutrophils, CD8+ T cells and CD68+ macrophages; proinflammatory cytokines such as interleukin-8, interferon-γ (IFNγ) and tumour necrosis factor-α (TNFα) are also released.[10,11]

Salmeterol/fluticasone propionate 50μg/500μg twice daily demonstrated broad-spectrum anti-inflammatory activity in patients with COPD, according to the results of two recent studies.[10,11] After 12[11] or 13[10] weeks' therapy, significantly ($p < 0.05$) greater reductions from baseline in the number of CD8+ T cells seen on endobronchial biopsy occurred with salmeterol/fluticasone propionate than with placebo[10,11] or fluticasone propionate alone (500μg twice daily).[11] In addition, significantly ($p < 0.05$) greater reductions from baseline in the number of CD68+ macrophages were seen with salmeterol/fluticasone propionate than with placebo or fluticasone propionate alone in one study,[11] although there was no significant difference between salmeterol/fluticasone propionate and placebo in the other.[10] No significant change from baseline in the neutrophil or eosinophil count seen on biopsy occurred in salmeterol/fluticasone propionate recipients in one study,[11] although in the other, a significant ($p < 0.05$) reduction in the sputum neutrophil differential cell count occurred with salmeterol/fluticasone propionate.[10] Moreover, significant reductions in biopsy CD4+ and CD45+ cell counts and in the number of cells expressing genes for TNFα or IFNγ were also seen with salmeterol/fluticasone propionate (all $p < 0.05$ vs placebo).[10]

Fluticasone propionate may also have a beneficial effect on systemic inflammation in patients with COPD.[12] During a 4-week washout period, mean serum C-reactive protein (CRP) levels increased by 70.7% among those patients who discontinued inhaled corticosteroid therapy. Subsequently, the reduction from baseline in mean serum CRP levels was significantly greater with fluticasone propionate 500μg twice daily than with placebo (−50.3% vs −7.6%; adjusted $p = 0.042$) after 2 weeks' therapy.

2.4 Other Effects

The systemic effects of salmeterol/fluticasone propionate are similar to those of the individual agents, with no evidence of systemic pharmacodynamic interaction.[7] In a crossover study, healthy volunteers received twice-daily salmeterol/fluticasone propionate 100μg/500μg, salmeterol 100μg, fluticasone propionate 500μg or placebo for

11 days.[7] There were no significant differences between salmeterol/fluticasone propionate and salmeterol alone in terms of pulse rate, systolic and diastolic blood pressure, the corrected QT interval or serum potassium and glucose levels.[7] Tachyphylaxis was seen in salmeterol recipients who received cumulative doses of salbutamol on day 12; co-administration of fluticasone propionate did not alter this response.

Urinary cortisol excretion over 24 hours was significantly ($p < 0.001$) lower with salmeterol/fluticasone propionate or fluticasone propionate alone than with placebo, with no significant difference between the two active treatments.[7] The effect of salmeterol/fluticasone propionate on hypothalamic-pituitary-adrenal axis function in patients with COPD is discussed in section 5.

3. Pharmacokinetic Properties

Pharmacokinetic data are available from a subgroup of patients with COPD (n = 83)[40] from the TORCH (Towards a Revolution in COPD Health) study[41] (see section 4.1) who received inhaled salmeterol/fluticasone propionate 50μg/500μg twice daily, with additional data obtained from other sources. Some of the data included in this section were obtained from abstracts.[40,42,43] It should be noted that data concerning the plasma profile of salmeterol are limited, as the low plasma concentration achieved following the inhalation of salmeterol at therapeutic dosages means that there are technical difficulties associated with assaying the drug.[44]

3.1 Absorption and Distribution

The pharmacokinetics of inhaled salmeterol/fluticasone propionate are similar to those of the individual components.[45] Both salmeterol and fluticasone propionate are lipophilic and act locally in the lung, so plasma concentrations are not predictive of therapeutic effect.[17,26,44]

Following administration of salmeterol/fluticasone propionate via dry powder inhaler to healthy adults, the maximum plasma concentration (C_{max}) of salmeterol was reached in ≈5 minutes.[17] The steady-state plasma concentration of salmeterol achieved 10 minutes after administration in patients with COPD who received salmeterol/fluticasone propionate 50μg/500μg twice daily via dry powder inhaler is shown in table I.[40] Topical salmeterol concentrations of up to 1 μmol/L are achieved in the main bronchi.[44]

The majority of a fluticasone propionate dose delivered to the lung following inhalation undergoes systemic absorption.[17] In patients with COPD (n = 10), the least squares mean bioavailability of inhaled fluticasone propionate 1000 μg/day was 13.3%.[42]

At steady state, the C_{max} of fluticasone propionate was achieved 1 hour after administration of salmeterol/fluticasone propionate 50μg/500μg twice daily via dry powder inhaler in patients with COPD.[40] Other absorption parameters are shown in table I.[40]

At concentrations much higher than those achieved with therapeutic dosages of salmeterol, the drug was 96% plasma protein bound *in vitro*.[17] Following intravenous administration, fluticasone propionate had an average volume of distribution of 4.2 L/kg.[17] The plasma protein binding of fluticasone propionate was 99%.[43]

3.2 Metabolism and Elimination

Salmeterol underwent extensive hydroxylation (via the cytochrome P450 [CYP] isoenzyme CYP3A4) to α-hydroxysalmeterol in an *in vitro*

Table I. Steady-state pharmacokinetics of inhaled salmeterol/fluticasone (SAL/FLU) in patients (pts) with chronic obstructive pulmonary disease (COPD). A subgroup analysis of the TORCH study in which 83 pts with COPD received SAL/FLU 50μg/500μg bid, SAL 50μg bid, FLU 500μg bid or placebo (all administered via dry powder inhaler) [the analysis is available as an abstract].[40] Pharmacokinetics were assessed on week 36 (mean values unless specified otherwise)

Parameter	SAL/FLU 50μg/500μg bid		SAL 50μg bid	FLU 500μg bid
	SAL	FLU		
C_{max} (pg/mL)		105		115
t_{max}[a] (h)		1		1
C_{10min}[b] (pg/mL)	53.3		29.4	
AUC_{last} (pg • h/mL)		736		790

a Median value.

b Geometric mean value.

AUC_{last} = area under the plasma concentration-time curve from time zero to time of last measurable concentration; **bid** = twice daily; **C_{max}** = maximum plasma concentration; **C_{10min}** = plasma concentration 10 minutes after administration; **t_{max}** = time to C_{max}.

study.[17] Following oral administration of radiolabelled salmeterol 1mg in healthy men, 57% of the radioactivity was detected in the faeces and 23% was detected in the urine.[46] A negligible amount of unchanged salmeterol is detected in the urine or faeces.[17] Salmeterol has a terminal elimination half-life ($t_{1/2}\beta$) of ≈5.5 hours.[17]

The main route of fluticasone propionate clearance is hepatic metabolism.[17] CYP3A4 is responsible for the formation of the only circulating fluticasone propionate metabolite detected in man, a 17β-carboxylic acid derivative.[17] This metabolite had negligible pharmacological activity in animal studies.[17]

Fluticasone propionate has an average total clearance of 1093 mL/min, with renal clearance accounting for <0.02% of the total.[17] Fluticasone propionate has an average $t_{1/2}\beta$ of 5.3–7.7 hours following administration of salmeterol/fluticasone propionate via dry powder inhaler.[17]

3.3 Special Patient Populations

Data are not available concerning the pharmacokinetics of salmeterol/fluticasone propionate in special patient populations (e.g. the elderly or patients with renal or hepatic impairment), or if there are gender differences.[17] Thus, the following data pertain to the pharmacokinetics of the component drugs in special patient populations.

Neither age nor gender appeared to affect the pharmacokinetics of fluticasone propionate in patients with COPD.[17]

Given that hepatic metabolism is predominantly responsible for the clearance of both salmeterol and fluticasone propionate, impaired liver function may result in drug accumulation in plasma.[17] Thus, patients with hepatic disease who receive salmeterol or fluticasone propionate should be closely monitored.[17]

3.4 Potential Drug Interactions

In terms of systemic exposure, no significant drug interactions were observed between salmeterol and fluticasone propionate when they were administered in combination via dry powder inhaler to healthy volunteers.[7]

Since both salmeterol and fluticasone propionate are CYP3A4 substrates, caution is recommended when they are co-administered with potent CYP3A4 inhibitors.[17] For example, an increase in fluticasone propionate exposure was seen when inhaled fluticasone propionate was co-administered with the CYP3A4 inhibitor ketoconazole.[17] Moreover, a significant increase in plasma fluticasone propionate exposure was seen when fluticasone propionate nasal spray was co-administered with the potent CYP3A4 inhibitor ritonavir.[17] Thus, co-administration of these drugs is not recommended.[17]

4. Therapeutic Efficacy

The focus of this section is on well designed trials comparing the efficacy of inhaled salmeterol/fluticasone propionate with that of various comparators in patients with COPD.

Efficacy endpoints included mortality, exacerbation rates, lung function, health status and various other symptoms. Health status was assessed using St George's Respiratory Questionnaire (SGRQ) [scores range from 0 to 100 with lower scores indicating better health status; a change from baseline of ≥4 is considered clinically meaningful] or the Chronic Bronchitis Symptom Questionnaire (CRDQ) [total scores range from 20 (worst) to 140 (best), with a change from baseline of ≥10 considered clinically meaningful]. Dyspnoea was usually assessed using the Baseline Dyspnoea Index (BDI) [scores range from 0 (worst) to 12 (best)] and the Transitional Dyspnoea Index (TDI) focal score, which assesses the change from baseline in dyspnoea (scores range from −9 [major deterioration] to +9 [major improvement], with a 1-unit between-treatment difference considered clinically meaningful).

4.1 Comparisons with Salmeterol Alone, Fluticasone Propionate Alone or Placebo

Several studies have compared the efficacy of twice-daily salmeterol/fluticasone propionate 50μg/250μg[47] or 50μg/500μg[41,48-50] with twice-daily salmeterol 50μg alone,[41,47-50] twice-daily fluticasone propionate 250[47] or 500μg[41,49,50] alone or placebo[41,47,49,50] in the treatment of patients with COPD (691–6184 randomised patients). Studies

were of randomised, double-blind, multicentre design[41,47-50] and ranged in duration from 24 weeks to 3 years.[41,47-49]

Eligible patients were aged ≥40 years[41,47,48,50] (mean age 63–65 years[41,47-50]) with a (prebronchodilator[41,49]) FEV_1 : FVC of ≤0.7,[41,47-50] a (prebronchodilator[41,49]) FEV_1 of 25–70%,[49] <60%[41] or <65%[47,50] of predicted (but >0.70L[47,50] [or >40% of predicted if ≤0.70L[47]]), a postbronchodilator FEV_1 of <50% of predicted,[48] and an increase in FEV_1 of <10% of predicted with salbutamol 400μg.[41,49]

Study drugs were administered via dry powder inhaler.[41,47-50] The trials included run-in periods of 2[41,47,49,50] or 4[48] weeks; use of corticosteroids and inhaled long-acting bronchodilators was discontinued prior to or during the run-in period.[41,47-50]

Primary endpoints included time to death from any cause,[41] the number of moderate to severe exacerbations,[48] predose FEV_1[47,49,50] and 2-hour postdose FEV_1.[47,50] More specifically, in two trials the primary endpoints were the change from baseline in predose FEV_1 for salmeterol/fluticasone propionate versus salmeterol (i.e. assessing the fluticasone propionate contribution [the anti-inflammatory effect])[47,50] and for fluticasone propionate versus placebo,[50] and the change from baseline in 2-hour postdose FEV_1 for salmeterol/fluticasone propionate versus fluticasone propionate (i.e. assessing the salmeterol contribution [bronchodilation])[47,50] and for salmeterol versus placebo.[50]

Where specified, efficacy analyses were conducted in the modified intent-to-treat (ITT) population.[41,48]

4.1.1 Effect on Mortality

Salmeterol/fluticasone propionate was not associated with a statistically significant reduction in mortality compared with placebo in patients with COPD, according to the results of the TORCH study.[41] The probability of death at 3 years was 12.6% with salmeterol/fluticasone propionate, 13.5% with salmeterol alone, 16.0% with fluticasone propionate alone and 15.2% with placebo. The adjusted hazard ratio (HR) for salmeterol/fluticasone propionate versus placebo was 0.83 (95% CI 0.68, 1.00) [p = 0.052]; the HR was adjusted because an interim analysis had been performed (the unadjusted HR for salmeterol/fluticasone propionate vs placebo was 0.82 [95% CI 0.68, 0.99]; p = 0.04). In addition, no significant mortality differences were seen between each monotherapy and placebo, or between combination therapy and salmeterol monotherapy. However, patients receiving salmeterol/fluticasone propionate had a significantly lower probability of death than those receiving fluticasone propionate alone (HR 0.77 [95% CI 0.64, 0.93]; p = 0.007).[41]

Similar results were seen for the endpoint of COPD-related deaths, with a probability of death at 3 years of 4.7% with salmeterol/fluticasone propionate, 6.1% with salmeterol alone, 6.9% with fluticasone propionate alone and 6.0% with placebo.[41] No significant differences were seen between any of the active treatments and placebo, or between salmeterol/fluticasone propionate and salmeterol alone. However, the probability of COPD-related death was significantly lower in salmeterol/fluticasone propionate recipients than in recipients of fluticasone propionate alone (HR 0.67 [95% CI 0.50, 0.90]; p = 0.008).[41]

4.1.2 Effect on Chronic Obstructive Pulmonary Disease (COPD) Exacerbations

The number of moderate to severe COPD exacerbations experienced over a 44-week treatment period was significantly lower in patients receiving salmeterol/fluticasone propionate than in those receiving salmeterol alone (table II).[48] In addition, the annual rate of moderate to severe exacerbations was significantly lower with salmeterol/fluticasone propionate than with salmeterol alone[41,48] or fluticasone propionate alone,[41] according to the results of the 44-week study[48] and the TORCH study,[41] although no significant differences between the active treatments were seen in the TRISTAN study,[49] which examined exacerbations of all severities (table II). All active treatments were associated with significantly lower COPD exacerbation rates (all severities[49] or moderate to severe severity[41]) than placebo (table II). In the TORCH trial, the number needed to treat for salmeterol/fluticasone propionate versus placebo was 4 to prevent one exacerbation in 1 year and 32 to prevent one hospitalisation in 1 year.[41]

Table II. Efficacy of salmeterol/fluticasone propionate (SAL/FLU) against chronic obstructive pulmonary disease (COPD) exacerbations. Results of randomised, double-blind multicentre studies in patients with COPD

Study (trial name)	Duration	Treatment regimen (μg bid)	No. of pts	No. of exacerbations[a]	Annual exacerbation rate[a] [baseline]
Calverley et al.[41]	3y	SAL/FLU 50/500	1533		0.85**†‡
(TORCH)		SAL 50	1521		0.97**
		FLU 500	1534		0.93**
		PL	1524		1.13
Calverley et al.[49]	52wk	SAL/FLU 50/500	358		0.97***
(TRISTAN)		SAL 50	372		1.04*
		FLU 500	374		1.05*
		PL	361		1.30
Kardos et al.[48]	44wk	SAL/FLU 50/500	507	334††[b]	0.92†† [2.91]
		SAL 50	487	464[b]	1.4 [2.87]

a Only moderate to severe exacerbations were included in two trials.[41,48] In one trial, a moderate to severe exacerbation was defined as symptomatic deterioration requiring antibacterials, systemic corticosteroids and/or hospitalisation.[41] In the other trial, a moderate exacerbation was defined as a symptomatic deterioration requiring a change of respiratory medication and medical assistance, and a severe exacerbation was defined as symptomatic deterioration requiring hospitalisation or emergency room treatment.[48]

b Primary endpoint.

bid = twice daily; **PL** = placebo; * $p < 0.01$, ** $p < 0.001$, *** $p < 0.0001$ vs PL; † $p < 0.01$, †† $p < 0.0001$ vs SAL; ‡ $p < 0.05$ vs FLU.

4.1.3 Effects on Lung Function

The results of the 3-year TORCH study suggest that long-term therapy with salmeterol/fluticasone propionate reduced the rate of decline in lung function in COPD.[41,51] An additional analysis, available as an abstract, revealed that compared with placebo, the rate of decline in FEV_1 was reduced by 0.016 L/year with salmeterol/fluticasone propionate and by 0.013 L/year with both salmeterol alone and fluticasone propionate alone (all $p \leq 0.003$ vs placebo).[51] The improvement in postbronchodilator FEV_1 values seen in salmeterol/fluticasone propionate recipients was significantly greater than the reduction in postbronchodilator FEV_1 values seen in the other three treatment arms (table III).[41]

As expected, improvements in predose FEV_1 were significantly greater with salmeterol/fluticasone propionate or fluticasone propionate alone than with placebo[47,49,50] (and with salmeterol alone vs placebo in the one study making this statistical comparison),[49] and improvements in 2-hour postdose FEV_1 were significantly greater with salmeterol/fluticasone propionate or salmeterol alone than with placebo[47,50] (table III). In general, postbronchodilator FEV_1[41,49] and PEF[47,49,50] values also increased to a significantly greater extent with salmeterol/fluticasone propionate or its components than with placebo (table III).

Predose FEV_1 increased to a significantly greater extent with salmeterol/fluticasone propionate than with salmeterol (indicating the contribution of the fluticasone propionate component),[47,49,50] and with salmeterol/fluticasone propionate versus fluticasone propionate alone in the one study making this statistical comparison[49] (table III). Two-hour postdose FEV_1 increased to a significantly greater extent with salmeterol/fluticasone propionate than with fluticasone propionate (indicating the contribution of the salmeterol component) [table III].[47,50] In general, postbronchodilator FEV_1[41,49] and PEF[47-50] values also increased to a significantly greater extent with salmeterol/fluticasone propionate than with its individual components (table III).

4.1.4 Other Effects

Health status and dyspnoea scores improved to a significantly greater extent with salmeterol/fluticasone propionate than with placebo (table IV).[41,47-50] Mixed results were seen when comparing salmeterol/fluticasone propionate with salmeterol or fluticasone propionate monotherapy; significant between-group differences were seen in some but not all studies (table IV).[41,47-50] Among salmeterol/fluticasone propionate recipients, changes from baseline in mean CRDQ scores were considered clinically meaningful.[47,50] The change in the TDI score was also clinically meaningful with

Table III. Effect of salmeterol/fluticasone propionate (SAL/FLU) on lung function in patients with chronic obstructive pulmonary disease (COPD). Results (mean values) of randomised, double-blind multicentre studies

Study (trial name)	Duration	Treatment (μg bid)	No. of pts	Baseline FEV_1[a] (L)	Change from baseline in FEV_1 (L)[b]			Baseline PEF (L/min)	Change from baseline in PEF [L/min]
					predose	2h postdose	postbronch[c]		
Calverley	3y	SAL/FLU 50/500	1392	1.24			+0.029***†††‡‡‡		
et al.[41]d		SAL 50	1334	1.23			−0.021***		
(TORCH)		FLU 500	1356	1.23			−0.015***		
		PL	1261	1.26			−0.062		
Calverley	52wk	SAL/FLU 50/500	358	1.308	1.396****†††††‡‡‡e		1.484****†††e	247	274****†††††‡‡‡‡e
et al.[49]		SAL 50	372	1.245	1.323****e		1.436e	235	257****e
(TRISTAN)		FLU 500	374	1.260	1.302**e		1.454**e	246	255****e
		PL	361	1.266	1.264e		1.408e	243	242e
Hanania	24wk	SAL/FLU 50/250	178	1.252	+0.165***†	+0.281***‡‡‡		206	+31**††‡‡f
et al.[47]		SAL 50	177	1.245	+0.091	+0.200***		210	+15***f
		FLU 250	183	1.313	+0.109***	+0.147		220	+11***f
		PL	185	1.289	+0.001	+0.058		220	+1f
Kardos et al.[48]	44wk	SAL/FLU 50/500	507	1.17			+0.07		+18.0††††
		SAL 50	487	1.18			+0.05		+4.4
Mahler et al.[50]	24wk	SAL/FLU 50/500	165	1.268	+0.156***†	+0.261***‡‡‡		254	+31.9***†††‡‡‡
		SAL 50	160	1.237	+0.107	+0.233*		252	+16.8***
		FLU 500	168	1.233	+0.109***	+0.138		244	+12.9***
		PL	181	1.317	−0.004	+0.028		270	0f

a Predose[49] or postbronch[41,48] FEV_1 (where specified).

b Primary endpoints were predose FEV_1 at 52wk,[49] the change from baseline in predose FEV_1 for SAL/FLU vs SAL (i.e. the FLU contribution)[47,50] and for FLU vs PL,[50] and the change from baseline in 2h postdose FEV_1 for SAL/FLU vs FLU (i.e. the SAL contribution)[47,50] and for SAL vs PL.[50]

c Where specified, postbronch FEV_1 was assessed 30 min after inhalation of salbutamol 400μg.[48,49]

d Only patients for whom at least one measurement was obtained after baseline were included in the analysis.

e Value at 52wk (rather than change from baseline).

f Value estimated from a graph.

bid = twice daily; **FEV_1** = forced expiratory volume in 1 second; **PEF** = peak expiratory flow; **PL** = placebo; **postbronch** = postbronchodilator; * $p < 0.05$, ** $p < 0.01$, *** $p \leq 0.001$, **** $p < 0.0001$ vs PL; † $p < 0.05$, †† $p < 0.01$, ††† $p < 0.001$, †††† $p < 0.0001$ vs SAL; ‡ $p < 0.05$, ‡‡ $p < 0.01$, ‡‡‡ $p < 0.001$, ‡‡‡‡ $p < 0.0001$ vs FLU.

Table IV. Effect of salmeterol/fluticasone propionate (SAL/FLU) on health status, dyspnoea and rescue medication use in patients (pts) with chronic obstructive pulmonary disease (COPD). Results (mean values) of randomised, double-blind, multicentre studies

Study (trial name)	Duration	Treatment (μg bid)	No. of pts	SGRQ score		CRDQ score		BDI score	TDI score	Change from baseline in salbutamol use (puffs per day)
				baseline	change from baseline	baseline	change from baseline			
Calverley et al.[41]a (TORCH)	3y	SAL/FLU 50/500	1002	48.7	−3.0***†††‡					
		SAL 50	980	49.4	−0.8					
		FLU 500	1005	49.5	−1.8***					
		PL	924	48.4	+0.2					
Calverley et al.[49] (TRISTAN)	52wk	SAL/FLU 50/500	358	47.1	44.1***‡b					1****††††‡‡c
		SAL 50	372	48.7	45.2b					2*c
		FLU 500	374	49.8	45.5b					2**c
		PL	361	47.1	46.3b					2c
Hanania et al.[47]	24wk	SAL/FLU 50/250	178			84.1	+10.0**	6.1	+1.7*	−1.0**‡
		SAL 50	177			86.3	+6.4	6.1	+1.6*	−0.7
		FLU 250	183			85.5	+10.4**	6.2	+1.7	−0.2
		PL	185			84.8	+5.0	5.7	+1.0	+0.1
Kardos et al.[48]	44wk	SAL/FLU 50/500	507	51.9	−2.9*†					−0.2††
		SAL 50	487	51.8	−0.7					+0.06
Mahler et al.[50]	24wk	SAL/FLU 50/500	165			87.1	+10.0**‡	6.2	+2.1***††‡	−1.2*‡
		SAL 50	160			87.6	+8.0	5.9	+0.9	−0.9*
		FLU 500	168			88.5	+4.8	6.0	+1.3**	−0.4*
		PL	181			86.2	+5.0	5.8	+0.4	+0.5

a Only patients for whom at least one measurement was obtained after baseline were included in the analysis.

b Adjusted mean value at 52wk (rather than change from baseline).

c Median use of relief medication (per day).

BDI = Baseline Dyspnoea Index; **bid** = twice daily; **CRDQ** = Chronic Bronchitis Symptom Questionnaire; **PL** = placebo; **SGRQ** = St George's Respiratory Questionnaire; **TDI** = Transitional Dyspnoea Index; * $p < 0.05$, ** $p \leq 0.01$, *** $p < 0.001$, **** $p < 0.0001$ vs PL; † $p < 0.05$, †† $p \leq 0.001$, ††† $p \leq 0.0001$ vs SAL; ‡ $p < 0.05$, ‡‡ $p < 0.001$ vs FLU.

salmeterol/fluticasone propionate versus salmeterol alone or placebo in one study.[50] The change from baseline in the mean SGRQ score was not considered clinically meaningful in two studies (table IV),[41,48] although in the TRISTAN study, the raw mean change from baseline was −4.5 (i.e. clinically significant).[49]

Salmeterol/fluticasone propionate also resulted in significantly less use of reliever medication than placebo,[47,49,50] fluticasone propionate[47,49,50] or salmeterol (in two studies)[48,49] [table IV].

4.2 Comparison with Tiotropium Bromide

A 2-year, randomised, double-blind, multicentre trial (the INSPIRE [Investigating New Standards for Prophylaxis In Reduction of Exacerbations] study) has compared the efficacy of salmeterol/fluticasone propionate 50μg/500μg administered twice daily via dry powder inhaler with that of the long-acting bronchodilator tiotropium bromide 18μg administered once daily via Handihaler® in patients with severe COPD (n = 1323).[52]

Patients were aged 40–80 years (mean age 64 years) with a clinical history of COPD exacerbations, a postbronchodilator FEV_1 of <50% of predicted, and an increase in FEV_1 of ≤10% of predicted with salbutamol 400μg.[52]

The primary endpoint in INSPIRE was the rate of healthcare utilisation exacerbations.[52] Healthcare utilisation exacerbation was defined as the need for oral corticosteroids, antibacterials and/or hospitalisation. Efficacy analyses were conducted in the ITT population.[52]

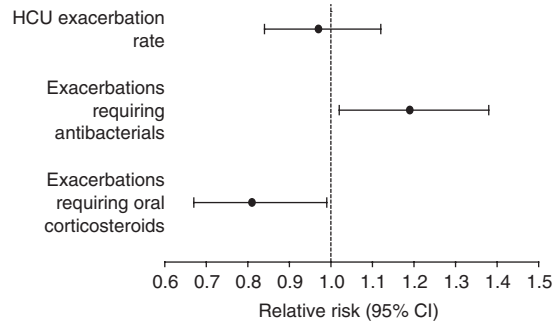

Fig. 1. Effect of salmeterol/fluticasone propionate on chronic obstructive pulmonary disease (COPD) exacerbations. Results of the randomised, double-blind, multicentre INSPIRE trial in patients with severe COPD who received salmeterol/fluticasone propionate 50μg/500μg twice daily (n = 658) or tiotropium bromide 18μg once daily (n = 665) for 2y.[52] Shown is the relative risk of exacerbations for salmeterol/fluticasone propionate vs tiotropium bromide. Healthcare utilisation (HCU) exacerbation (primary endpoint) was defined as exacerbations requiring antibacterials, oral corticosteroids and/or hospitalisation.

4.2.1 Effect on COPD Exacerbations

Twice-daily salmeterol/fluticasone propionate had a similar effect to once-daily tiotropium bromide in terms of the healthcare utilisation exacerbation rate in patients with severe COPD, according to the results of the INSPIRE trial.[52] At 2 years, there were no significant differences between salmeterol/fluticasone propionate recipients and tiotropium bromide recipients in the healthcare utilisation exacerbation rate (mean 1.28 vs 1.32 exacerbations per year) [figure 1].[52] However, exacerbations requiring antibacterials occurred significantly (p = 0.028) more frequently with salmeterol/fluticasone propionate than with tiotropium bromide (mean 0.97 vs 0.82 exacerbations per year), and those requiring oral corticosteroids occurred significantly (p = 0.039) less frequently with salmeterol/fluticasone propionate than with tiotropium bromide (mean 0.69 vs 0.85 exacerbations per year) [figure 1].[52]

4.2.2 Other Effects

At 2 years, the relative probability of all-cause mortality was reduced by 52% with salmeterol/fluticasone propionate versus tiotropium bromide (HR 0.48 [95% CI 0.27, 0.85]; p = 0.012) [mortality rate of 3% in salmeterol/fluticasone propionate recipients and 6% in tiotropium bromide recipients].[52] In addition, the likelihood of withdrawing from treatment was 29% higher in tiotropium bromide than in salmeterol/fluticasone propionate recipients (HR 1.29 [95% CI 1.08, 1.54]; p = 0.005), and the mean SGRQ total score at 2 years was significantly lower with salmeterol/fluticasone propionate than with tiotropium bromide (between-group difference in the change from baseline of −2.1 units; p = 0.038).[52]

There was no significant difference between patients receiving salmeterol/fluticasone propionate and those receiving tiotropium bromide in postdose FEV_1 in INSPIRE.[52]

4.3 Comparisons with Salbutamol/Ipratropium Bromide

Two randomised, double-blind, multicentre, 8-week studies compared the efficacy of twice-daily salmeterol/fluticasone propionate 50μg/250μg with that of four-times-daily salbutamol/ipratropium bromide 206μg/36μg in patients with COPD (n = 361[53] and 365[54]). Salmeterol/fluticasone propionate was administered via dry powder inhaler and salbutamol/ipratropium bromide was administered via metered-dose inhaler.[53,54]

Eligible patients with (moderate to severe[53]) COPD were aged ≥40 years (mean age 63[54] or 64[53] years) with a (prebronchodilator[54]) FEV_1 : FVC of ≤0.7[53,54] and an FEV_1 of ≤70% of predicted, but >0.70L (or ≥40% of predicted if ≤0.70L).[53,54]

The primary endpoint in both studies was morning predose FEV_1.[53,54] Efficacy analyses were conducted in the ITT population.[53,54]

Twice-daily salmeterol/fluticasone propionate 50μg/250μg was more effective than four-times-daily salbutamol/ipratropium bromide 206μg/36μg in the treatment of COPD.[53,54] After 8 weeks' treatment, the change from baseline in morning predose FEV_1 significantly favoured patients receiving salmeterol/fluticasone propionate in both studies (table V).[53,54] In addition, significantly greater improvements in prespecified secondary endpoints (such as the 6-hour area under the FEV_1 curve, morning PEF, the percentage of symptom-free nights, the TDI focal score and the overall combined daytime symptom score) were seen with salmeterol/fluticasone propionate than with salbutamol/ipratropium bromide (table V).[53,54]

Table V. Efficacy of salmeterol/fluticasone propionate (SAL/FLU) in patients (pts) with chronic obstructive pulmonary disease (COPD). Results of two randomised, double-blind, multicentre, 8wk trials comparing SAL/FLU with salbutamol/ipratropium bromide (SAB/IPR). Shown are the primary and prespecified secondary endpoints

Study	Treatment (μg)	No. of pts	Mean change from baseline [baseline]					
			morning predose FEV_1[a] (L)	FEV_1 AUC_6 (L • h)	morning PEF (L/min)	symptom-free nights (%)	TDI focal score	overall combined daytime symptom score[b]
Donohue et al.[54]	SAL/FLU 50/250 bid	182	+0.111*** [1.31]	1.39***[c] [1.07]	+37***	+28.4*	+2.7*** [5.7[d]]	−48*
	SAB/IPR 206/36 qid	183	−0.004 [1.26]	0.90[c] [1.17]	+7	+7.7	+1.2 [5.4[d]]	−24
Make et al.[53]	SAL/FLU 50/250 bid	180	+0.126*** [1.325]	+0.38*** [1.01]	+33*** [263]	+19.0** [25.5]	+2.6* [6.1[d]]	−46.7* [196.8]
	SAB/IPR 206/36 qid	181	−0.001 [1.180]	−0.18 [1.13]	+1 [244]	+8.0 [26.4]	+1.6 [5.7[d]]	−28.1 [201.3]

a Primary endpoint.

b Maximum score of 400.

c Week 8 value, rather than the change from baseline.

d Baseline Dyspnoea Index score.

bid = twice daily; **FEV_1** = forced expiratory volume in 1 second; **FEV_1 AUC_6** = 6-hour area under the FEV_1 curve; **PEF** = peak expiratory flow; **qid** = four times daily; **TDI** = Transitional Dyspnoea Index; * $p < 0.05$, ** $p \leq 0.01$, *** $p < 0.001$ vs SAB/IPR.

4.4 Comparison with Theophylline plus Fluticasone Propionate

The efficacy of salmeterol/fluticasone propionate was compared with that of sustained-release theophylline plus fluticasone propionate in patients with COPD in a randomised, nonblind study.[55] Patients were aged ≥50 years (mean age 66 years) with a postbronchodilator FEV_1 : FVC of <0.7 following salbutamol 400μg, and an FEV_1 of <70% of predicted, but >0.5L.

Following a 2-week run-in period, patients entered a theophylline titration phase during which oral sustained-release theophylline was titrated to a steady-state plasma concentration of 10–20 μg/mL.[55] Patients then received salmeterol/fluticasone propionate 50μg/500μg twice daily (n = 37) or fluticasone propionate 500μg plus oral sustained-release theophylline, both administered twice daily (n = 29), for 16 weeks. Salmeterol/fluticasone propionate and fluticasone propionate alone were administered via dry powder inhaler. The primary endpoint was predose FEV_1.[55]

After 4 months of treatment, there was no significant difference between patients receiving salmeterol/fluticasone propionate and those receiving theophylline plus fluticasone propionate in the change from baseline in FEV_1 (+0.172 vs +0.155L).[55] However, the reduction from baseline in the visual analogue scale score for dyspnoea was significantly ($p < 0.01$) greater with salmeterol/fluticasone propionate than with theophylline plus fluticasone propionate, as was the reduction from baseline in rescue medication use ($p < 0.001$).

4.5 In Combination with Tiotropium Bromide

Data are available from three randomised, double-blind trials examining the efficacy of combination therapy with salmeterol/fluticasone propionate plus tiotropium bromide in patients with COPD (n = 41,[56] 81[57] and 449[58]). One trial, only available as an abstract, was of crossover design[56] and another trial was of multicentre design.[58] The treatment period was of 2,[56] 12[57] or 52[58] weeks' duration. Where specified patients had moderate to severe[58] or severe to very severe[57] COPD.

Where specified, eligible patients were aged ≥35[58] or ≥50[57] years (mean age 65[57] or 67[58]

years), with ≥1 COPD exacerbation requiring systemic corticosteroids or antibacterials in the prior 12 months,[58] with a (postbronchodilator[57]) FEV_1 : FVC of <0.7[57,58] and a (postbronchodilator[58]) FEV_1 of <50%[57] or <65%[58] of predicted. Where specified, baseline predose FEV_1 values were 1.00–1.05L.[58]

Combination therapy comprised salmeterol/fluticasone propionate 50μg/500μg administered twice daily via dry powder inhaler and tiotropium bromide 18μg administered once daily via Handihaler®.[56-58] Comparator regimens included salmeterol/fluticasone propionate 50μg/500μg twice daily,[56,57] tiotropium bromide 18μg once daily[56-58] and salmeterol 50μg twice daily plus tiotropium bromide 18μg once daily.[58]

Primary endpoints included the proportion of patients in each treatment arm who experienced a COPD exacerbation,[58] the mean change from baseline in predose FEV_1[57] and the 4-hour area under the specific airways conductance curve (AUC_4 sGAW) postdose.[56]

4.5.1 Effect on COPD Exacerbations and Hospitalisation

In terms of the proportion of patients experiencing at least one acute COPD exacerbation, there was no significant difference between salmeterol/fluticasone propionate plus tiotropium bromide or salmeterol plus tiotropium bromide recipients and those receiving tiotropium bromide alone (60.0% and 64.8% vs 62.8%).[58] The median time to first exacerbation was 217, 128 and 130 days in the corresponding treatment groups.

In addition, there were no significant differences between patients receiving salmeterol/fluticasone propionate plus tiotropium bromide or salmeterol plus tiotropium bromide recipients and those receiving tiotropium bromide alone in the mean number of COPD exacerbations per patient-year (1.37 and 1.75 vs 1.61).[58] However, the number of hospitalisations for an acute exacerbation of COPD was significantly lower with salmeterol/fluticasone propionate plus tiotropium bromide than with tiotropium bromide alone (26 vs 49; incidence rate ratio of 0.53 [95% CI 0.33, 0.86]; p = 0.01), as was the number of all cause hospitalisations (41 vs 62; incidence rate ratio of 0.67 [95% CI 0.45, 0.99]; p = 0.04). Thirty-eight hospitalisations for an acute exacerbation of COPD and 48 hospitalisations for any cause occurred in patients receiving salmeterol plus tiotropium bromide.[58]

4.5.2 Effects on Lung Function

Improvements from baseline in predose[57] or prebronchodilator[58] FEV_1 were significantly ($p < 0.05$) greater with salmeterol/fluticasone propionate plus tiotropium bromide than with salmeterol/fluticasone propionate alone (+0.186 vs +0.140L[57]) or with tiotropium bromide alone (+0.186 vs +0.141L[57] and +0.086 vs +0.027L[58]) after 12[57] and 52[58] weeks' therapy. No significant difference in FEV_1 was seen between patients receiving salmeterol/fluticasone propionate plus tiotropium bromide and those receiving salmeterol plus tiotropium bromide.[58]

Preliminary data from the crossover study also indicate that 2 weeks' treatment with salmeterol/fluticasone propionate plus tiotropium bromide was superior to salmeterol/fluticasone propionate alone or tiotropium bromide alone in terms of postdose AUC_4 sGAW (both $p < 0.001$), predose AUC_4 sGAW (both $p < 0.01$) and predose FEV_1 (both $p < 0.05$).[56]

4.5.3 Other Effects

In terms of health status, changes in SGRQ scores significantly favoured patients receiving salmeterol/fluticasone propionate plus tiotropium bromide or salmeterol plus tiotropium bromide versus tiotropium bromide alone after 1 year's treatment (−8.6 and −6.3 vs −4.5 points; p = 0.01 and p = 0.02).[58]

No significant between-group differences in dyspnoea scores were seen after 12 weeks[57] or 1 year[58] of treatment, although TDI total scores improved to a significantly ($p < 0.001$) greater extent with salmeterol/fluticasone propionate plus tiotropium bromide than with tiotropium bromide alone in the 2-week study; the between-group difference (2.2) was clinically meaningful.[56] There were no significant between-group differences in salbutamol use in the 12-week study,[57] but in the 2-week study, use of rescue medication was significantly ($p \leq 0.01$) lower with salmeterol/fluticasone propionate plus tiotropium bromide than with tiotropium bromide alone or with salmeterol/fluticasone propionate alone.[56]

4.6 Fluticasone Propionate Withdrawal

A randomised, double-blind, multicentre trial examined the effect of discontinuing fluticasone propionate in patients with COPD who had been receiving salmeterol/fluticasone propionate 50μg/500μg twice daily for 3 months (497 patients enrolled).[59] Following this 3-month run-in period, patients were randomised to receive salmeterol/fluticasone propionate 50μg/500μg twice daily (n = 189) or salmeterol 50μg twice daily (n = 184) for 12 months.

Patients in these trials were aged 40–75 years (mean age 63 years), with a prebronchodilator FEV_1 : FVC of less than ≈0.9, a prebronchodilator FEV_1 of 30–70% of predicted and an increase in FEV_1 of <10% of predicted with salbutamol 400μg.[59] The primary endpoint was prebronchodilator FEV_1.[59]

Withdrawing fluticasone propionate resulted in a significant, albeit small, decline in FEV_1 in patients with COPD.[59] The mean reduction in FEV_1 from the start of the randomisation period was 0.1% in salmeterol/fluticasone propionate recipients versus 4.4% in salmeterol recipients ($p < 0.001$). Mean prebronchodilator FEV_1 values prior to randomisation were 47.4% and 48.2% of predicted in the corresponding treatment groups.

Significantly greater reductions from baseline in FEV_1 : FVC (−3.7% vs 0%; $p = 0.002$) and PEF (−4.1% vs −0.1%; $p = 0.01$) were seen with salmeterol alone versus salmeterol/fluticasone propionate.[59] Results were mixed in terms of other endpoints, with significant ($p < 0.05$) between-group differences favouring salmeterol/fluticasone propionate seen for some endpoints (e.g. rate of mild exacerbations, proportion of rescue medication-free days, dyspnoea score, percentage of disturbed nights), but not for others (e.g. rate of moderate and severe exacerbations, cough score, sputum score).

5. Tolerability

Data examining the tolerability of salmeterol/fluticasone propionate in patients with COPD were primarily obtained from the clinical trials discussed in section 4. The main focus of this section is tolerability data from the 3-year placebo-controlled TORCH study (n = 6184).[41]

In general, adverse events occurring with salmeterol/fluticasone propionate were those that would be expected with the component drugs (e.g. candidiasis as would be expected with the use of an inhaled corticosteroid).[47,50]

In the TORCH study, adverse events were experienced by 89% of salmeterol/fluticasone propionate recipients, 90% of salmeterol alone recipients, 90% of fluticasone propionate alone recipients and 90% of placebo recipients.[41] In the corresponding treatment groups, serious adverse events were reported by 43%, 40%, 42% and 41% of patients, drug-related adverse events by 18%, 12%, 19% and 13% of patients, and events resulting in withdrawal or discontinuation of study medication by 18%, 20%, 23% and 24% of patients.

In the TORCH study, common adverse events included upper respiratory tract infection, nasopharyngitis, pneumonia, candidiasis, bronchitis, headache, back pain, sinusitis, cough and hypertension; the annual rate of each of these adverse events was ≤0.11 in each treatment group.[41] In terms of COPD exacerbations, there were 0.67 episodes per year in salmeterol/fluticasone propionate recipients, compared with 0.76, 0.78 and 0.92 episodes per year in salmeterol, fluticasone propionate and placebo recipients, respectively.

The probability of patients experiencing pneumonia was found to be significantly ($p < 0.001$) greater with salmeterol/fluticasone propionate or fluticasone propionate alone than with placebo (19.6% and 18.3% vs 12.3% of patients); the incidence of pneumonia in patients receiving salmeterol alone was 13.3%.[41] The increased incidence of pneumonia did not appear to correspond to an increased number of deaths.[41] Pneumonia also occurred more frequently with salmeterol/fluticasone propionate than with tiotropium bromide in INSPIRE.[52] Pneumonia occurred in 8% of salmeterol/fluticasone propionate recipients and in 4% of tiotropium bromide recipients, with an HR of 1.94 (95% CI 1.19, 3.17) [$p = 0.008$].[52]

In TORCH, there were no significant differences between patients receiving salmeterol/fluticasone propionate or salmeterol alone and those receiving fluticasone propionate alone or placebo in the annual rate of cardiac disorders (0.087 and 0.114 vs 0.102 and 0.113).[41] Other studies revealed that

clinically significant ECG abnormalities were experienced by similar proportions of patients receiving salmeterol/fluticasone propionate, salmeterol alone, fluticasone propionate alone or placebo.[47,50]

It has been suggested that high-dose inhaled corticosteroid use may be associated with an increased fracture risk in patients with obstructive airways disease.[60,61] However, in the TORCH study, there were no significant differences between patients receiving salmeterol/fluticasone propionate, salmeterol alone, fluticasone propionate alone or placebo in the incidence of fracture (6.3%, 5.1%, 5.4% and 5.1%) or nontraumatic fracture (1.7%, 2.5%, 1.7% and 1.8%).[41] An additional safety analysis conducted in a subgroup of patients from the TORCH trial revealed that there were no significant between-group differences in the change from baseline in bone mineral density of the hip (277 evaluable patients) or lumbar spine (270 evaluable patients).[41]

In the TORCH study, there was no significant difference between patients receiving salmeterol/fluticasone propionate, salmeterol alone, fluticasone propionate alone or placebo in the incidence of eye disorders (5.2%, 4.3%, 4.1% and 3.6%).[41] When patients without cataracts at baseline were considered (n = 187), the additional safety analysis revealed no significant between-group differences in the proportion of these patients who developed cataracts during treatment (27% of evaluable salmeterol/fluticasone propionate recipients, 15% of evaluable salmeterol alone recipients, 17% of evaluable fluticasone propionate alone recipients and 21% of placebo recipients).[41]

Salmeterol/fluticasone propionate was not associated with an increased risk of clinically relevant suppression of the hypothalamic-pituitary-adrenal axis.[47,49,50] Similar proportions of patients receiving salmeterol/fluticasone propionate, salmeterol alone, fluticasone propionate alone or placebo had abnormal responses to tetracosactide (cosyntropin).[47,50] During the TRISTAN study, mean serum cortisol levels were significantly ($p < 0.05$) lower with salmeterol/fluticasone propionate than with placebo at week 24, and with fluticasone propionate than with placebo at weeks 24 and 52, although no clinical signs of hypoadrenalism were apparent.[49]

6. Pharmacoeconomic Considerations

Salmeterol/fluticasone propionate was a cost-effective option in the treatment of COPD, according to the results of a pharmacoeconomic analysis conducted in conjunction with the TORCH study[41] (section 4.1).[62] In this analysis, quality-adjusted life-years (QALYs) were estimated using the EuroQuality of Life 5-dimension (EuroQol-5D) questionnaire, which was administered to 4237 patients in 21 countries. Costs included all-cause hospitalisation, medication and outpatient care costs. The analysis was conducted from the perspective of the UK National Health Service; results are available as an abstract.[62]

Mean QALYs gained were 2.05 with salmeterol/fluticasone propionate 50µg/500µg twice daily, 1.97 with salmeterol 50µg twice daily, 1.99 with fluticasone propionate 500µg twice daily and 1.96 with placebo, with a significant difference seen between salmeterol/fluticasone propionate and placebo recipients (p-value not stated).[62] Costs in the corresponding treatment groups were £5094, £4302, £4894 and £3151 (year of costing not stated); costs were significantly higher in the active treatment groups than with placebo (p-values not stated). The incremental cost-effectiveness ratio (ICER) for salmeterol/fluticasone propionate versus placebo was £17 000 (95% CI 8100, 41 700) per QALY gained.[62]

Results of a modelling study conducted from the perspective of the Canadian Ministry of Health also found salmeterol/fluticasone propionate to be a potentially cost-effective option in the treatment of patients with poorly reversible COPD and frequent exacerbations.[63] The Markov model used efficacy data from the TRISTAN study[49] (section 4.1); costs included those associated with maintenance therapy (i.e. costs associated with drug acquisition, oxygen therapy, diagnostic tests, laboratory tests and clinic visits) and exacerbation-related costs (i.e. costs associated with hospitalisation, laboratory tests and additional drugs, and physician-related costs [major exacerbations], and costs associated with emergency room visits [minor exacerbations]). Cost effectiveness was modelled over the lifetime of the patient (maximum 25 years), with discounting of 5% per annum for costs and effects.

In the base-case analysis, salmeterol/fluticasone propionate 50μg/500μg twice daily was associated with a mean 4.21 QALYs at a cost of $Can25 780 and usual care (placebo) was associated with a mean 4.08 QALYs at a cost of $Can16 415 (2002 values).[63] This yielded an ICER of $Can74 887 per QALY gained. Sensitivity analyses revealed that the cost effectiveness of salmeterol/fluticasone propionate improved as exacerbation rates increased.

Limitations of the model include that FEV_1, age, gender and smoking status were the only factors considered in determining COPD prognosis, that utility weights were applied to exacerbation events, and that smoking cessation during the model timeframe could not be taken into account.[63]

7. Dosage and Administration

In the EU, salmeterol/fluticasone propionate 50μg/500μg twice daily is approved for use in the symptomatic treatment of patients with COPD who have a prebronchodilator FEV_1 of <60% of predicted, a history of repeat COPD exacerbations and significant symptoms despite the regular use of bronchodilator therapy.[45] In the US, salmeterol/fluticasone propionate 50μg/250μg twice daily is approved for maintenance therapy in patients with COPD associated with chronic bronchitis; the use of salmeterol/fluticasone propionate 50μg/500μg twice daily is not approved in the US.[17]

Local prescribing information should be consulted for information regarding contraindications, warnings and precautions.

8. Place of Salmeterol/Fluticasone Propionate in the Management of COPD

COPD poses a significant burden to both the individual and society, and morbidity and mortality associated with this condition are expected to increase in the next few decades.[6] According to the GOLD guidelines, the management of COPD should be individualised according to disease severity and the response of patients to various therapies.[3] GOLD classifies COPD severity according to postbronchodilator FEV_1 values: mild COPD (stage I) is defined as a FEV_1 : FVC of <0.7 and an FEV_1 of ≥80% of predicted; moderate COPD (stage II) is defined as a FEV_1 : FVC of <0.7 and an FEV_1 of <80% but ≥50% of predicted; severe COPD (stage III) is defined as FEV_1 : FVC of <0.7 and an FEV_1 of <50% but ≥30% of predicted; and very severe COPD (stage IV) is defined as an FEV_1 : FVC of <0.7 and an FEV_1 of <30% of predicted or an FEV_1 of <50% of predicted plus chronic respiratory failure.

The GOLD guidelines indicate that the goals of COPD management are to relieve symptoms, prevent the progression of disease, improve exercise tolerance and disease status, prevent and treat complications and exacerbations, and reduce mortality.[3] The management of COPD encompasses both pharmacological and nonpharmacological measures. Important nonpharmacological measures include encouraging smoking cessation, oxygen therapy and pulmonary rehabilitation.[4,64] Surgery may also be an option in carefully selected patients.[4]

Bronchodilators play a central role in the symptomatic management of COPD.[3] Although the improvement in FEV_1 achieved with bronchodilators may be small, it is often associated with larger changes in lung volume, which contribute to a reduction in perceived breathlessness.[65] The three most commonly used types of bronchodilator are β_2-adrenoceptor agonists, anticholinergics and methylxanthines: short-acting β_2-adrenoceptor agonists include salbutamol, fenoterol and terbutaline; long-acting β_2-adrenoceptor agonists include salmeterol and formoterol; short-acting anticholinergics include ipratropium bromide and oxitropium bromide; long-acting anticholinergics include tiotropium bromide; and methylxanthines include sustained-release theophylline and aminophylline.[3,65] The GOLD guidelines recommend the regular use of long-acting bronchodilators in patients with COPD of at least moderate severity, with the addition of an inhaled corticosteroid (e.g. fluticasone propionate, beclometasone, budesonide or triamcinolone) in patients with severe or very severe disease who experience repeated exacerbations.[3]

Salmeterol is a highly selective β_2-adrenoceptor agonist with, among other effects, long-acting bronchodilator activity, and fluticasone propionate is a corticosteroid with anti-inflammatory activity. Together, they appear to have additive, or even synergistic, effects (section 2). For example, the

anti-inflammatory effects of salmeterol/fluticasone propionate exceeded those of fluticasone propionate alone in patients with COPD (section 2.3).[11] There has been increasing emphasis on the role of inflammation in COPD in recent times.[66,67] Indeed, it has been suggested that inflammation may not be limited to the airways in patients with COPD, but may spill over into the systemic circulation.[66,67] It is hypothesised that this systemic inflammation may explain the apparent association between COPD and cardiovascular disease, independent of cigarette smoking.[66] Fluticasone propionate reduced systemic inflammation (assessed using serum CRP levels) in a small study in patients with COPD (section 2.3). A large well designed study examining the effect of salmeterol/fluticasone propionate on systemic inflammation in COPD is currently underway, with CRP levels being used as a surrogate marker of coronary risk.[68]

Previous retrospective studies have suggested that combination therapy with a long-acting β_2-adrenoceptor agonist and an inhaled corticosteroid may be associated with a survival benefit in patients with COPD,[69-72] although the results of these trials should be interpreted with caution, given their design. By contrast, the 3-year TORCH study did not reveal a statistically significant reduction in mortality with salmeterol/fluticasone propionate versus placebo (section 4.1). It has been suggested that the trial was underpowered to detect an effect of salmeterol/fluticasone propionate on mortality.[41] A contributing factor may have been the significantly ($p < 0.001$) higher drop-out rate seen in placebo recipients than in patients receiving salmeterol/fluticasone propionate, salmeterol alone or fluticasone propionate alone (44% vs 34%, 36% and 38%); placebo recipients were then permitted to receive active treatment subsequently.[41] The 2.6% difference in absolute mortality seen between salmeterol/fluticasone propionate and placebo recipients may be clinically relevant; indeed, the TORCH trial raises the question of what constitutes a clinically important between-group difference in mortality.[73]

In general, salmeterol/fluticasone was more effective than the component monotherapies or placebo in terms of exacerbation rates and lung function, according to the results of the TORCH study, the TRISTAN study and various other trials (section 4.1). Results of the TORCH trial suggest that salmeterol/fluticasone propionate reduced the rate of decline of FEV_1 (section 4.1). In addition, clinically significant improvements in CRDQ and TDI scores occurred in salmeterol/fluticasone propionate recipients.

Twice-daily salmeterol/fluticasone propionate had similar efficacy to monotherapy with once-daily tiotropium bromide in terms of the healthcare utilisation exacerbation rate and lung function; however, results of the 2-year INSPIRE trial suggest significantly lower all-cause mortality with salmeterol/fluticasone propionate than with tiotropium bromide (it should be noted that mortality was not a primary endpoint in this study and that there was no placebo arm; more data are needed to confirm this mortality result) [section 4.2].

In addition, twice-daily salmeterol/fluticasone propionate was more effective than four-times-daily combination therapy with the short-acting agents salbutamol/ipratropium bromide (section 4.3). Data examining the concurrent use of these two combination therapies would be of interest, given that, in the US at least, salmeterol/fluticasone propionate is sometimes prescribed to patients with COPD as maintenance therapy, with salbutamol/ipratropium bromide prescribed as rescue therapy.[74]

It has been suggested that oral theophylline should only be used in COPD when symptoms persist despite optimal bronchodilator therapy.[75] A small trial found that salmeterol/fluticasone propionate had similar effects on lung function to sustained-release theophylline plus fluticasone propionate in patients with COPD, although salmeterol/fluticasone propionate was associated with greater symptomatic improvement (section 4.4).

Triple therapy has been suggested as an option in patients with advanced COPD and frequent exacerbations.[74] However, combining treatment with salmeterol/fluticasone propionate plus tiotropium bromide did not confer additional benefit in terms of exacerbation rates, although some benefits were seen in terms of hospitalisation rates, lung function and health status (section 4.5).

The vast majority of the above-mentioned studies examined a salmeterol/fluticasone propionate dosage of 50μg/500μg twice daily, the dosage approved for use in the EU (section 7). A lower dosage of

salmeterol/fluticasone is approved for use in the US (50μg/250μg twice daily) [section 7]; approval of the higher dosage was recently declined.[76] In the EU, salmeterol/fluticasone was previously approved for use in patients with COPD and a prebronchodilator FEV_1 of <50% of predicted. However, this label was recently amended meaning that salmeterol/fluticasone propionate is now indicated for use in patients with a prebronchodilator FEV_1 of <60% of predicted.[45]

Administering salmeterol and fluticasone propionate together in a dry powder inhaler is convenient and has potential advantages in terms of patient adherence.[77] Moreover, breath-actuated dry powder inhalers have an advantage over metered-dose inhalers in that patients do not have to coordinate inspiration with actuation.[65,77]

Salmeterol is generally held to have a slower onset of action than the long-acting β_2-adrenoceptor agonist formoterol.[6] However, the two drugs were shown to have a similar onset of action in one study in patients with COPD (section 2.2).[16] Formoterol administered in combination with budesonide in a single inhaler has also been shown to have beneficial effects in patients with COPD.[78,79] Data comparing salmeterol/fluticasone propionate with budesonide/formoterol are limited; two single-dose studies have compared the combination therapies (section 2.2),[9,15] but data from larger multiple-dose studies would be of interest.

The tolerability of drugs in patients with COPD is of particular interest, given that these patients are often older and have significant co-morbid illnesses.[6,80] Salmeterol/fluticasone propionate was generally well tolerated in patients with COPD, with reported adverse events generally being those expected with the component monotherapies (section 5). It is possible that even highly selective β_2-adrenoceptor agonists such as salmeterol may be associated with cardiac adverse events, given that β_2-adrenoceptors comprise 10–15% of the total β-adrenoceptors in the heart.[17] However, such events were seen infrequently in salmeterol/fluticasone propionate recipients in clinical trials (section 5). The adverse effects of oral corticosteroids (e.g. osteoporosis) are well established.[80] By contrast, the fluticasone propionate component of inhaled salmeterol/fluticasone propionate was not associated with an increased fracture risk or an increase in eye disorders after 3 years of therapy in the TORCH study (section 5), although a longer duration of follow-up may be needed to detect such effects.[41] Pneumonia occurred in more patients receiving salmeterol/fluticasone propionate or fluticasone propionate alone versus placebo in the TORCH trial, and in more patients receiving salmeterol/fluticasone propionate versus tiotropium bromide in the INSPIRE trial; further research is needed concerning this finding.

COPD is a condition associated with significant costs. Salmeterol/fluticasone propionate appears to be a cost-effective option in the treatment of COPD, although more pharmacoeconomic data are needed (section 6).

In conclusion, salmeterol/fluticasone propionate administered twice daily via dry powder inhaler is effective and generally well tolerated in patients with COPD. Although not associated with a statistically significant reduction in mortality versus placebo in the TORCH trial ($p = 0.052$), salmeterol/fluticasone propionate reduced the rate of decline in lung function over the 3 years of the trial and was associated with lower exacerbation rates than the component monotherapies or placebo; other trials revealed clinically significant improvements in health status and dyspnoea scores with salmeterol/fluticasone propionate. Results of the INSPIRE trial suggest that salmeterol/fluticasone propionate is associated with a significantly lower mortality rate than tiotropium bromide monotherapy in patients with COPD; the two treatments had similar effects in terms of exacerbation rates and lung function. Thus, salmeterol/fluticasone propionate is an important option in the treatment of patients with COPD who are appropriate candidates for combination therapy with a long-acting bronchodilator and an inhaled corticosteroid.

Disclosure

During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

References

1. Barnes PJ, Shapiro SD, Pauwels RA. Chronic obstructive pulmonary disease: molecular and cellular mechansims. Eur Respir J 2003 Oct; 22 (4): 672-88
2. Lopez AD, Shibuya K, Rao C, et al. Chronic obstructive pulmonary disease: current burden and future projections. Eur Respir J 2006; 27 (2): 397-412
3. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2007 Sep 15; 176 (6): 532-55
4. Rodríguez-Roisin R. The airway pathophysiology of COPD: implications for treatment. COPD 2005 Jun; 2: 253-62
5. Agusti AGN. COPD, a multicomponent disease: implications for management. Respir Med 2005 Jun; 99 (6): 670-82
6. Dransfield MT, Bailey WC. Fluticasone propionate/salmeterol for the treatment of chronic-obstructive pulmonary disease. Expert Opin Pharmacother 2004 Aug; 5 (8): 1815-26
7. Kirby S, Falcoz C, Daniel MJ, et al. Salmeterol and fluticasone propionate given as a combination: lack of systemic pharmacodynamic and pharmacokinetic interactions. Eur J Clin Pharmacol 2001; 56: 781-91
8. Tay HL, Armoogum N, Tan LKS. Nasal mucociliary clearance and salmeterol. Clin Otolaryngol 1997; 22: 68-70
9. Lindberg A, Szalai Z, Pullerits T, et al. Fast onset of effect of budesonide/formoterol versus salmeterol/fluticasone and salbutamol in patients with chronic obstructive pulmonary disease and reversible airway obstruction. Respirology 2007 Sep; 12 (5): 732-9
10. Barnes NC, Qiu Y-S, Pavord ID, et al. Antiinflammatory effects of salmeterol/fluticasone propionate in chronic obstructive lung disease. Am J Respir Crit Care Med 2006 Apr 1; 173 (7): 736-43
11. Bourbeau J, Christodoulopoulos P, Maltais F, et al. Effect of salmeterol/fluticasone propionate on airway inflammation in COPD: a randomized controlled trial. Thorax. Epub 2007 Jun 8
12. Sin DD, Lacy P, York E, et al. Effects of fluticasone on systemic markers of inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004 Oct 1; 170 (7): 760-5
13. Di Marco F, Milic-Emili J, Boveri B, et al. Effect of inhaled bronchodilators on inspiratory capacity and dyspnoea at rest in COPD. Eur Respir J 2003; 21: 86-94
14. Cazzola M, Matera MG, Santangelo G, et al. Salmeterol and formoterol in partially reversible severe chronic obstructive pulmonary disease: a dose-response study. Respir Med 1995 May; 89: 357-62
15. Cazzola M, Santus P, Di Marco F, et al. Bronchodilator effect of an inhaled combination therapy with salmeterol + fluticasone and formoterol + budesonide in patients with COPD. Respir Med 2003 May; 97 (5): 453-7
16. Cazzola M, Santangelo G, Piccolo A. Effect of salmeterol and formoterol in patients with chronic obstructive pulmonary disease. Pulm Pharmacol 1994 Apr; 7 (2): 103-7
17. GlaxoSmithKline. Advair Diskus® 100/50, 250/50, 500/50 prescribing information [online]. Available from URL: http://www.gsk.com/products/advair_us.htm [Accessed 2007 Jul 30]
18. Buchwald A, Hochhaus G. Pharmacokinetic and pharmacodynamic aspects of salmeterol therapy. Int J Clin Pharmacol Ther 1998 Dec; 36 (12): 652-60
19. Sin DD, Man SFP. Corticosteroids and adrenoceptor agonists: the compliments for combination therapy in chronic airways diseases. Eur J Pharmacol 2006 Mar 8; 533 (1-3): 28-35
20. Sekut L, Champion BR, Page K, et al. Anti-inflammatory activity of salmeterol: down-regulation of cytokine production. Clin Exp Immunol 1995; 99 (3): 461-6
21. Pang L, Knox AJ. Regulation of TNF-α-induced eotaxin release from cultured human airway smooth muscle cells by β_2-agonists and corticosteroids. FASEB J 2001 Jan; 15: 261-9
22. Proud D, Reynolds CJ, Lichtenstein LM, et al. Intranasal salmeterol inhibits allergen-induced vascular permeability but not mast cell activation or cellular infiltration. Clin Exp Allergy 1998 Jul; 28 (7): 868-75
23. Kanthakumar K, Cundell DR, Johnson M, et al. Effect of salmeterol on human nasal epithelial cell ciliary beating: inhibition of the ciliotoxin, pyocyanin. Br J Pharmacol 1994; 112: 493-8
24. Piatti G, Ambrosetti U, Santus P, et al. Effects of salmeterol on cilia and mucus in COPD and pneumonia patients. Pharmacol Res 2005 Feb; 51 (2): 165-8
25. Sin DD, Man SFP. Do chronic inhaled steroids alone or in combination with a bronchodilator prolong life in chronic obstructive pulmonary disease patients? Curr Opin Pulm Med 2007 Mar; 13 (2): 90-7
26. Mollmann H, Wagner M, Krishnaswami S, et al. Single-dose and steady-state pharmacokinetic and pharmacodynamic evaluation of therapeutically equivalent doses of inhaled fluticasone propionate and budesonide, given as Diskus or Turbohaler dry-powder inhalers to healthy subjects. J Clin Pharmacol 2001; 41: 1329-38
27. Thorsson L, Edsbäcker S, Källen A, et al. Pharmacokinetics and systemic activity of fluticasone via Diskus® and pMDI, and of budesonide via Turbuhaler®. Br J Clin Pharmacol 2001; 52: 529-38
28. Pang L, Knox AJ. Synergistic inhibition by β_2-agonists and corticosteroids on tumor necrosis factor (TNF)-α-induced interleukin-8 release from cultured human airway smooth-muscle cells. Am J Respir Cell Mol Biol 2000; 23 (1): 79-85
29. Pace E, Gagliardo R, Melis M, et al. Synergistic effects of fluticasone propionate and salmeterol on *in vitro* T-cell activation and apoptosis in asthma. J Allergy Clin Immunol 2004 Nov; 114 (5): 1216-23
30. Wallin A, Sue-Chu M, Bjermer L, et al. Effect of inhaled fluticasone with and without salmeterol on airway inflammation in asthma. J Allergy Clin Immunol 2003 Jul; 112 (1): 72-8
31. Baraniuk JN, Ali M, Brody D, et al. Glucocorticoids induce β_2-adrenergic receptor function in human nasal mucosa. Am J Respir Crit Care Med 1997 Feb; 155 (2): 704-10
32. Kalavantavanich K, Schramm CM. Dexamethasone potentiates high-affinity β-agonist binding and $G_s\alpha$ protein expression in airway smooth muscle. Am J Physiol Lung Cell Mol Physiol 2000 May; 278 (5): L1101-6
33. Mak JCW, Nishikawa M, Shirasaki H, et al. Protective effects of a glucocorticoid on downregulation of pulmonary β_2-adrenergic receptors in vivo. J Clin Invest 1995; 96: 99-106
34. Eickelberg O, Roth M, Lörx R, et al. Ligand-independent activation of the glucocorticoid receptor by β_2-adrenergic receptor agonists in primary human lung fibroblasts and vascular smooth muscle cells. J Biol Chem 1999 Jan 8; 274 (2): 1005-10
35. Usmani OS, Ito K, Maneechotesuwan K, et al. Glucocorticoid receptor nuclear translocation in airway cells after inhaled combination therapy. Am J Respir Crit Care Med 2005 Sep 15; 172 (6): 704-12
36. Haque RA, Torrego A, Essilfie-Quaye S, et al. Effect of salmeterol and fluticasone on glucocorticoid receptor translocation in sputum macrophages and peripheral blood mononuclear cells from patients with chronic obstructive pulmonary disease [abstract]. Proc Am Thoracic Soc 2006 Apr; 3 Suppl.: A848
37. Vestbo J, Pauwels R, Anderson JA, et al. Early onset of effect of salmeterol and fluticasone propionate in chronic obstructive pulmonary disease. Thorax 2005 Apr; 60 (4): 301-4

38. Dowling RB, Johnson M, Cole PJ, et al. Effect of salmeterol on *Haemophilus influenzae* infection of respiratory mucosa *in vitro*. Eur Respir J 1998; 11: 86-90
39. Dowling RB, Johnson M, Cole PJ, et al. Effect of fluticasone propionate and salmeterol on *Pseudomonas aeruginosa* infection of the respiratory mucosa in vitro. Eur Respir J 1999; 14: 363-9
40. Mehta RS, Kathman SJ, Daley-Yates PT, et al. Pharmacokinetics and pharmacodynamics in COPD patients following long-term twice-daily treatment with salmeterol/fluticasone propionate 50/500mg and the individual components [abstract]. Am J Respir Crit Care Med 2007 Apr; 175 Suppl.: 127
41. Calverley PMA, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007 Feb 22; 356 (8): 775-89
42. Singh SD, Whale C, Hatton A, et al. Comparison of the pharmacokinetics (PK) of inhaled fluticasone propionate (FP) in patients with chronic obstructive pulmonary disease (COPD) and healthy subjects [abstract]. Am J Rep Crit Care Med 2001 Apr; 163 (5 Suppl. Pt 2): A281
43. Daley-Yates PT, Harker AJ, Taylor S, et al. Plasma protein binding (PPB) of corticosteroids (CS): reappraisal of its significance in systemic pharmacological activity [abstract no. 13]. J Allergy Clin Immunol 2005 Feb; 115 (2 Suppl. 1): S4
44. Cazzola M, Testi R, Matera MG. Clinical pharmacokinetics of salmeterol. Clin Pharmacokinet 2002; 41 (1): 19-30
45. Allen & Hanburys. Seretide 100, 250, 500 Accuhaler [online]. Available from URL: http://emc.medicines.org.uk [Accessed 2007 Sep 26]
46. Manchee GR, Barrow A, Kulkarni S, et al. Disposition of salmeterol xinafoate in laboratory animals and humans. Drug Metab Dispos 1993; 21 (6): 1022-8
47. Hanania NA, Darken P, Horstman D, et al. The efficacy and safety of fluticasone propionate (250 μg)/salmeterol (50 μg) combined in the Diskus inhaler for the treatment of COPD. Chest 2003 Sep; 124 (3): 834-43
48. Kardos P, Wencker M, Glaab T, et al. Impact of salmeterol/fluticasone propionate versus salmeterol on exacerbations in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2007 Jan 15; 175 (2): 144-9
49. Calverley P, Pauwels R, Vestbo J, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 2003 Feb 8; 361 (9356): 449-56
50. Mahler DA, Wire P, Horstman D, et al. Effectiveness of fluticasone propionate and salmeterol combination delivered via the Diskus device in the treatment of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2002 Oct 15; 166 (8): 1084-91
51. Celli B, Ferguson GT, Anderson JA, et al. Salmeterol/fluticasone propionate (SFC) improves lung function and reduces the rate of decline over three years in the TORCH survival study [abstract]. Am J Respir Crit Care Med 2007 Apr; 175 Suppl.: A763
52. Wedzicha JA, Calverley PMA, Seemungal TA, et al. The prevention of COPD exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med. Epub 2007 Oct 4
53. Make B, Hanania NA, ZuWallack R, et al. The efficacy and safety of inhaled fluticasone propionate/salmeterol and ipratropium/albuterol for the treatment of chronic obstructive pulmonary disease: an eight-week, multicenter, randomized, double-blind, double-dummy, parallel-group study. Clin Ther 2005 May; 27 (5): 531-42
54. Donohue JF, Kalberg C, Emmett A, et al. A short-term comparison of fluticasone propionate/salmeterol with ipratropium bromide/albuterol for the treatment of COPD. Treat Respir Med 2004; 3 (3): 173-81
55. Cazzola M, Noschese P, Centanni S, et al. Salmeterol/fluticasone propionate in a single inhaler device versus theophylline + fluticasone proionate in patients with COPD. Pulm Pharmacol Ther 2004; 17: 141-5
56. Singh D, Brooks J, Hagan G, et al. Superiority of the 'triple' therapy of salmeterol/fluticasone propionate (SFC) and tiotropium (TIO) vs. individual components in COPD [abstract]. 17th Annual Congress of the European Respiratory Society; 2007 Sep 15-19; Stockholm
57. Cazzola M, Andò F, Santus P, et al. A pilot study to assess the effects of combining fluticasone propionate/salmeterol and tiotropium on the airflow obstruction of patients with severe-to-very severe COPD. Pulm Pharmacol Ther 2007; 20 (5): 556-61
58. Aaron SD, Vandemheen KL, Fergusson D, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med 2007 Apr 17; 146 (8): 545-55
59. Wouters EFM, Postma DS, Fokkens B, et al. Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial. Thorax 2005 Jun; 60 (6): 480-7
60. Lee TA, Weiss KB. Fracture risk associated with inhaled corticosteroid use in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004 Apr 1; 169 (7): 855-9
61. de Vries F, van Staa TP, Bracke MSGM, et al. Severity of obstructive airway disease and risk of osteoporotic fracture. Eur Respir J 2005; 25: 879-84
62. Glick H, Briggs A, Lozano-Ortega G, et al. Is treatment with ICS/LABA combination good value for money in COPD? Evidence from the TORCH study [abstract]. Am J Respir Crit Care Med 2007 Apr; 175 Suppl.: A763
63. Spencer M, Briggs AH, Grossman RF, et al. Development of an economic model to assess the cost effectiveness of treatment interventions for chronic obstructive pulmonary disease. Pharmacoeconomics 2005; 23 (6): 619-37
64. Halpin DMG, Miravitlles M. Chronic obstructive pulmonary disease: the disease and its burden to society. Proc Am Thoracic Soc 2006; 3 (7): 619-23
65. American Thoracic Society and European Respiratory Society. Standards for the diagnosis and treatment of patients with chronic obstructive pulmonary disease [online]. Available from URL: http://www.thoracic.org/COPD/default.asp [Accessed 2007 Jul 27]
66. Calverley PMA, Scott S. Is airway inflammation in chronic obstructive pulmonary disease (COPD) a risk factor for cardiovascular events? COPD 2006 Dec; 3 (4): 233-42
67. Agustí AGN, Noguera A, Sauleda J, et al. Systemic effects of chronic obstructive pulmonary disease. Eur Respir J 2003; 21: 347-60
68. ClinicalTrials.gov. Can Advair and Flovent reduce systemic inflammation related to chronic obstructive pulmonary disease (COPD)? A multi-center randomized controlled trial [online]. Available from URL: http://clinicaltrials.gov [Accessed 2007 Aug 16]
69. Soriano JB, Vestbo J, Pride NB, et al. Survival in COPD patients after regular use of fluticasone propionate and salmeterol in general practice. Eur Respir J 2002 Oct; 20 (4): 819-25
70. Soriano JB, Kiri VA, Pride NB, et al. Inhaled corticosteroids with/without long-acting β-agonists reduce the risk of rehospitalization and death in COPD patients. Am J Respir Med 2003; 2 (1): 67-74
71. Mapel DW, Nelson LS, Lydick E, et al. Survival among COPD patients using fluticasone/salmeterol in combination versus other inhaled steroids and bronchodilators alone. COPD 2007 Jun; 4 (2): 127-34

72. Mapel DW, Hurley JS, Roblin D, et al. Survival of COPD patients using inhaled corticosteroids and long-acting beta agonists. Respir Med 2006; 100: 595-609
73. Rabe KF. Treating COPD; the TORCH trial, p values, and the dodo. N Engl J Med 2007 Feb 22; 356 (8): 851-4
74. Donohue JF. Combination therapy for chronic obstructive pulmonary disease: clinical aspects. Proc Am Thorac Soc 2005; 2 (4): 272-81
75. Meinke L, Chitkara R, Krishna G. Advances in the management of chronic obstructive pulmonary disease. Expert Opin Pharmacother 2007; 8 (1): 23-37
76. GlaxoSmithKline. GSK receives decision from FDA on Advair 500/50 for COPD [media release]. Available from URL: http://www.gsk.com [Accessed 2007 Aug 16]
77. Atkins PJ. Dry powder inhalers: an overview. Respir Care 2005 Oct; 50 (10): 1304-12
78. Szafranski W, Cukier A, Ramirez A, et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. Eur Respir J 2003; 21: 74-81
79. Calverley PM, Boonsawat W, Cseke Z, et al. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. Eur Respir J 2003; 22: 912-9
80. Decramer M, Ferguson G. Clinical safety of long-acting β_2-agonist and inhaled corticosteroid combination therapy in COPD. COPD 2006 Sep; 3: 163-71

Correspondence: *Gillian M. Keating*, Wolters Kluwer Health | Adis, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore 0754, Auckland, New Zealand.
E-mail: demail@adis.co.nz