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Inhaled Salmeterol/ Fluticasone Propionate

A Review of its Use in Asthma

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Data Selection

Sources: Medical literature published in any language since 1980 on salmeterol/fluticasone propionate, identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). 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 Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.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 and EMBASE search terms were 'salmeterol fluticasone propionate' and 'asthma'. AdisBase search terms were 'salmeterol/fluticasone propionate' and 'asthma'. Searches were last updated 12 July 2005.

Selection: Studies in patients with asthma 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: Asthma, fluticasone propionate, salmeterol, salmeterol/fluticasone propionate, pharmacodynamics, pharmacoeconomics, pharmacokinetics, therapeutic use.

Contents

Summary

Abstract

Salmeterol/fluticasone propionate, administered twice daily via a multidose dry powder inhaler (Seretide/Advair Diskus®, Seretide Accuhaler®) or metered-dose hydrofluoroalkane (chlorofluorocarbon-free) inhaler (Seretide Evohaler®), is a combination of the long-acting β_2-adrenoceptor agonist (β_2-agonist) [LABA] salmeterol and the corticosteroid fluticasone propionate.

Maintenance therapy with combined salmeterol/fluticasone propionate is at least as effective in improving lung function and symptoms and is as well tolerated in patients with asthma as concurrent salmeterol plus fluticasone propionate. In patients previously receiving as-required short-acting β_2-agonists (SABAs) or inhaled corticosteroids, salmeterol/fluticasone propionate was significantly more effective in providing asthma control than fluticasone propionate and in improving lung function and asthma symptoms than inhaled corticosteroids (at equivalent or higher dosages), salmeterol or montelukast (as monotherapy or in combination with fluticasone propionate). Salmeterol/fluticasone propionate was more effective in improving asthma symptoms than adjusted-dose budesonide/formoterol in patients with uncontrolled asthma despite treatment with inhaled corticosteroids with or without a LABA in a well designed 1-year study. In pharmacoeconomic analyses, salmeterol/fluticasone propionate compared favourably with inhaled corticosteroids and mono- or combination therapy with oral montelukast. Salmeterol/fluticasone propionate is, therefore, an effective, well tolerated and cost-effective option for the maintenance treatment of patients with asthma.

Pharmacological Properties

Salmeterol protects against bronchoconstriction caused by a variety of agents or exercise in patients with asthma and possesses a range of anti-inflammatory actions. Fluticasone propionate inhibits the number and function of a wide range of proinflammatory cells in the bronchial epithelium and submucosa and reduces bronchial hyperresponsiveness to various stimuli in patients with asthma. *In vitro* data suggest additive or synergistic effects between LABAs and corticosteroids that may benefit patients with asthma.

The pharmacokinetics of salmeterol and fluticasone propionate administered concomitantly using the same inhaler are generally similar to those of the two agents administered separately. The absolute bioavailability of fluticasone propionate is 10–30% of the inhaled dose. Salmeterol is extensively metabolised by hydroxylation, whereas fluticasone propionate is metabolised by the cytochrome P450 (CYP) isoenzyme CYP3A4 to an inactive metabolite. Drug interactions between fluticasone propionate and potent CYP3A4 inhibitors may occur.

Therapeutic Efficacy

Combined salmeterol/fluticasone propionate was as least as effective in improving lung function and asthma symptoms as the two agents administered using separate inhalers in adults, adolescents and children (aged 4–11 years).

Significantly more patients receiving twice-daily salmeterol/fluticasone propionate than those receiving twice-daily fluticasone propionate achieved totally controlled asthma in a large 1-year study in patients with asthma of varying severity. Moreover, in 12- or 24-week studies in asthmatic patients previously receiving as-required SABAs or inhaled corticosteroids, improvements from baseline in lung function and asthma symptoms were significantly greater with salmeterol/fluticasone propionate than with monotherapy with inhaled corticosteroids, salmeterol or montelukast, or combination therapy with montelukast plus fluticasone propionate. In several studies, this was achieved at substantially lower corticosteroid dosages. In addition, salmeterol/fluticasone propionate provided more effective protection against exercise-induced asthma than fluticasone propionate. In a well designed 1-year trial in patients with uncontrolled asthma despite receiving inhaled corticosteroids with or without a LABA, salmeterol/fluticasone propionate was more effective in improving asthma symptoms and preventing exacerbations than adjusted-dose budesonide/formoterol.

Twice-daily salmeterol/fluticasone propionate produced clinically meaningful improvements from baseline in asthma-related quality of life scores.

Tolerability

Salmeterol/fluticasone propionate was well tolerated in patients with asthma in trials of 4–52 weeks' duration. The most frequently occurring adverse events were headache, throat irritation/cough, hoarseness/dysphonia and candidiasis. No significant differences in markers of systemic glucocorticoid activity were seen between patients receiving concurrent or combined salmeterol/fluticasone propionate 50μg/100μg or 50μg/500μg twice daily in 12- or 28-week studies, or between patients receiving salmeterol/fluticasone propionate 50μg/250μg or 50μg/500μg twice daily or the same nominal dosage of fluticasone propionate.

Pharmacoeconomic Studies

In pharmacoeconomic analyses from a healthcare payer perspective, salmeterol/fluticasone propionate was cost effective. It was associated with favourable incremental function- and symptom-based cost-effectiveness ratios relative to monotherapy with inhaled corticosteroids or oral montelukast in the UK, US and Sweden. Salmeterol/fluticasone propionate was cost saving relative to combination therapy with montelukast plus fluticasone propionate with regard to the cost per successfully treated patient in the US and with regard to the cost per successfully treated week, symptom-free day, symptom-free night and episode-free day in The Netherlands.

1. Introduction

Asthma is a disorder of the airways, characterised by chronic inflammation and involving infiltration of the airway by inflammatory cells, denudation of the airway epithelium, deposition of collagen in the sub-basement membrane, smooth muscle hypertrophy and hyperplasia, mast cell degranulation and goblet cell hyperplasia.[1] The cycle of chronic inflammation and subsequent healing leads to remodelling of the airways.[1] The increased responsiveness of the airways to a range of stimuli produces the characteristic symptoms of asthma (i.e. wheeze, breathlessness, chest tightness and cough).[1]

This article focuses on the therapeutic use of salmeterol/fluticasone propionate administered twice daily via a multidose dry power inhaler (DPI) [Seretide/Advair Diskus®, Seretide Accuhaler®][1] or

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

metered-dose hydrofluoroalkane (chlorofluorocarbon-free) inhaler (MDI) [Seretide Evohaler®], hereafter referred to as salmeterol/fluticasone propionate, as maintenance treatment of asthma. Reported dosages of salmeterol/fluticasone propionate via DPI are those delivered at the mouthpiece and via MDI are metered.

2. Pharmacodynamic Profile

This section provides a brief summary of the well established pharmacodynamic properties of salmeterol and fluticasone propionate in asthma based on information reviewed in detail elsewhere.[2-5]

Salmeterol is a long-acting β_2-adrenoceptor agonist (β_2-agonist) [LABA] which provides protection for at least 12 hours against bronchoconstriction produced by a variety of agents (histamine, methacholine, cold air or sulphur dioxide) or exercise in patients with asthma.[2] Salmeterol inhibits the release of inflammatory mediators, the activity of inflammatory cells and changes in vascular permeability.[2] Reports of tolerance to the effects of salmeterol on induced bronchoconstriction following regular administration are conflicting, and their clinical relevance is uncertain.[2]

The corticosteroid fluticasone propionate inhibits the recruitment, activation, number and function of a wide range of proinflammatory cells in the bronchial epithelium and submucosa, and reduces plasma exudation, mucus secretion and goblet cell hyperplasia.[3] It also decreases the thickness of the airways basement membrane and reduces bronchial hyperresponsiveness induced by various substances in patients with asthma.[3]

The concomitant administration of inhaled salmeterol and fluticasone propionate produces similar β_2-agonist- or corticosteroid-mediated effects on various parameters (e.g. pulse rate, corrected QT interval, serum potassium or glucose level, morning plasma cortisol level and 24-hour urinary cortisol excretion) to those observed when the two products were administered separately in 23 healthy volunteers.[6]

However, the combination of an inhaled corticosteroid and a LABA exhibits beneficial additive or synergistic effects *in vitro*.[4,5] LABAs enhance intracellular binding of corticosteroids and potentiate the anti-inflammatory action of corticosteroids.[4,5] Moreover, corticosteroids protect against the loss of β-receptors during long-term LABA therapy.[4,5]

3. Pharmacokinetic Properties

Limited pharmacokinetic data on the combination of salmeterol/fluticasone propionate in patients with asthma are available and most have been obtained from the manufacturer's prescribing information.[7-9] Pharmacokinetic data on the single agents (which have been previously reviewed[2,3]) are provided where appropriate.

The pharmacokinetics of concomitantly administered inhaled salmeterol and fluticasone propionate are generally similar to those seen when the two products are administered independently and no interaction between the two drugs has been seen.[6] No significant differences in peak serum concentration (C_{max}), time to C_{max} (t_{max}) or elimination half-life ($t_{1/2}$) for either agent were seen when they were administered concomitantly or alone, although an ≈8% increase in the fluticasone propionate area under the serum concentration-time curve was reported with concomitant administration ($p < 0.05$).[6] In patients with asthma, inhalation of salmeterol/fluticasone propionate 50μg/500μg twice daily via a Diskus® DPI resulted in a fluticasone propionate C_{max} of 57 pg/mL (salmeterol C_{max} not reported); the t_{max} of fluticasone propionate is 1–2 hours.[9]

Few data are available on the pharmacokinetics of salmeterol because of technical difficulties in measuring the low plasma levels seen at therapeutic doses (≤200 pg/mL).[7,8] However, in patients with asthma, inhalation of salmeterol 50μg twice daily via a Diskus® DPI results in a C_{max} of 167 pg/mL; the t_{max} is 20 minutes.[9]

In healthy volunteers, the absolute bioavailability of fluticasone propionate after inhalation is 10–30% of the nominal dose, depending upon the device used.[7,8] Swallowed drug has a low bioavailability (<1%) because of its low absorption and high first-pass metabolism.[7-9] In plasma, fluticasone propion-

ate is 99.3% protein bound;[10] its volume of distribution is 4.2 L/kg.[9]

Both drugs are metabolised by the liver.[7-9] Salmeterol undergoes extensive metabolism by hydroxylation and is eliminated in the faeces.[9] Fluticasone propionate is principally metabolised to an inactive carboxylic acid metabolite by the cytochrome P450 (CYP) isoenzyme CYP3A4 and excreted in the faeces along with unchanged drug.[7-9] Less than 5% of a dose is excreted in the urine.[7-9] The $t_{1/2}$ of salmeterol and fluticasone propionate are ≈5.5 and 5.3–7.7 hours when administered as the combination product.[9]

No pharmacokinetic data on salmeterol/fluticasone propionate are available in elderly patients, or those with impaired hepatic or renal function.[9] Salmeterol and fluticasone propionate are both hepatically metabolised, so accumulation of both drugs may be expected to occur in patients with impaired liver function.[9]

Increased systemic exposure to fluticasone propionate is likely when it is coadministered with potent CYP3A4 inhibitors such as ritonavir or ketoconazole.[7-9] Coadministration of ritonavir and fluticasone propionate is not recommended, based on the increased plasma concentrations of fluticasone propionate and reduced serum cortisol levels seen in healthy volunteers who received concomitant ritonavir and intranasal fluticasone propionate.[7-9] No data on this interaction are available for inhaled fluticasone propionate, but increased plasma levels of the drug are anticipated.[7-9]

4. Therapeutic Efficacy

Twice-daily salmeterol/fluticasone propionate (50μg/100μg, 50μg/250μg or 50μg/500μg) has been compared with widely used asthma treatments, including mono- (section 4.1 and 4.2) and combination (section 4.3) therapy with inhaled corticosteroids, LABAs and montelukast in large, randomised, multicentre clinical trials of 4–52 weeks' duration.[11-37] Of note, monotherapy with salmeterol or montelukast is not recommended in some countries.

Where stated, salmeterol/fluticasone propionate was administered via a Diskus® DPI[11,13,15-21,23-36] or MDI.[12,14,22] In large, well designed studies in adults and adolescents aged ≥12 years[38,39] and children aged 4–11 years,[40] the two delivery devices demonstrated clinical equivalence with respect to improvements in lung function and asthma symptoms.

Where stated, patients enrolled in these trials were adults,[15,16,35] adults and adolescents,[11-14,17-21,23-29,31-33,36] or children aged 4–11 years,[30,34,40] with a medical history of asthma and reversible airways obstruction. Prior to randomisation, patients were receiving as-required short-acting β_2-agonist (SABA) alone,[11-15,22,25,26] inhaled corticosteroids[11,16-24,27-36,40] or a LABA with[35] or without[21,22] a corticosteroid. Patients continued to receive as-required treatment with inhaled SABAs.

Primary efficacy outcomes included lung function measures (mean morning peak expiratory flow [PEF],[12,16-18,24,27-33,40] predose forced expiratory volume in 1 second [FEV_1],[13,14,19,21,25,26] area under the serial FEV_1-time curve over 12 hours [$AUC_{12}FEV_1$],[13,14,19,21,22] or maximal percentage decrease in FEV_1 after exercise challenge testing[23]), asthma control,[11,36] the percentage of days[35] or 24-hour periods[15] free from symptoms, exacerbation rate[37] and withdrawal because of lack of efficacy.[19-21]

Secondary endpoints included changes in lung function, asthma symptoms and exacerbation rate. Several studies evaluated the effect of salmeterol/fluticasone propionate combination product on health-related quality of life (HR-QOL) in clinical trials in patients with asthma (section 4.4).[11,16,26,41-45]

Where stated, analysis was performed in the intent-to-treat population.[11,13,15-23,25-36]

Patients kept a diary in which they recorded morning and evening PEF, asthma symptom score and the use of rescue medication. Daytime symptom score was generally assessed on a scale between 0 (no symptoms) and 5 (symptoms causing discomfort or preventing normal daily activities) and night-time score on a scale between 0 (no symptoms) and 4 (unable to sleep at all because of asthma symptoms).

Asthma exacerbations were categorised as mild (a clinically relevant increase in the use of relief medication), moderate (the need for additional inhaled or oral corticosteroids, or bronchodilators) or severe (asthma deterioration requiring hospital treatment).[17,18,33] Exacerbations were also defined as a requirement for additional drugs other than study or rescue medication[20,25,26,32,34] or a requirement for oral corticosteroids, an emergency visit or hospitalisation.[11,35,36] HR-QOL was assessed using the asthma quality-of-life questionnaire (AQLQ), a widely recognised, validated 32-item instrument divided into four domains: activity limitation; symptoms; emotional function; and environmental exposure. Each item is scored using a scale between 1 (most impairment) and 7 (no impairment); a change of ≥0.5 points in overall or individual domain score is considered clinically meaningful.

Some data are available only as abstracts/posters.[12,24,37,41,42,44,45]

4.1 Comparison with Inhaled Corticosteroid or Salmeterol Monotherapy

4.1.1 Effects on Asthma Control

The ability of salmeterol/fluticasone propionate to control asthma, assessed using a multifactorial endpoint, was compared with that of fluticasone propionate in the double-blind, 52-week GOAL (Gaining Optimal Asthma controL) study.[11] Patients with uncontrolled asthma (n = 3421) were stratified according to corticosteroid use at randomisation: stratum 1 (no inhaled corticosteroid); stratum 2 (≤500 μg/day beclometasone dipropionate or equivalent); and stratum 3 (501–1000 μg/day).[11] Patients had at least a 6-month history of asthma and a demonstrated improvement of FEV_1 of ≥15% after SABA inhalation.

Composite measures of asthma control were derived from the treatment goals in the Global Initiative for Asthma (GINA) guidelines[46] and used a multifactorial endpoint comprising seven equally weighted asthma outcomes: morning PEF, rescue β_2-agonist use, daytime symptoms, night-time awakenings, exacerbations, emergency visits and adverse events.[11] Totally and well controlled weeks were defined as achieving all specified criteria each week; the criteria for well controlled asthma allowed a low level of symptoms and rescue medication use, whereas the criteria for totally controlled asthma required the complete absence of all asthma features. Control was assessed over 8-week periods. To be considered to have totally or well controlled asthma, 7 of 8 consecutive weeks must have been totally or well controlled weeks. Automatic failure of totally or well controlled asthma status resulted from failure of the exacerbation, emergency room visits or adverse event criteria at any time during the 8-week period, irrespective of how well asthma was controlled at other timepoints.

During phase I, the corticosteroid dose was increased every 12 weeks until total asthma control was achieved or until the maximum dose was reached (twice-daily salmeterol/fluticasone propionate 50μg/500μg or fluticasone propionate 500μg), at which point patients entered phase II.[11] In strata 1 and 2, the three treatment steps for the salmeterol/fluticasone propionate group were 50μg/100μg, 50μg/250μg and 50μg/500μg twice daily, and for the fluticasone propionate group were 100μg, 250μg and 500μg twice daily. In stratum 3, the lowest dose of salmeterol/fluticasone propionate and fluticasone propionate was omitted.[11] In phase II, patients remained at the dosage at which they achieved totally controlled asthma or the maximum dosage until study end.[11]

The proportions of salmeterol/fluticasone propionate recipients achieving well controlled and totally controlled asthma in all three strata during phase I of the GOAL study were significantly greater than those of fluticasone propionate recipients (table I). The cumulative proportion of patients achieving well or totally controlled asthma at the end of phase II was significantly greater with salmeterol/fluticasone propionate than with fluticasone propionate in all strata (table I).[11] Asthma control was sustained across both treatment groups and all strata; 77–83% of salmeterol/fluticasone propionate and 75–77% of fluticasone propionate recipients who achieved well controlled asthma at the end of phase I remained well controlled at the end of phase

Table I. Effect of salmeterol/fluticasone propionate (S/FP) versus FP on asthma control and lung function in the GOAL (Gaining Optimal Asthma controL) study. In this randomised, double-blind multicentre study,[11] adults and adolescents (age ≥12 years) received S/FP or FP for 1 year and were stratified according to corticosteroid use at randomisation: stratum 1 (no inhaled corticosteroid); stratum 2 (≤500 μg/day beclometasone dipropionate or equivalent); and stratum 3 (501–1000 μg/day). In phase I, the corticosteroid dose was increased every 12 weeks until total asthma control was achieved or until the maximum dose was reached. In phase II, patients (pts) remained at the dosage at which they achieved totally controlled asthma or the maximum dosage. Results shown are for the intent-to-treat population

Regimen (no. of pts)	Asthma control[a] (% of pts)				Mean change from baseline in FEV_1 (L)	
	phase I		phase II		phase I	phase II
	well	total	well	total		
Stratum 1						
S/FP (548)	71*	42**	78*	50**	0.45**	0.52**
FP (550)	65	31	70	40	0.31	0.34
Stratum 2						
S/FP (585)	69**	32**	75**	44**	0.35**	0.37**
FP (578)	52	20	60	28	0.22	0.24
Stratum 3						
S/FP (576)	51**	19**	62**	29**	0.29**	0.32**
FP (579)	31	8	47	16	0.17	0.18

a Based on a multifactorial endpoint comprising morning peak expiratory flow, rescue β_2-adrenoceptor agonist use, daytime symptoms, night-time awakenings, exacerbations, emergency visits and adverse events. Pts achieving total asthma control also achieved well controlled asthma.

FEV_1 = forced expiratory volume in 1 second; * $p < 0.05$, ** $p < 0.001$ vs FP.

II. Of patients who achieved total control at the end of phase I, 69–70% of those receiving salmeterol/fluticasone propionate and 62–74% of those receiving fluticasone propionate maintained totally controlled asthma at the end of phase II.[11]

4.1.2 Effects on Lung Function

Salmeterol/fluticasone propionate improves lung function to a greater extent than monotherapy with inhaled corticosteroids (at equivalent or higher dosages), salmeterol or montelukast.[11-22]

In the 52-week GOAL study, mean morning FEV_1 values improved to a significantly ($p < 0.001$) greater extent with salmeterol/fluticasone propionate than with fluticasone propionate monotherapy in both phases and in all three strata (table I).[11]

In trials of 12 or 24 weeks' duration, salmeterol/fluticasone propionate 50μg/100μg or 50μg/250μg twice daily produced significantly better improvements in lung function than monotherapy with inhaled corticosteroids, salmeterol or placebo in patients with asthma previously treated with as-required SABAs alone, inhaled corticosteroids or salmeterol (table II).[12-22] Importantly, patients receiving salmeterol/fluticasone propionate twice daily generally had significantly greater increases from baseline in mean measures of lung function than recipients of twice-daily fluticasone propionate at equivalent[14,21,22] or higher dosages.[20]

The $AUC_{12}FEV_1$ at 12 weeks was significantly (all $p < 0.05$) greater in patients receiving twice-daily salmeterol/fluticasone propionate 50μg/100μg or 50μg/250μg than in patients receiving twice-daily fluticasone propionate at the same nominal dosage,[13,14,19,21,22] salmeterol 50μg[13,14,19,21,22] or placebo.[19,21,22]

4.1.3 Effects on Exacerbations and Asthma Symptoms

In each stratum in the 52-week GOAL study, salmeterol/fluticasone propionate was associated with significantly lower mean annual rates of exacerbations requiring oral corticosteroids and/or hospitalisation or emergency visits than fluticasone propionate ($p \leq 0.009$).[11] In preliminary data from a randomised, double-blind 12-week trial,[12] the proportion of patients experiencing one or more exacerbations was significantly lower with salmeterol/fluticasone propionate than with beclometasone dipropionate (27% vs 48%; $p < 0.05$).

Twice-daily salmeterol/fluticasone propionate 50μg/100μg or 50μg/250μg was generally signifi-

Table II. Clinical effectiveness of salmeterol/fluticasone propionate (S/FP) versus monotherapy with other agents in patients (pts) with asthma.[a] Results shown are in the intent-to-treat population in randomised, double-blind, multicentre 12- or 24-week trials in adults[15,16] or adults and adolescents[12-14,17-22,25,26] receiving S/FP administered twice daily (bid) via a single Diskus® dry powder[13,15-21] or metered-dose[12,14,22] inhaler versus monotherapy with inhaled FP, S, beclometasone dipropionate (BDP), budesonide (BUD) or placebo (PL) bid. Pts continued to receive as-required inhaled short-acting β_2-adrenoceptor agonists (SABAs)

Study [trial duration (wk)]	Regimen [μg bid] (no. of pts)	Increase from baseline (mean value unless otherwise noted)						
		FEV_1 (L)	morning PEF (L/min)	evening PEF (L/min)	symptom-free days (%)	SABA-free days (%)	SABA use (puffs/day)	nights with no awakenings (%)
In pts previously treated with as-required SABAs alone								
McCarthy et al.[12]b (12)	S/FP 50/100 (78)		68***		48‡‡‡c,d	52‡‡‡c		
	BDP 200 (78)		30		9c,d	14c		
Murray et al.[13] (12)	S/FP 50/100 (88)	0.51§	68*	51*	40.6*		−2.8*	29.8
	FP 100 (89)	0.50	37	30	24.6		−1.8	21.1
	S 50 (90)	0.38	33	24	25.6		−2.6	26.4
Nelson et al.[14] (12)	S/FP 50/100 (95)	0.69*	67*	52*	30.3	40.0‡	−2.4	19.6
	FP 100 (97)	0.51	43	30	24.9	26.5	−1.8	20.5
	S 50 (91)	0.47	29	22	29.6	34.3	−1.6	17.2
Strand and Luckow[15] (24)	S/FP 50/100 (78)		56‡‡	40‡	41‡	49§d		27e
	FP 100 (72)		23	14	26	38d		19e
In pts previously treated with inhaled corticosteroids								
Bergmann et al.[16] (12)	S/FP 50/250 (170)		52*	46*	49*		−1.6***	
	FP 500 (177)		36	29	38		−1.0	
Jenkins et al.[17] (24)	S/FP 50/250 (180)		45***		60.0***c			
	BUD 800 (173)		19		34.0c			
Johansson et al.[18] (12)	S/FP 50/100 (176)	0.3	43*		39	37		36e
	BUD 400 (173)	0.3	33		39	39		34e
Shapiro et al.[19] (12)	S/FP 50/250 (81)	0.48*	54*	45*	33.8*		−2.3*	7.2*
	FP 250 (81)	0.25†	15†	8†	15.4†		−0.9†	2.8†
	S 50 (84)	0.05†	−12	−14	2.1		0.0†	−8.0
	PL (90)	−0.11	−14	−16	−7.9		0.9	−12.0
Corticosteroid step-down								
Busse et al.[20]f (24)	S/FP 50/100 (281)	0.1*	45	49*	11.6	14.9*	−0.43*	
	FP 250 (277)	0.0	33	31	6.2	8.3	−0.21	
In pts previously treated with inhaled corticosteroids, LABAs or SABAs								
Kavuru et al.[21]g (12)	S/FP 50/100 (87)	0.51*	53*	35*	22.6*		−1.9*	4.6†§
	FP 100 (85)	0.28†	17†	18†	7.2		−0.4†	2.4†
	S 50 (86)	0.11	−2†	−7	8.0†		−0.3†	−5.3†
	PL (77)	0.01	−24	−13	−3.8		1.7	−16.5
Pearlman et al.[22]h (12)	S/FP 50/100 (92)		58**	47**	39.7**	42.1**		9.0**
	FP 100 (89)		27	20	9.5	13.5		5.3
	S 50 (92)		25	16	15.8	21.1		1.8
	PL (87)		1	3	5.2	3.2		−4.3

a Pts had an FEV_1 40–85%,[22] 50–80%,[16] 50–85%,[17] 40–85%,[13,14,19,21] 65–85%[18] or 65–95%[20] of predicted normal value, a PEF 65–85%[18] or 50–85%[17] of predicted normal value, or baseline diurnal variation ≥20%.[15]

b Abstract.

c Median.

Continued next page

Table II. Contd

d 24-hour period.

e Number of symptom-free nights.

f Prior to randomisation, pts had unstable asthma with fluticasone propionate 100μg bid, but regained asthma control with fluticasone propionate 250μg bid for 4 weeks.

g 250 pts received inhaled corticosteroids and 106 pts received S prior to randomisation.

h 134 pts received inhaled corticosteroids, 84 pts received S and 142 pts received SABAs prior to randomisation.

FEV_1 = forced expiratory volume in 1 second; **LABA** = long-acting β_2-adrenoceptor agonist; **PEF** = peak expiratory flow; * $p < 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ vs all comparators; † $p < 0.05$ vs PL; ‡ $p < 0.05$, ‡‡ $p < 0.01$, ‡‡‡ $p < 0.001$ vs FP or BDP; § $p < 0.05$ vs S.

cantly better at improving asthma symptoms than inhaled corticosteroids (at equivalent or higher dosages) or salmeterol.[11-13,15-22]

In most trials of 12- or 24-weeks' duration, this was most notable in the significantly higher increase from baseline in the percentage of days free from symptoms[12,13,15-17,19,21,22] and the significantly lower use of rescue β_2-agonist[12,13,15,16,19-22] with salmeterol/fluticasone propionate than with inhaled corticosteroid recipients (table II). In one study,[15] the percentage of symptom-free 24-hour periods (primary endpoint) increased from baseline to a significantly greater extent with salmeterol/fluticasone propionate 50μg/100μg than with fluticasone propionate 100μg (from 20% to 64% vs from 24% to 51%; $p = 0.008$). Night-time symptoms were better controlled with salmeterol/fluticasone propionate than with fluticasone propionate[19] or salmeterol[21] in two studies (table II).

In Children

In 12-week safety study in children aged 4–11 years with asthma symptoms despite receiving inhaled corticosteroids,[34] the proportion of patients experiencing an asthma exacerbation or withdrawing from treatment due to worsening asthma were numerically smaller with salmeterol/fluticasone propionate 50μg/100μg twice daily (n = 101) than with fluticasone propionate 100μg twice daily (n = 102) [3% vs 8% and 2% vs 5%; statistical significance not reported]. Increases in mean FEV_1 and morning and evening PEF were numerically greater with salmeterol fluticasone propionate than with fluticasone propionate monotherapy.

4.1.4 Corticosteroid-Sparing Effect

Salmeterol/fluticasone propionate displays a corticosteroid-sparing effect.[16,20] Lung function and asthma symptoms generally improved to a significantly greater extent with salmeterol/fluticasone propionate 50μg/100μg than with fluticasone propionate 250μg[20] and with salmeterol/fluticasone propionate 50μg/250μg than with twice the dosage of fluticasone propionate (500μg)[16] [table II].

The fluticasone propionate step-down trial (table II)[20] enrolled patients with unstable asthma when receiving fluticasone propionate 100μg twice daily, but stable asthma with fluticasone propionate 250μg twice daily. Salbutamol/fluticasone propionate 50μg/100μg was corticosteroid-sparing; patients were able to reduce their total daily inhaled corticosteroid dose by 60% while maintaining asthma stability. Salmeterol/fluticasone propionate 50μg/100μg twice daily was also associated with a significantly lower proportion of SABA-free days and number of SABA inhalations per day than the higher dosage of fluticasone propionate (250μg twice daily) [table II].[20] The proportion of symptom-free days was significantly greater with salmeterol/fluticasone propionate 50μg/100μg than with fluticasone propionate 250μg after 12 weeks (11.8% vs 5.8%; $p = 0.028$), but not after 24 weeks (11.6% vs 6.2%).[20]

4.1.5 In Exercise-Induced Asthma

Salmeterol/fluticasone propionate was more effective than fluticasone propionate in providing protection against exercise-induced asthma in patients previously receiving inhaled corticosteroids in a 4-week study.[23] Patients (n = 192) who demonstrated a ≥20% decrease from baseline in FEV_1 or after a standardised stepped exercise challenge test re-

ceived nonblind treatment with fluticasone propionate 250μg twice daily for 2–5 weeks, after which they continued double-blind treatment with fluticasone propionate at the same dosage or received salmeterol/fluticasone propionate 50μg/250μg twice daily.[23] FEV_1 was measured immediately before and at various timepoints after a stepped exercise challenge test.[23]

After the nonblind run-in period, salmeterol/fluticasone propionate recipients had a significantly lower mean maximal decline in FEV_1 than fluticasone propionate recipients 1 hour (11.4% vs 20.0%; $p < 0.001$), but not 8.5 hours (11.6% vs 12.6%) after administration of the study drug.[23] After 4 weeks, the mean maximal decline in FEV_1 was significantly lower with salmeterol/fluticasone propionate than with fluticasone propionate at both timepoints (10.9% vs 18.4% and 8.9% vs 12.9%; both $p \leq 0.01$) and mean morning PEF was significantly increased (19 vs 6 L/min; $p = 0.03$).[23]

4.1.6 Step-Down to Monotherapy

'Stepping down' asthma therapy from salmeterol/fluticasone propionate to monotherapy with fluticasone propionate, salmeterol or montelukast resulted in worsening of lung function and symptoms in patients with asthma.[24] In preliminary data from a combined analysis of two identical studies, 1288 patients previously receiving inhaled corticosteroids received salmeterol/fluticasone propionate 50μg/100μg twice daily for 4 weeks and were then randomised to continue to receive salmeterol/fluticasone propionate twice daily or to receive monotherapy with fluticasone propionate 100μg twice daily, salmeterol 50μg twice daily or montelukast 10mg once daily.[24]

At 16 weeks, patients continuing treatment with salmeterol/fluticasone propionate had significantly ($p < 0.001$) greater improvements from baseline than those switched to fluticasone propionate, salmeterol or montelukast in mean morning PEF (5 vs −16, −21 and −30 L/min) and FEV_1 (0.08 vs −0.06, −0.15 and −0.23L) values.[24] Changes from baseline in the percentage of days free from symptoms (5.4% vs −1.1%, −3.5% and −11.8%) or free from rescue medication (6.5% vs −8.4%, −10.5% and −21.5%) were also significantly ($p < 0.001$) greater in the salmeterol/fluticasone propionate group than in the respective monotherapy groups.[24]

4.2 Comparison with Montelukast Monotherapy

Salmeterol/fluticasone propionate 50μg/100μg twice daily was significantly more effective than montelukast 10mg once daily in improving lung function and symptoms in patients with asthma receiving as-required SABAs alone in two 12-week studies (table III).[25,26] In one trial,[25] patients receiving salmeterol/fluticasone propionate experienced significantly fewer asthma exacerbations than those receiving montelukast (table III).

Table III. Clinical effectiveness of inhaled salmeterol/fluticasone propionate 50μg/100μg twice daily (S/FP) versus oral montelukast 10mg once daily (MON) in patients (pts) with asthma previously treated with as-required short-acting β_2-adrenoceptor agonists (SABAs) alone. Pts had a forced expiratory volume in 1 second (FEV_1) 50–80% of predicted normal value. Results shown are for the intent-to-treat population in randomised, double-blind, multicentre 12-week trials in adults and adolescents receiving S/FP administered via a single Diskus® dry powder inhaler. Pts continued to receive as-required inhaled SABAs

Study	Regimen (no. of pts)	Increase from baseline (mean value unless otherwise noted)							≥1 exacerbation (% of pts)
		FEV_1 (L)	morning PEF (L/min)	evening PEF (L/min)	symptom-free days (%)	SABA-free days (%)	SABA use (puffs/day)	nights with no awakenings (%)	
Calhoun et al.[25]	S/FP (211)	0.54**	90**	70**	48.9**	53.0**		23.0**	0**
	MON (212)	0.27	34	31	21.7	26.2		15.5	5
Pearlman et al.[26]	S/FP (216)	0.61**	81**	65**	40.3**	53.4**	−3.6**	29.8*	3
	MON (216)	0.32	42	39	27.0	26.7	−2.3	19.6	6

PEF = peak expiratory flow; * $p < 0.05$, ** $p \leq 0.001$ vs MON.

Table IV. Clinical effectiveness of salmeterol/fluticasone propionate (S/FP) versus other concurrently administered or combination therapies in patients (pts) with asthma[a] previously treated with inhaled corticosteroids. Results shown are for the intent-to-treat populations of randomised, double-blind, multicentre 12- or 28-week trials of SP/F administered twice daily (bid) via a single Diskus® dry powder inhaler. Pts continued to receive as-required inhaled short-acting β_2-adrenoceptor agonists (SABAs). Unless otherwise noted, pts were adults and adolescents

Study [trial duration (wk)]	Treatment [μg bid][b] (no. of pts)	Increase from baseline (mean value unless noted otherwise)				
		FEV_1 (L)	morning PEF (L/min)	evening PEF (L/min)	symptom-free days (%)[c]	SABA-free days (%)
Compared with concurrent S plus FP bid						
Aubier et al.[27] (28)	S/FP 50/500 (167)	0.25[d]	35†[e]	29†[e]		
	S 50 + FP 500 (171)	0.15[d]	33[e]	23[e]		
	FP 500 (165)	0.18[d]	15[e]	9[e]		
Bateman et al.[28] (12)	S/FP 50/100 (121)	0.20	42	36	43	
	S 50 + FP 100 (123)	0.17	33	30	49	
Chapman et al.[29] (28)	S/FP 50/250 (180)	0.26	43[e]	35*[e]	34[e]	
	S 50 + FP 250 (191)	0.24	36[e]	25[e]	30[e]	
In children aged 4–11 years						
Van den Berg et al.[30] (12)	S/FP 50/100 (125)	0.21	33	25	37	32[c,d]
	S 50 + FP 100 (132)	0.13	28	29	39	40[c,d]
Compared with concurrent budesonide (BUD) plus formoterol (FOR) bid						
Ringdal et al.[31] (12)	S/FP 50/250 (212)	0.27	43			
	BUD 800 + FOR 12 (216)	0.26	41			
Compared with oral montelukast 10mg once daily (MON) plus FP bid						
Nelson et al.[32] (12)	S/FP 50/100 (222)	0.34‡‡	25‡‡	19‡‡		26.3‡
	MON + FP 100 (225)	0.20	13	10		19.1
Ringdal et al.[33] (12)	S/FP 50/100 (356)	0.26‡‡	37‡‡	31‡‡	42.9‡	47.9‡[c]
	MON + FP 100 (369)	0.17	21	15	31.5	46.0[c]

a Pts had a PEF 50–80%,[31,32] ≥50%[30] or 50–85%[28] of predicted normal value, or 50–85%[29] or 51–84%[33] of post-bronchodilator value, or an FEV_1 50–80%[32] or 50–100%[27] of predicted normal value.

b With the exception of MON.

c Median value.

d Data estimated from graph.

e 12wk data reported.

FEV_1 = forced expiratory volume in 1 second; **PEF** = peak expiratory flow; * $p < 0.01$ vs S + FP; † $p < 0.001$ vs FP; ‡ $p < 0.05$, ‡‡ $p < 0.001$ vs MON + FP.

4.3 Comparisons with Concurrently Administered or Combination Therapies

4.3.1 Concurrent Salmeterol Plus Fluticasone Propionate

Combined salmeterol/fluticasone propionate was at least as effective as salmeterol and fluticasone propionate administered concurrently using separate inhalers in improving lung function and asthma symptoms and reducing the use of rescue medication in symptomatic patients with asthma receiving inhaled corticosteroids (table IV).[27-29] No significant differences in increases from baseline in mean morning PEF or FEV_1 were seen in patients receiving concurrent or combined therapy with twice-daily administration of salmeterol and fluticasone propionate 50μg/100μg,[28] 50μg/250μg[29] or 50μg/500μg.[27] In one study,[29] mean evening PEF improved significantly more from baseline in patients receiving combination compared with concurrent salmeterol/fluticasone propionate 50μg/250μg twice daily (table IV). Further, there were no significant between-group differences at endpoint in the percentage of patients with daytime or night-time

symptom scores of zero,[27-29] or who did not require rescue medication on ≥75% of days or nights,[28,29] or in the number of days or nights free from rescue medication.[27]

In a meta-analysis[47] of four clinical trials,[27-30] (including one study in children[30]), patients receiving combined salmeterol/fluticasone propionate experienced a significantly greater increase in mean morning (between-group difference 5 L/min; $p = 0.006$) and evening PEF (6 L/min; $p < 0.001$) than concurrent salmeterol and fluticasone propionate recipients. Relative to patients receiving concurrent therapy, those receiving combination therapy had an ≈40% increase in the odds of achieving a >15 L/min (predefined as the threshold for clinical meaningful change) or >30 L/min improvement in morning PEF. No significant between-group difference in FEV_1 or days free from symptoms or rescue medication were reported.[47]

In Children

Salmeterol/fluticasone propionate was effective in improving lung function and asthma symptoms in 12-week trials in asthmatic children aged 4–11 years.[30,40] In a trial comparing delivery devices,[40] mean morning PEF improved by ≈38 L/min in both the salmeterol/fluticasone propionate Diskus® DPI and salmeterol/fluticasone propionate MDI groups. Improvements were shown across all age groups, evident by weeks 1–4 and sustained through to weeks 9–12. Mean evening PEF values, and percentages of both symptom- and rescue-free days and nights also improved from baseline in both treatment groups.

Salmeterol/fluticasone propionate 50μg/100μg twice daily was as effective in improving lung function and controlling symptoms or exacerbations as concurrent salmeterol 50μg and fluticasone propionate 100μg twice daily in children previously receiving inhaled corticosteroids.[30] No significant differences were shown between combined and concurrent salmeterol/fluticasone in mean FEV_1, morning or evening PEF, number of days free from symptoms or number of days without use of rescue medication (table IV).

4.3.2 Budesonide Plus Formoterol

Combination

In the double-blind CONCEPT (CONtrol CEntered Patient Treatment) 52-week study (n = 688), salmeterol/fluticasone propionate was more effective in controlling asthma symptoms than adjusted-dose budesonide/formoterol in patients with uncontrolled asthma despite receiving inhaled corticosteroids with or without a LABA.[35] Patients received salmeterol/fluticasone propionate at the fixed dose of 50μg/250μg twice daily or budesonide/formoterol 160μg/4.5μg with the dosage adjusted according to the severity of their symptoms. After an initial period of two inhalations of budesonide/formoterol 160μg/4.5μg twice daily for 4 weeks, patients decreased their dose to one inhalation twice daily. From week 16 onwards, patients were instructed to reduce their budesonide/formoterol dosage to one inhalation daily if control criteria were met, but to revert to one inhalation twice daily if criteria were not met at later visits; if asthma worsened at any time during weeks 5–52, patients increased their inhalations to four inhalations twice daily for 7 or 14 days and then stepped down to one inhalation twice daily.[35]

At trial endpoint, the median percentage of symptom-free days was significantly greater with salmeterol/fluticasone propionate than with budesonide/formoterol (58.8% vs 52.1%; $p = 0.034$); both groups had no symptom-free days at baseline.[35] Although the percentage of symptom-free days was 25% in both groups at week 4, during weeks 5–52 when dosage-adjustment of budesonide/formoterol was allowed, the percentage of symptom-free days was significantly higher in the salmeterol/fluticasone propionate group than in the budesonide/formoterol group (73.8% vs 64.9%; $p = 0.03$).[35] The adjusted annual mean exacerbation rate was significantly lower with salmeterol/fluticasone propionate than with budesonide/formoterol (0.18 vs 0.33; $p = 0.008$; relative risk reduction 47%), with 11% and 18% of patients in the respective groups experiencing an exacerbation.[35]

In a randomised, open-label 6-month study in patients with asthma previously treated with inhaled

corticosteroids (n = 658),[36] salmeterol/fluticasone propionate 50μg/250μg twice daily was as effective as budesonide/formoterol at a fixed- (160μg/4.5μg two inhalations twice daily) or adjusted- (160μg/4.5μg one to four inhalations twice daily) dosage at achieving a well controlled asthma week (defined as a week without exacerbations, change in asthma treatment due to adverse events, or night-time awakenings due to asthma plus two of three other parameters [≤2 days with asthma symptom score >1 point or rescue medication use, or a morning PEF ≥80% of predicted normal value every day]). The number of well controlled asthma weeks achieved was not significantly different between treatment arms (quantitative data not reported).[36] However, in secondary endpoint analysis, salmeterol/fluticasone propionate recipients experienced significantly more asthma exacerbations in the 6-month period than adjusted-dose budesonide/formoterol recipients (59 vs 35 exacerbations; $p = 0.018$).[36]

In preliminary results of a fixed-dose, double-blind 24-week trial in patients with persistent asthma,[37] the rate of exacerbations was not significantly different between one inhalation of salmeterol/fluticasone propionate 50μg/250μg twice daily (n = 694) and two inhalations of budesonide/formoterol 160μg/4.5μg twice daily (n = 697) [2.69 vs 2.79 exacerbations]. Both treatment groups showed similar improvements in lung function and asthma symptoms (quantitative data not reported). However, in a *post hoc* analysis of exacerbation rates, the benefits of salmeterol/fluticasone propionate over budesonide/formoterol increased over time. In weeks 17–24 of the trial, the moderate-to-severe exacerbation rate was significantly lower with salmeterol/fluticasone propionate than with budesonide/formoterol (0.11 vs 0.24; $p = 0.006$).

Concurrent

Improvements in lung function were similar with combined salmeterol/fluticasone propionate 50μg/250μg twice daily and budesonide 800μg plus formoterol 12μg twice daily administered concurrently using separate inhalers in symptomatic patients with asthma previously receiving high-dose inhaled corticosteroids (table IV).[31] However, salmeterol/fluticasone propionate was significantly more effective in preventing exacerbations and reducing night-time symptoms than concurrent budesonide plus formoterol;[31] salmeterol/fluticasone propionate recipients experienced significantly fewer exacerbations of any severity (129 vs 206; $p < 0.001$), significantly more nights free from symptoms (86% vs 73%; $p < 0.05$) or awakenings (81% vs 61%; $p < 0.05$), but a similar number of nights without use of rescue medication (93% vs 88%) [some results estimated from a graph].[31]

4.3.3 Montelukast Plus Fluticasone Propionate

In symptomatic patients with asthma receiving inhaled corticosteroids, salmeterol/fluticasone propionate 50μg/100μg twice daily was significantly more effective than montelukast 10mg daily plus fluticasone propionate 100μg twice daily (table IV).[32,33] Salmeterol/fluticasone propionate was associated with significantly greater improvements in mean FEV_1 and morning and evening PEF, and more symptom-free days and days without use of rescue medication than montelukast plus fluticasone propionate.

Significantly fewer salmeterol/fluticasone propionate than montelukast plus fluticasone propionate recipients experienced an asthma exacerbation (2% vs 6%[32] and 9.6% vs 14.6%;[33] both $p < 0.05$), and a significantly longer time to first exacerbation was reported with salmeterol/fluticasone propionate in one study (quantitative data not reported; $p < 0.05$).[33]

4.4 Effects on Health-Related Quality of Life

Twice-daily salmeterol/fluticasone propionate 50μg/100μg[26,42,44] or 50μg/250μg[11,16,43] produced clinically meaningful improvements from baseline in HR-QOL based on overall AQLQ scores.

In the GOAL study (section 4.1.1), patients in both the salmeterol/fluticasone propionate and fluticasone propionate arms in strata 1, 2 and 3 experienced clinically relevant improvements from baseline in AQLQ overall score during phase I (mean increase from baseline 1.5 vs 1.3, 1.3 vs 1.0 and 1.1 vs 0.8 points) and during phase II (1.6 vs 1.4, 1.3 vs 1.2 and 1.2 vs 1.0 points).[11] AQLQ scores im-

proved to a significantly greater extent with salmeterol/fluticasone propionate than with fluticasone propionate in strata 2 and 3 during phases I and II ($p < 0.01$); however, the between-group differences were not clinically relevant.[11] At baseline, 6–10% of patients had near-maximal overall AQLQ scores. At week 52, the proportion of patients with near-maximal overall AQLQ scores increased in both the salmeterol/fluticasone propionate and fluticasone propionate groups in stratums 1, 2 and 3 (62% vs 62%, 64% vs 53% and 57% vs 45%).

In symptomatic patients previously treated with as-required SABAs alone (sections 4.1 and 4.2), maintenance therapy with combined salmeterol/fluticasone propionate 50μg/100μg twice daily improved AQLQ overall and/or domain scores to a significantly greater extent than fluticasone propionate 100μg twice daily,[42] salmeterol 50μg twice daily[42] or montelukast 10mg once daily.[26,41] The between-group differences were generally clinically meaningful.

In patients previously receiving inhaled corticosteroids, salmeterol/fluticasone propionate 50μg/100μg[44] or 50μg/250μg[43,45] twice daily improved AQLQ overall scores and most domain scores to a significantly greater extent than twice-daily placebo,[44,45] salmeterol 50μg,[44,45] fluticasone propionate 100[44] or 250[45] and budesonide 800μg.[43] Between-group differences in overall AQLQ scores and individual domain scores were clinically meaningful for salmeterol/fluticasone propionate 50μg/100μg or 50μg/250μg versus salmeterol 50μg[44,45] and placebo.[44,45] Salmeterol/fluticasone propionate also produced clinically relevant greater increases in domain scores for asthma symptoms and emotional function than budesonide,[43] and clinically relevant greater increases in the domain score for emotional function in than fluticasone propionate 100μg[44] and 250μg.[45]

5. Tolerability

Tolerability data for salmeterol/fluticasone propionate 50μg/100μg, 50μg/250μg and 50μg/500μg are available from many of the studies presented in section 4 and the manufacturer's prescribing information.[7,8] The tolerability profile of salmeterol/fluticasone propionate administered via a Diskus® DPI[7] or MDI[8] is the same as that for the individual components and no increased incidence of adverse events has been seen after concurrent administration of the two drugs.

Salmeterol/fluticasone propionate combination product was well tolerated in patients with asthma in clinical studies of 4–52 weeks' duration.[11,13,14,16-23,25-36] The incidence of drug-related adverse events in patients receiving salmeterol/fluticasone propionate 50μg/100μg, 50μg/250μg and 50μg/500μg was 4–17%, 6–14% and 17%, respectively, and was generally similar to that of comparator treatment arms.[13,14,17,20,22,23,25-28,30,34,35] The most frequent treatment-related adverse effects were headache (incidence 1–5%), throat irritation/cough (1–5%), hoarseness/dysphonia (2–7%) and candidiasis (oropharyngeal 1–5%; unspecified site 2–3%).[11,13,17,19,21,23,25-30,32,34,36] Salmeterol/fluticasone propionate was not associated with clinically relevant changes in heart rate, ECG, laboratory tests, vital signs or physical examination.

Studies in adults and adolescents aged ≥12 years[11,19,27,28] or children aged 4–11 years[30,34] with asthma reported no significant differences between salmeterol/fluticasone propionate and comparator treatment arms in the effect on markers of systemic glucocorticoid function.

6. Pharmacoeconomic Considerations

Pharmacoeconomic analyses on the use of salmeterol/fluticasone propionate in the management of asthma have been previously reviewed.[48] This section provides a brief summary of several fully published studies,[49-56] which were based on well designed clinical trials described in section 4, are from a healthcare payer perspective and considered only direct costs.

Salmeterol/fluticasone propionate was cost effective versus monotherapy with inhaled corticosteroids[49,50,52,53,55] or oral montelukast[54] in analyses examining lung function- and symptom-based cost-effectiveness endpoints (table V). The additional costs of a successfully treated week (incremental

Table V. Pharmacoeconomic studies of salmeterol/fluticasone propionate (S/FP) administered twice daily (bid) via a single Diskus® dry powder inhaler in patients (pts) with asthma. Analyses were based on clinical trials of S/FP versus inhaled FP or budesonide (BUD) or oral montelukast 10mg once daily (MON) in adults and adolescents (see section 4 for study details). Analyses included direct costs and were from the perspective of the healthcare payer

Study	Country (year of costing)	Base study	Comparators (μg bid)[a]	Incremental cost-effectiveness ratio per pt per			
				successfully treated week	successfully treated patient[b]	symptom-free day	episode-free day[c]
Compared with monotherapy with FP, BUD or MON							
Johansson et al.[49]	Sweden (1998)	Kavuru et al.[21]	S/FP 50/100 vs FP 100	$US16.18[d]		$US5.40	$US5.63
Lundbäck et al.[50]	Sweden (1998)	Jenkins et al.[17]	S/FP 50/250 vs BUD 800	$US3.90[d]		$US1.12	$US0.93
Palmqvist et al.[52]	Sweden (1998)	Shapiro et al.[19]	S/FP 50/250 vs FP 250	$US1.52[d]		$US0.47	$US0.47
Pieters et al.[53]	Sweden (1998)	Aubier et al.[27]	S/FP 50/500 vs FP 500	$US23.31[d]		$US8.10	$US14.56
Price and Briggs[55]	UK (2000)	Kavuru et al.[21]	S/FP 50/100 vs FP 100	£20.83[e]			
Sheth et al.[54]	US (2001)	Calhoun et al.[25]	S/FP 50/100 vs MON		$US1.33	$US1.69	
Compared with MON + FP							
O'Connor et al.[51]	US (2001)	Nelson et al.[32]	S/FP 50/100 vs MON + FP 100		Cost saving		
Pieters et al.[56]	The Netherlands (2000)	Ringdal et al.[33]	S/FP 50/100 vs MON + FP 100	Cost saving[d]		Cost saving	Cost saving

a With the exception of MON.

b Defined as ≥12% improvement from baseline in forced expiratory volume in 1 second at 12wk.

c Defined as a 24h period without an asthma attack, sleep disturbance caused by asthma, adverse effect or requirement for rescue medication.

d Successfully treated week defined as a week with ≥5% improvement from baseline in mean morning predicted peak expiratory flow.

e Successfully treated week was a composite endpoint comprising peak expiratory flow, rescue medication use, asthma symptoms, night-time awakenings, exacerbations, emergency visits and adverse events.

cost-effectiveness ratio) gained by using salmeterol/fluticasone propionate 50μg/100μg, 50μg/250μg or 50μg/500μg instead of the same nominal dosage of fluticasone propionate,[49,52,53,55] budesonide 800μg,[50] or montelukast 10 mg/day were considered to be modest in view of the gains in improved asthma control. In the UK study,[55] incremental cost per quality-adjusted life-year (QALY) using salmeterol/fluticasone propionate 50μg/100μg twice daily instead of fluticasone propionate 100μg twice daily was £1357 (2000 values), and compares favourably with the cost per QALY gained with other healthcare interventions.[55]

Salmeterol/fluticasone propionate 50μg/100μg twice daily was cost effective versus once-daily montelukast 10mg combined with inhaled fluticasone propionate 100μg twice daily[51,56] with regard to lung function and symptoms (table V). Salmeterol/fluticasone propionate was dominant (i.e. more effective and associated with lower costs) over montelukast plus fluticasone propionate with regard to the cost per successfully treated patient in the US study[51] and per successfully treated week, symptom-free day, symptom-free night and episode-free day in the Dutch study.[56]

Sensitivity analysis showed results to be robust to changes in key parameters.[49-56]

7. Dosage and Administration

Salmeterol fluticasone propionate is indicated in the long-term maintenance treatment of asthma in adults, adolescents (age ≥12 years) and children (age ≥4 years).[7-9] The fluticasone propionate dosage of the inhaler should ensure that the patient receives the appropriate fluticasone propionate dosage for the severity of their disease and should be reviewed regularly and adjusted in a stepwise manner as required.[7-9]

In the US,[9] salmeterol/fluticasone propionate 50μg/100μg, 50μg/250μg or 50μg/500μg Diskus® DPI twice daily is recommended in asthmatic adults

and adolescent patients regardless of whether or not they are currently receiving an inhaled corticosteroid. In patients who are already receiving an inhaled corticosteroid, the recommended starting dosage is based on their current daily dose of inhaled corticosteroid. In patients not currently receiving inhaled corticosteroids, the recommended starting dosage is salmeterol/fluticasone propionate 50μg/100μg twice daily.[9] In children aged 4–11 years, salmeterol/fluticasone propionate 50μg/100μg twice daily is approved for use in patients who are symptomatic when receiving an inhaled corticosteroid.[9]

In Europe, salmeterol/fluticasone propionate is indicated in patients in whom the use of a combination LABA and inhaled corticosteroid is appropriate (i.e. patients not adequately controlled with inhaled corticosteroids and an inhaled SABA, or patients already adequately controlled with both an inhaled corticosteroid and a LABA).[7,8] Two inhalations twice daily of the salmeterol/fluticasone propionate 25μg/50μg, 25μg/125μg and 25μg/250μg Evohaler® MDI[8] or one inhalation twice daily of the salmeterol/fluticasone propionate 50μg/100μg, 50μg/250μg or 50μg/500μg Diskus® DPI[7] are recommended in adults and adolescent patients aged ≥12 years. The recommended dosage for children aged 4–11 years is two inhalations twice daily of the salmeterol/fluticasone propionate 25μg/50μg Evohaler® MDI[8] or one inhalation twice daily of the salmeterol/fluticasone propionate 50μg/100μg Diskus® DPI.[7]

Refer to the manufacturer's prescribing information for further information on dosage adjustments and specific recommendations in special patient populations, warnings, precautions and drug interactions.[7-9]

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

Asthma management aims to achieve and maintain control of symptoms, prevent exacerbations and asthma-related mortality, maintain lung function at a level as close to normal as possible, maintain normal activity levels, prevent development of irreversible airflow limitation and avoid drug-related adverse events.[46,57] Many patients require treatment of both the airway inflammation and smooth muscle components of the disease for optimal control. Failure of asthma management contributes to asthma-related mortality and morbidity, adversely affects the patients HR-QOL and increases asthma-related costs.[46]

A stepwise approach to the treatment of asthma is advocated by expert groups in consensus guidelines.[46,57] Low-dose inhaled corticosteroids are the first-choice controller medication for mild persistent asthma in patients whose asthma symptoms are not adequately controlled using as-required SABAs. In patients with moderate persistent asthma, an inhaled corticosteroid plus a LABA is considered first-line therapy. In patients initially receiving inhaled corticosteroids alone, the addition of a LABA is recommended when asthma control cannot be achieved with introductory dosages of inhaled corticosteroids. Although the threshold for the initiation of add-on therapy has not established,[46,57] the therapeutic effect of inhaled corticosteroids plateaus at moderate dosages, after which little therapeutic benefit is gained, but systemic effects increase.[46] In patients with severe persistent asthma, therapy with high-dose inhaled corticosteroids plus a LABA may be supplemented by other agents, if required.[46,57]

Salmeterol/fluticasone propionate, the combination of a LABA and an inhaled corticosteroid, achieves and maintains asthma control. Despite the optimal management and treatment steps provided in asthma treatment guidelines, many patients do not achieve asthma control.[58] Guideline-defined asthma control is, however, a realistic goal for many patients, especially those who are corticosteroid naive and, in the majority of patients with uncontrolled asthma, is achievable with salmeterol/fluticasone propionate. Most clinical studies of asthma control therapies evaluate improvements in individual lung function or asthma severity endpoints, rather than whether control or not is achieved. The level of asthma control achieved may be overestimated by this method.[59] Based on the GINA guidelines on

treatment and definitions of asthma control, the GOAL study (section 4.1.1) assessed the benefits of aiming for complete comprehensive and sustained clinical control in a well designed study that allowed for dose escalation.[11] This study compared the efficacy in achieving asthma control of two recommended therapies: a stepwise increasing dose of fluticasone propionate as monotherapy or in combination in a single inhalation device with salmeterol. Although the patients had previously uncontrolled asthma across a wide range of severities, the majority achieved the goal of guideline-derived asthma control (section 4.1.1).[11] Patients receiving salmeterol/fluticasone propionate achieved control more rapidly and at a lower corticosteroid dosage than patients receiving fluticasone propionate monotherapy. Moreover, treatment aimed at achieving and maintaining control resulted in the almost complete elimination of exacerbations (section 4.1.3) and near-normal HR-QOL (section 4.4) in the majority of patients. Patients who did not attain the stringent definitions of control also showed considerable improvement in health status and a reduction in exacerbation rates. Therefore, stepping up treatment by adding salmeterol to fluticasone propionate treatment has considerable benefits in patients with asthma.

The use of salmeterol/fluticasone propionate also improves lung function and prevents exacerbations (sections 4.2 and 4.3). Greater improvements in lung function and asthma symptoms were generally produced with salmeterol/fluticasone propionate than with inhaled corticosteroids (at equivalent or higher dosages), salmeterol or oral montelukast (with or without inhaled fluticasone propionate) in patients previously treated with as-required SABAs or inhaled corticosteroids. Moreover, stepping down therapy from salmeterol/fluticasone propionate to monotherapy with fluticasone propionate, salmeterol or montelukast significantly worsened lung function and asthma symptoms (section 4.1.6); however, monotherapy with salmeterol or montelukast is not recommended as first-line treatment strategies in many countries.[46,57]

Salmeterol/fluticasone propionate was more effective in controlling asthma symptoms than adjusted-dose budesonide/formoterol regimens in patients who had previously received inhaled corticosteroids, with or without LABAs, in the large double-blind 52-week CONCEPT study (section 4.3.2). Although adjustable maintenance dosing may lead to a reduction in the amount of maintenance treatment used, the number of exacerbations likely increase over time if a minimum daily amount of maintenance treatment is not maintained. Once asthma control is lost, it may be difficult to regain, even with prompt intervention with high dosages of maintenance treatment. Treatment should consider the long-term control of airway inflammation rather than symptom control alone.[35] A higher daily amount of maintenance treatment may improve symptoms that take longer to respond (e.g. changes in bronchial hyperresponsive and airway remodeling). Therefore, the level of treatment that eliminates disease variability, keeps patients symptom free for as long as possible and addresses the underlying airway inflammation may be more effective than minimising the amount of asthma treatment by responding to daily changes in symptoms.

Normal activity levels may be maintained with treatment with salmeterol/fluticasone propionate. Asthma has a significant impact on the normal physical and social activities of daily living and on psychological well being and is associated with an increase in the number of illness-related absences from school or work.[46] Salmeterol/fluticasone propionate produced clinically meaningful improvements in HR-QOL relative to treatment with asthma monotherapies or placebo (section 4.4). Optimal benefit in reducing the severity of exercise-induced bronchospasm is obtained when an inhaled corticosteroid is used in combination with LABA, such as salmeterol/fluticasone propionate.[23] Salmeterol/fluticasone propionate was more effective than fluticasone propionate against exercise-induced asthma in patients with moderate persistent asthma requiring treatment with inhaled corticosteroids (section 4.1.5).

Salmeterol/fluticasone propionate addresses both the airway inflammation and smooth muscle components of asthma and could help prevent the development of irreversible airflow limitation (section 2). Combination inhalers are as effective as administering each drug individually and are more convenient.[46] When salmeterol and fluticasone propionate are administered via one inhaler, patients are unable to use the LABA as monotherapy, which is strongly cautioned against,[46] simultaneous delivery of both drugs may enhance the additive or synergistic pharmacodynamic effects (section 2), and patient compliance may be improved.[60] Low compliance contributes to poor control of asthma, whereas improved adherence to treatment regimens is associated with a decrease in asthma morbidity and mortality, and healthcare expenditure.[60]

Salmeterol/fluticasone propionate is generally well tolerated (section 5). Importantly, it is corticosteroid-sparing (i.e. more effective in improving lung function and asthma symptoms than higher dosages of inhaled corticosteroid monotherapy; section 4.1.4) and, therefore, helps avoid the systemic adverse events related to long-term use of moderate-to-high dosages of corticosteroids.

The economic burden of asthma affects individuals and society at large, and a large part is accounted for by the cost of prescription medications and hospitalisation.[48] Although the cost of preventative treatment for asthma is high, the cost of not treating the disease is even greater.[46] In pharmacoeconomic analyses (section 6), salmeterol/fluticasone propionate was cost effective relative to inhaled corticosteroids and oral montelukast, used alone or in combination with fluticasone propionate. Pharmacoeconomic analyses comparing salmeterol/fluticasone propionate with combination budesonide/formoterol are needed.

In conclusion, maintenance therapy with combined salmeterol/fluticasone propionate is at least as effective in improving lung function and symptoms and is as well tolerated in patients with asthma as concurrent salmeterol plus fluticasone propionate. In patients previously receiving as-required SABAs or inhaled corticosteroids, salmeterol/fluticasone propionate is significantly more effective in providing asthma control than fluticasone propionate and in improving lung function and asthma symptoms than inhaled corticosteroids (at equivalent or higher dosages), salmeterol or montelukast (as monotherapy or in combination with fluticasone propionate). Salmeterol/fluticasone propionate was more effective in improving asthma symptoms than adjusted-dose budesonide/formoterol in patients with uncontrolled asthma despite treatment with inhaled corticosteroids with or without a LABA in a well designed 1-year study. In pharmacoeconomic analyses, salmeterol/fluticasone propionate compared favourably with inhaled corticosteroids and mono- or combination therapy with oral montelukast. Salmeterol/fluticasone propionate is, therefore, an effective, well tolerated and cost-effective option for the maintenance treatment of patients with asthma.

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